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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report was requested and funded by the National Institutes of Health (NIH) Office of Medical Applications of Research. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions, and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ—based on deliberations by the Planning Committee convened by OMAR and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)—and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc@ahrq.gov.**

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Structured Abstract

Objectives: Synthesize evidence of the natural history of chronic hepatitis B (CHB) and effects and harms of antiviral drugs on clinical, virological, histological, and biochemical outcomes.

Data Sources: MEDLINE®, electronic databases, and manual searches of systematic reviews.

Review Methods: We included original observational studies to assess natural history and randomized controlled trials (RCTs) of adults with CHB published in English to assess treatment effects and harms if they reported mortality, incidence of hepato-cellular carcinoma (HCC), cirrhosis or failure, HBeAg or HBsAg, viral load (HBV DNA), alanine aminotransferase (ALT) levels, histological necroinflammatory and fibrosis scores, and adverse events after interferon alfa-2b, pegylated interferon alfa 2-a, lamivudine, adefovir, entecavir, tenovir or telbivudine. We excluded pregnant women, transplant patients, and individuals undergoing cancer chemotherapy. We calculated relative risk or absolute risk differences at end of treatment and post-treatment.

Results: Observational studies (41 publications) suggested that male gender, coinfection with hepatitis C, D, or HIV, increased HBV DNA, and cirrhosis were associated with increased risk of HCC and death. Drugs did not reduce death, liver failure, or HCC in 16 RCTs not designed to test long-term clinical outcomes. Evidence from 93 publications of 60 RCTs suggested drug effects on viral load or replication, liver enzymes, and histology at end of treatment and lasting from <3 to >6 months off treatment. No one treatment improved all outcomes and there was limited evidence on comparative effects. Two RCTs suggested interferon alfa-2b increased CHB resolution versus placebo. Interferon alfa-2b or lamivudine improved off treatment HBV DNA and HBeAg clearance and seroconversion and ALT normalization. Adefovir improved off treatment ALT normalization and HBV DNA clearance. Pegylated interferon alfa 2-a versus lamivudine improved off-treatment HBV DNA and HBeAg clearance and seroconversion, ALT normalization and liver histology. Lamivudine combined with interferon alfa-2b versus lamivudine improved off treatment HBV DNA clearance and HBeAg seroconversion and reduced HBV DNA mutations. Pegylated interferon alfa 2-a plus lamivudine improved off treatment HBV DNA and HBeAg clearance and seroconversion and ALT normalization compared to lamivudine but not pegylated interferon alfa 2-a monotherapy. Adverse events were common but generally mild and did not result in increased treatment discontinuation. Longer hepatitis duration, male gender, baseline viral load and genotype, HBeAg, and histological status may modify treatment effect on intermediate outcomes. Adefovir and pegylated interferon alfa 2-a with lamivudine improved off treatment viral clearance in HBeAg negative patients. There was insufficient evidence to determine if biochemical, viral, or histological measures are valid surrogates of treatment effect on mortality, liver failure, or cancer.

Conclusion: Adults with CHB have an increased risk of death, hepatic decompensation, and HCC. Mono or combined drug therapy improves selected virological, biochemical, and histological markers with no consistent effects on all examined outcomes. Patient and disease characteristics may modify treatment-induced intermediate outcomes. Evidence was insufficient to assess treatment effect on clinical outcomes, predict individualized patient response, or determine if intermediate measures are reliable surrogates. Future research should assess long-term drug effects on clinical outcomes and among patient subpopulations.

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Executive Summary

Introduction

Hepatitis B is a highly prevalent disease with 350 million chronic cases worldwide[1] and more than 4,000 incident cases in the United States in 2006.[2,3] An estimated 2,000 to 4,000 deaths per year are related to Chronic Hepatitis B (CHB) liver diseases.[4,5] The natural history of CHB is variable but generally indolent for many years to decades. Only 5 percent of acutely infected immunocompetent adults develop CHB. Demographic, clinical, and hepatitis B disease factors are believed associated with the development of CHB and poorer prognosis among those who develop CHB.

Treatment goals include prevention of cirrhosis, hepatocellular cancer, and liver failure. Suppressing replication of hepatitis B virus (HBV) is believed a key process to achieving this goal.[6] Hepatitis B treatments include nucleos(t)ide analogues that suppress viral replication and interferons, naturally occurring cytokines with antiviral and immunomodulatory properties.[7,8] Six agents used as monotherapy or in combination have been approved, as of June 2008, for use in the United States (standard interferon alfa-2b, peginterferon alfa-2a, lamivudine, telbivudine, adefovir, and entecavir). A seventh, tenovir, was approved in August 2008. Two basic therapeutic approaches exist. A defined self-limited course (e.g., 4-12 months) followed by monitoring off treatment is generally used with interferon-based therapy. Long-term continuous suppressive therapy is used for other direct antiviral agents. Researchers have proposed clinical outcomes and biochemical, virologic, and histologic measures to determine an individual's risk for disease progression, identify candidates for treatment, and assess treatment effectiveness and harms.[1,9,10]

Demographic and virologic diversity within HBV infected populations and within individuals over extended periods of time, including different genotypes of HBV and developing viral mutations, make it difficult to predict individualized outcomes from population-based studies and in patients with antiviral drug resistance.[11] Furthermore, much of the literature provides incomplete detail to characterize risk factors for progression.

The Minnesota Evidence-based Practice Center (EPC) conducted a systematic review to address the following questions for a National Institutes of Health (NIH) Consensus Conference related to Management of Chronic Hepatitis B in Adults.

Key Questions

Consensus conference question 1. What is the natural history of Hepatitis B?

EPC question 1. What is the evidence that the following population characteristics or clinical features associated with hepatitis B are predictive of hepatocellular carcinoma, liver failure, cirrhosis, liver-related death, and all-cause mortality?

Consensus conference question 2. What are the benefits and risks of the current therapeutic options for hepatitis B with defined or continuous courses of treatment?

EPC question 2a. What is the efficacy (or effectiveness) of interferon therapy, oral therapy, and various combinations in treating hepatitis B with defined or continuous courses of treatment?

EPC question 2b. What are the known harms of interferon therapy, oral therapy, and various combinations in treating hepatitis B with defined or continuous courses of treatment?

Surrogate outcomes of interest. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels, HBV viral load, change in Hepatitis B e antigen (HBeAg) status, hepatitis B surface antigen (HBsAg) conversion, liver biopsy findings (necroinflammatory activity or stage of fibrosis), and drug resistance.

Clinical outcomes of interest include hepatocellular carcinoma, liver failure, cirrhosis, liver-related death, all-cause mortality.

Consensus conference question 3. Which persons with hepatitis B should be treated?

EPC question 3a. Are there differences in efficacy/effectiveness of treatments for treatment naïve versus drug-resistant patients, chronic HBeAg-positive versus HBeAg-negative patients, or for other subpopulations (as defined previously)?

EPC question 3b. Is there evidence that specific subpopulations do not require treatment for hepatitis B (i.e., that the surrogate and/or clinical outcomes are equivalent or superior when not exposed to treatment?)

Consensus conference question 4. What measures are appropriate to monitor therapy and assess outcomes?

EPC question 4. What is the evidence that changes in surrogate endpoints in response to treatment are reliable predictors of long-term resolution or slowed progression of disease?

Patient Population: Adults (≥ 18 years of age), including elderly and members of racial/ethnic minority populations.

Methods

We searched MEDLINE®, the Cochrane library,[12] Medwatch,[13] United Kingdom Current Problems in Pharmacovigilance,[14] and the European Public Assessment Report[15] to find original studies of adults with CHB published in English that reported clinical and intermediary outcomes[16] for observational studies and randomized controlled trials (RCTs) of antiviral drug therapies approved by the Food and Drug Administration (FDA) for CHB.[17]

For question 1, we included studies if they reported clinical outcomes, had at least 1 year of followup between the measurement of predictive factors, had at least one of the outcomes of interest, and reported results for a CHB only population. All studies meeting these criteria were included if the study reported results from a U.S. population. Only studies of at least 1,000 participants outside of the United States were included. For questions 2-4, RCTs of drugs approved by the FDA for CHB[17] were eligible. We included pegylated interferon alfa-2b that has been intensively examined in patients with CHB[18] but not yet approved in the United States**.** We included observational studies of more than 50 treated adults with more than 1 year followup that examined surrogate predictors of clinical outcomes for question 4. We prioritized clinical outcomes and criteria of complete and sustained response for intermediate virological, biochemical, and histological outcomes.

We excluded studies evaluating children and adolescents, pregnant women, adults with hepatocellular carcinoma, patients undergoing transplantation or treatment for malignancies, and trials of reverse transcriptase inhibitor that included fewer than 50 patients or examined treatments for less than 24 weeks. We assessed level and confidence (low, medium, or high) of evidence using a subset of the U.S. Preventive Services Task Force criteria.

We determined low levels of evidence and confidence when data were from small RCTs, from RCTs or observational studies with serious flaws in design/analysis, and from post hoc subgroup analysis**;** moderate levels when large multinational RCTs or observational studies or several RCTs reported consistent associations or effect of the same drugs; and high levels from multiple high quality RCTs or observational studies in applicable patients reporting consistent sustained (off therapy at least 6 months) effects. We synthesized the results calculating relative risk and absolute risk difference (ARD) at 95 percent confidence levels and used meta-analyses to assess the consistency of the association between treatments and outcomes with random effects models.[9 10]

Results

EPC Question 1. What is the evidence that the following population characteristics or clinical features associated with hepatitis B are predictive of hepatocellular carcinoma, liver failure, cirrhosis, liver-related death, and all-cause mortality?

Forty-one articles met inclusion criteria,[19-59] including 14 publications representing eight unique populations within the United States.

Chronic carriers of HBsAg had substantially higher rates of hepatocellular carcinoma, cirrhosis, and death than people who have never been chronically HBsAg-positive.[21 24 30 39 45] The annual incidence of hepatocellular carcinoma (HCC) was only 0.1 percent in asymptomatic HBsAg individuals, 1 percent in patients with CHB, but increased to 3-10 percent in patients with cirrhosis.[60] Patients with CHB developed cirrhosis at a rate of 2 percent per year. Reports have shown large differences in clinical event rates across diagnostic groups such as inactive HBsAg carriers, CHB without cirrhosis, and CHB with cirrhosis. A U.S. cohort study followed 400 HBsAg patients (70 percent born in Asia) for over 7 years.[47] Among 110 inactive carriers, none developed HCC or died of a liver-related disease, and only one died of any cause. Among patients with CHB but no cirrhosis, 6 percent developed HCC and died from it, while another 2 percent died from nonliver related causes. Among those with CHB and cirrhosis, 16 percent were diagnosed with HCC and 42 percent died during followup (all from liver-related causes).

Increased age was generally associated with small to moderately increased clinical outcomes; however, the evidence was inconclusive regarding whether the association between age and clinical outcomes is explained by duration of infection, age of infection, comorbidities in older individuals, and other factors that might be different between older and younger patients. Likewise, there was inconclusive evidence that geographic location or race/ethnicity contribute meaningfully for the prediction of clinical outcomes. There was high confidence that males have greater than twofold increased rates of clinical outcomes compared to women. A positive family history of HCC was associated with an increased risk of HCC, but the extent this was independent of age of infection and duration of disease is unclear. Estimates regarding coinfection and clinical outcomes could only be made with low confidence due to the paucity or inconsistency of the data; coinfection with either human immunodeficiency virus (HIV) or hepatitis delta virus (HDV) appeared associated with strongly increased liver-related mortality, and coinfection with hepatitis C virus (HCV) appeared associated with moderately increased HCC risk. Cirrhosis is a strong predictor of HCC and death. There was little to no evidence

regarding the impact of nonalcoholic liver disease or alcohol consumption on future development of cirrhosis, HCC, or death.

Increased HBV deoxyribonucleic acid (DNA) viral load was strongly associated with increased HCC and liver-related mortality after accounting for baseline cirrhosis, HBeAg status, and ALT levels. There was no evidence regarding whether reduction in HBV DNA viral load was associated with better outcomes. HBV genotypes may be associated with differing risk of clinical outcomes. HBsAg loss was associated with a reduction in risk of cirrhosis, but data were sparse. There was no evidence as to whether HBsAg loss was associated with other improved outcomes. HBeAg-positive status was associated with poorer outcomes independent of other disease factors. Reversion or multiple switches in HBeAg status was associated with increased HCC; however, the mechanism of this is unclear. Basal core promoter mutations (T1762/A1764) and the precore (PC) mutation (A1896) were associated with increased HCC and basal core promoter mutations may be associated with small increases in liver-related death rates. ALT was modestly associated with associated with increased risk of HCC and cirrhosis after accounting for baseline cirrhosis, HBeAg status and HBV viral load.

Questions 2 and 3

Ninety-three articles represented 60 unique randomized trials of interferon alfa-2b,[61-92] peginterferon alfa-2a,[93-97] peginterferon alfa-2b,[98-109] adefovir,[10,110-120] entecavir,[121-126] lamivudine,[64,67,95,96,119,127-142] or telbivudine.[109,120,127,143] Treatment duration averaged 44±22 weeks and followup post-treatment 98±158. Most enrollees were Asian (64 percent) or white (30 percent) ethnicity/race.[61 63,66,69 81,83,84,86,87,90]

Sixteen articles reporting on mortality, HCC, hepatic decompensation, or cirrhosis were not of sufficient size or duration to adequately assess the effect of treatments on these outcomes.[70,83,85,86,90,91,96,106,111,121,122,124-126,132,141] Most studies reported on serologic, virologic, or histologic outcomes with marked variation in patients enrolled, dose or duration of interventions and comparators, time to evaluate outcomes at the end of or at followup off therapies, and definitions of outcomes. When treatment effects were noted, they were rarely reassessed or reported in similar patient populations, and/or drug combinations, doses, or durations. No study assessed outcomes according to the multiple patient and disease characteristics frequently used to determine treatment strategies (e.g., according to HBeAg plus HBV DNA plus ALT plus cirrhosis status). There was a low level of evidence from individual studies or inconsistent results from several studies for most outcomes.

Question 2a. What is the efficacy (or effectiveness) of interferon therapy, oral therapy, and various combinations in treating hepatitis B with defined or continuous courses of treatment?

Clinical outcomes.

Mortality. Antiviral medications did not reduce mortality versus placebo, other antiviral medications, or in combination with corticosteroids, regardless of baseline HBeAg or cirrhosis status in 14 RCTs that were not designed to test long-term clinical outcomes.[70,83,86,90,96,106,111,121, 122,124-126,132]

Cirrhosis. A small trial failed to demonstrate that interferon alfa-2b prevented cirrhosis in HBeAg-positive patients.[83] Another small RCT found no significant difference in histologically

confirmed cirrhosis after interferon alfa-2b alone or with simultaneous prednisone.[85] No data were available from RCTs for other antiviral drugs or longer followup.

Hepatic decompensation was not prevented by lamivudine compared to placebo[141] or entecavir compared to lamivudine[122,126] in three underpowered trials.[122,126,141]

Hepatocellular carcinoma was not prevented in four studies with inadequate size and duration.[85,91,111,132] In one RCT, analysis that adjusted for country, sex, baseline ALT level, Child-Pugh score, and Ishak fibrosis score and excluded five individuals who developed HCC within the first year of the study found a borderline significant effect of lamivudine.[132] This study noted a nonsignificant increase in all cause mortality.

Intermediate outcomes. Evidence suggested drug effects on viral load or replication, liver enzymes, and histology at end-of-treatment and lasting from at least <3 to >6 months off treatment. No one treatment improved all examined outcomes and few assessed complete response or sustained outcomes (i.e., at >6 months off treatment).

HBV DNA clearance was assessed using assays with different sensitivities to detect HBV DNA. Adefovir[10,110,112,113] and lamivudine [67,127,129,131,133,136,139] increased HBV DNA clearance at end of treatment versus placebo. Entecavir increased clearance versus lamivudine[121, 122,123,126] with inconsistent effect size. Lamivudine was less effective than adefovir in lamivudine-resistant patients[119] and less effective than telbivudine in HBeAg-positive patients.[127] Limited evidence suggested that HBV DNA clearance was maintained at followup off therapy ranging from 18-24 weeks after interferon alfa-2b,[69,87] lamivudine,[139] or adefovir administration.[10]

HBeAg loss was assessed in 35 trials. [61,62,64,66,67,69,72,75,80,83,86-88,92,94,96,98,99,102,106,109,112,113,117,119,120,122-125,127,136,140,143,144] HBeAg clearance off treatment was demonstrated for interferon alfa-2b.[64,83,87] Lamivudine for 52 weeks versus placebo increased HBeAg loss at 16 weeks off therapy.[67,136] HBeAg loss at 24 weeks post treatment was greater after peginterferon alfa-2a versus lamivudine.[94,96]

HBeAg seroconversion was assessed in 36 studies.[10,62-64,66-68,75,80,83,88,91,94,96,99,106,109,111-113,117,119,120,122-127,133,136,140,141,143-145] Lamivudine[64,67,127,136,140,141] or adefovir increased HBeAg seroconversion versus placebo.[112,113] Interferon alfa-2b[64,83] increased post-treatment seroconversion. Lamivudine monotherapy failed to sustain seroconversion.[67,136] Interferon alfa-2b plus lamivudine demonstrated inconsistent effects on seroconversion at 6-28 weeks of followup[64,67] with significant benefit in a pooled analysis from four RCTs using individual patient data.[64] Telbivudine versus adefovir[120] or peginterferon alfa-2a versus lamivudine increased post treatment HBeAg seroconversion.[96] Peginterferon alfa-2a plus lamivudine increased HBeAg seroconversion versus lamivudine alone but not versus peginterferon alfa-2a alone.[96]

HBsAg clearance. Nine studies compared active drugs with placebo or no treatment.[10,67,70,83,84,91] Only one RCT of HBeAg-positive patients found a significant increase in HBsAg loss after interferon alfa-2b.[84] Steroid pretreatment followed by interferon alfa-2b versus no antiviral drugs increased HBsAg loss at the end of treatments.[70,84] Active treatments compared to each other did not demonstrate differences post-treatment HBsAg loss or combined outcomes that included loss HBsAg clearance.[61,63,66,67,69,71,73,74,76,80,82-85,87-91,98,99,109,111,119,122,126,136,139]

ALT normalization was greater after adefovir versus placebo.[10,113] Lamivudine increased rates of ALT normalization versus placebo at 24 weeks off treatment in HBeAg-negative patients.[139] Interferon Alfa-2b at doses 35 million units (MU)/week compared to no antiviral treatment increased rates of ALT normalization at 8-24 weeks of followup.[84 87] Sustained ALT

normalization at 24 weeks off treatment was greater after peginterferon alfa-2a compared to lamivudine[95,96] and after combined therapy of peginterferon alfa-2a with lamivudine compared to lamivudine alone.[95,96]

Histological improvement off treatment in necroinflammatory scores was reported in only one RCT[95] after peginterferon alfa-2a compared to lamivudine in HBeAg-negative patients.[95]

Combined virologic and biochemical outcomes. Low to moderate evidence suggested that some examined drugs or their combinations improved combined virologic and biochemical outcomes immediately after[75,81,84,91,122,126,127,139] and post treatment.[61,73,75,81,82,85,87,89,91,106,122,125,139]

Question 2b. What are the known harms of interferon therapy, oral therapy, and various combinations in treating hepatitis B with defined or continuous courses of treatment?

Nucleos(t)ide analogues were well tolerated during the duration studied with safety profiles and withdrawal comparable to placebo. Adverse events were usually mild, including fatigue, headache, abdominal pain, nausea, and diarrhea. Pegylated interferon therapy, alone or combined with lamivudine, was not as well tolerated as lamivudine monotherapy. Subjects treated with combined or monotherapy were more likely to withdraw from a study or require dose modification due to an adverse event compared to lamivudine. Adverse events associated with pegylated interferon include flu-like illness, hair loss, anorexia, and less commonly depression. Pegylated interferon and conventional interferon therapy had comparable safety profiles.

Similar incidences of Grade 3 or 4 laboratory abnormalities were observed for adefovir and placebo with the exception of increases in ALT and AST levels. Subjects with or at risk of impaired renal function may develop nephrotoxicity with adefovir. Twenty-five percent of lamivudine subjects had an ALT level at least three times the baseline level compared to 8 percent of placebo subjects during the post-treatment period. One trial noted greater incidences in Grade 1-4 creatine kinase (CK) elevations with telbivudine compared to lamivudine. Higher frequencies of Grade 3-4 elevations in ALT and AST occurred with lamivudine compared to telbivudine. ALT flares occurred in 24 percent and 9 percent of the lamivudine and entecavir groups, respectively. Laboratory abnormalities were higher in the peginterferon alfa-2a monotherapy and combined therapy groups compared to lamivudine. Overall, dose modification, due mainly to laboratory abnormalities, was required for 46 and 47 percent of peginterferon mono and combined therapy recipients, respectively. Neutropenia and thrombocytopenia were cited as the most common abnormalities.

Question 3a. Are there differences in efficacy/effectiveness of treatments for treatment naïve versus drug-resistant patients, HBeAg-positive versus HBeAg-negative patients, or for other subpopulations (as defined previously)?

Potential modifiers of treatment effectiveness and harm include patient, disease, viral, biochemical and therapeutic factors. Fifteen studies examined treatment effects among patient subpopulations immediately[61,64,75,93,105,107,124,127,130,132,133,135,140,141,143] and at followup off active drugs (n=23 studies).[61-65,72,73,75,84,85,90,93,96,97,99,100,102,104,106,108,109,114,126] No RCTs directly compared patients with eAg+ versus eAg-, treatment naive versus prior treated, or drug resistant

with baseline cirrhosis versus no-cirrhosis. Results from studies enrolling relatively pure populations indicate that there is inconsistent data that baseline treatment status, eAg status, or cirrhosis influence histological, virological, or biochemical end points.

Younger patient age was associated with enhanced HBV DNA clearance and ALT normalization in patients treated with pegylated interferon versus lamivudine.[93,109]

Baseline body weight was not associated with HBV DNA clearance and ALT normalization.[93]

Disease progression or treatment induced sustained ALT normalization and HBV DNA clearance did not vary by gender (five studies, three antiviral agents used as monotherapy).[72,93,109,132,141]

Patients with longer duration of hepatitis responded to therapy 2.5 times less frequently compared to those with shorter duration of the disease. Sustained virologic response at 48 weeks off therapy (HBeAg and HBV DNA loss) to interferon alfa-2b combined with lamivudine was greater in those with an estimated duration of hepatitis of 10 years or less after adjustment for patient gender and age.[63]

Treatment induced followup histology, HBeAg loss or DNA clearance and ALT normalization did not clearly vary by baseline histology severity.[63,64,97,127] HBeAg loss was higher per unit increase in baseline histological activity index (HAI) score.[64] Lamivudine improved histology compared to placebo among patients with moderate or severe hepatitis but failed in those with mild hepatitis.[145] Interferon alfa-2b increased post-treatment HBeAg loss compared to placebo among patients with pretreatment HAI score 5-9 but not in patients with pretreatment HAI score 0-4 or >10.[64] Interferon alfa-2b combined with lamivudine compared to placebo increased post-treatment HBeAg clearance in patients with pretreatment HAI score 5-9 with no significant effects in those with pretreatment HAI score 0-4 or >10.[64] Off treatment virologic response to interferon alfa-2b plus lamivudine increased in those with a baseline inflammation score of seven or more, independent of gender and age.[63] Presence of steatosis did not modify the effect of peginterferon alfa-2a combined with lamivudine on post-treatment response defined as HBV DNA disappearance and ALT normalization in both HBeAg-positive and negative patients.[97] Adjusted rates of post-treatment response were greater per increase in baseline Knodell HAI.[97]

It was difficult to draw conclusions on the effect of viral load on outcomes off therapy due to varying assays and cut offs of baseline DNA. There were inconsistent effects with no dose-response relationship observed. Compared to placebo, lamivudine reduced disease progression regardless of baseline viral load. Compared to lamivudine, peginterferon plus lamivudine was more effective for combined end points regardless of baseline viral load. No studies reported subgroups with very low viral load. Treatment induced HBeAg loss, ALT normalization, or histology improvement varied with baseline viral load. At followup post treatment, interferon alfa-2b increased loss of HBV DNA and HBeAg among patients with baseline HBV DNA 2-99 pg/ml but failed among those with higher baseline HBV DNA.[84] There was not a significant HBV DNA unit dose-response versus no treatment.[61] Interferon alfa-2b increased off treatment rates of HBeAg loss among patients with baseline HBV DNA <10pg/ml but not in those with higher viral loads.[61] Interferon alfa-2b with steroid pretreatment increased post-treatment treatment rates of HBV and HBeAg loss among patients with baseline HBV DNA 2-99 pg/ml but failed in those with HBV DNA >100 pg/ml.[84] Combined administration of interferon alfa-2b with lamivudine resulted in greater off treatment HBV DNA clearance and HBeAg seroconversion in patients with baseline HBV DNA $>10^7$ copies/mL.[75] Peginterferon alfa 2-a

provided greater sustained response compared to lamivudine in patients with baseline HBV DNA range in the 25-75 percentile[93,96] with random differences at other percentiles.

Low quality evidence indicates that treatment effects may vary by baseline HBeAg status.[124,132,143] Lamivudine versus placebo decreased overall disease progression among HBeAg-positive[132] but failed in HBeAg-negative patients.[132] Telbivudine versus lamivudine improved outcomes among HBeAg-positive with random differences in HBeAg-negative patients.[109,143] Patients who were HBeAg-negative at baseline experienced improvement in biochemical, virological, and histological outcomes after adefovir therapy and pegylated interferon alfa 2-a monotherapy or combination with lamivudine.[10,71,74,76,79,81,91,93,95,110,111] Adefovir[10,110] and pegylated interferon alfa 2-a with lamivudine[95] improved off-treatment viral clearance in HBeAg-negative patients.

Treatment induced ALT normalization and HBV DNA clearance or HBeAg seroconversion varied by HBV DNA genotype. There was better response among patients with genotype B and C at the end of treatments[93] and at followup off therapies.[65,93,96,99,100,108,109] Patients with genotype A had lower adjusted odds of response compared to patients with genotype C.[93] Off treatment response to the same treatments also differed with greater adjusted odds of success among patients with genotype B versus D and with genotype C versus D.[93]

Baseline ALT levels. Treatment induced HBeAg clearance and seroconversion, HBeAg loss or virologic clearance varied by baseline ALT levels with inconsistent evidence of better response among patients with elevated baseline ALT (ten studies; three medications used as mono or combination therapy).

HBeAg seroconversion after peginterferon alfa-2a alone or in combination with lamivudine was higher versus lamivudine alone among patients naïve to lamivudine,[96] with no significant differences among patients previously treated with lamivudine. Five RCTs enrolled lamivudine resistant patients.[118,119,124,125,141] Adefovir plus lamivudine versus lamivudine increased ALT normalization and HBV DNA clearance but not HBeAg clearance or seroconversion in lamivudine-resistant patients[119] without improvement in outcomes compared to adefovir monotherapy.[119] Entecavir increased HBV DNA and HBeAg clearance and normalization of ALT in lamivudine-refractory HBeAg-positive patients compared to lamivudine[125,124] and improved necroinflammatory Knodell scores and Ishak fibrosis scores in lamivudine resistant patients.[125] Patients who failed previous interferon therapy did not benefit from adding lamivudine.[92]

Question 3b. Is there evidence that specific subpopulations do not require treatment for hepatitis B (i.e., that the surrogate and/or clinical outcomes are equivalent or superior when not exposed to treatment?)

Studies did not demonstrate improvement in clinical outcomes. However, RCTs were not adequately designed to accurately assess clinical outcomes. Evidence in key question 1 demonstrates that the clinical course of CHB is asymptomatic and indolent in most adults. Therefore, the majority would be unlikely to benefit from treatment for many years. Treatment to reduce viral transmissibility is of potential immediate and long-term public health benefit. Patient, disease, and comorbidity factors are of limited value in assessing prognosis in order to make treatment decisions in an individual patient. A key exception is the presence of cirrhosis where there was high confidence that this led to a large increased risk of poor clinical outcomes.

Therefore, clinicians may decide to initiate therapy in these individuals because of a poor natural history.

Specific subpopulations would not require treatment if their clinical outcomes (and possibly validly defined surrogate measures) were equivalent or superior to similar populations not receiving treatment or if harms of therapy outweighed benefits. The effects of eligible drugs on asymptomatic carriers have not been published in RCTs. Monotherapy with interferon alfa-2b or lamivudine and a combination of interferon alfa-2b with steroids failed to sustain virologic response in patients with CHB. Individuals who failed previous interferon alfa-2b therapy did not benefit after combined interferon and lamivudine treatment. Patients with HBeAg did not experience greater off treatment HBeAg seroconversion after interferon alfa-2b combined with lamivudine. Interferon alfa-2b did not improve histology or increase rates of resolved hepatitis.[82-84,89,91] Interferon alfa-2b combined with lamivudine compared to placebo failed to increase HBeAg clearance or sustained HBeAg seroconversion in patients treated with lamivudine[64] and in nonresponders to the previous interferon therapy.[67] Lamivudine compared to placebo failed to sustain HBeAg seroconversion in interferon nonresponders[67] and in treatment naïve patients.[136] Lamivudine did not sustain HBsAg loss, HBV DNA clearance, or ALT normalization.[67,136,139]

We assessed whether certain patient or hepatitis characteristics were associated with risk of serious adverse events or noncompliance that might lead to a decision not to initiate treatment. Few data were available. Several adverse effects were specific for patients with different HBeAg baseline status. Only HBeAg-negative patients experienced dose modification due to neutropenia or thrombocytopenia.[95] Combined therapy did not prevent worsening of fibrosis scores in HBeAg-negative patients.[95] In HBeAg-positive patients depression, diarrhea, dizziness, nausea, pruritus, rash, or rigors were more common after combined therapy with lamivudine compared to lamivudine alone.[96] YMDD mutations were more common in HBeAg-positive patients after combined therapy compared to peginterferon alfa-2a alone.[96] Pyrexia was more prevalent after peginterferon alfa-2a compared to lamivudine.[95,96] Only HBeAg-positive at baseline patients experienced ≥1 serious adverse event,[96] while only HBeAg-negative patients needed dose modification due to neutropenia or thrombocytopenia.[95] The rates of YMDD mutations were lower after interferon compared to lamivudine in patients with HBeAg-positive CHB.[96]

Question 4: What is the evidence that changes in surrogate endpoints in response to treatment are reliable predictors of long-term resolution or slowed progression of disease?

Studies were not adequately designed to assess the effectiveness of treatments on clinical outcomes, a necessary prerequisite for determining surrogates. Treatments did not improve all-cause mortality, liver-related death, hepatic carcinoma, or hepatic decompensation. We found even fewer studies that assessed the association of baseline 'surrogates' with clinical outcomes. We did not find any RCTs that evaluated whether change in a clinical outcome was explained by a treatment related change in a potential surrogate. We found associations of intermediate markers with clinical outcomes and advise caution against calling them surrogates. Four included studies were either long-term followup of prior RCTs, with randomization no longer preserved, or cohort studies of once-treated patients, where surrogate markers were assessed in relation to long-term clinical outcomes. There was lack of uniformity in surrogate and endpoint measurement, timing of measurement, definitions, and measurement of effect controlling for relevant effect. We have low confidence whether any of the listed biochemical, histologic, or

virologic measures are adequate surrogate markers. Patients who are positive for HBsAg are considered to be capable of transmitting hepatitis B virus to uninfected individuals. Clearance of HBsAg, HBV DNA, or HBeAg seroconversion could be considered an appropriate clinical outcome from the perspective of transmission prevention and public health rather than or in addition to possibly being a surrogate for clinical outcomes in infected patients.

There is limited information on the association of potential surrogates of ALT normalization, detectable HBV DNA, worsening histology, and change in HBeAg on the composite endpoint of decompensation, cirrhosis and HCC, and all-cause mortality among patients treated with peginterferon alpha-2a plus lamivudine, interferon alpha-2a or 2b, or lamivudine. Among HBeAg-positive patients treated with interferon alpha-2a or 2b, a 2-point increase in HAI score at the end of treatment may be a potential surrogate for liver complications. Among HBeAg-positive patients treated with lamivudine alone or in combination with peginterferon interferon alpha-2a, HBeAg seroconversion may be an incomplete surrogate for decompensation. There are no available data that assess HBsAg seroconversion among treated patients on clinical outcomes. There are no data that assess drug resistance among treated patients or following treatment with adefovir or telbuvidine on clinical outcomes.

Discussion

Predicting CHB natural history and accurately evaluating the effectiveness of treatments is difficult, in part due to the long-term and heterogeneous nature of the disease. There is little high quality information with which to make accurate prognostic and treatment decisions. Limited evidence from observational studies suggested that increased age and duration of infection, male gender, coinfection with HIV, HCV, or HDV, increased HBV DNA viral load, and cirrhosis were associated with increased risk of death and cancer. RCTs were not designed to detect effects of drugs on clinical outcomes. Only one trial reported significant protective effect. The beneficial effect of lamivudine on HCC occurred only after secondary adjusted analyses and exclusion of five individuals who developed hepatocellular cancer within the first year of the study.[132] This study also reported a nonsignificant increase in all-cause mortality with lamivudine. Treatment goals proposed by present guidelines include intermediate outcomes (HBV DNA and HBeAg loss, ALT normalization, improvement in histology) with very limited evidence that such measures are associated with significant prevention of liver failure or cancer. Ongoing clinical trials registered in www.clinicatrials.gov defined intermediate measures as primary outcomes with no expected increase in the rates of resolved hepatitis or prevention of cirrhosis, liver failure, or HCC. Low to moderate levels of evidence suggested that improvements off treatment (<3 months to >6 months) in intermediate outcomes occurred after mid-duration treatment. The majority of treatments demonstrated marginal or random effects for off treatment HBsAg seroconversion combined with other criteria of complete response or resolved hepatitis B. Consistent pooled risk reductions from multiple studies were observed for the following: interferon alfa-2b (HBeAg loss and HBV DNA loss); adefovir (ALT normalization and HBV DNA loss); and lamivudine (HBeAg seroconversion, HBV DNA loss, improved necroinflammatory scores, ALT normalization). Biological markers to monitor the effects of drug therapies have not been evaluated in RCTs.

Very limited low level evidence was available for patient subpopulations. Few large working groups conducted appropriate analyses controlling for possible confounding factors, however, consistency in the effects was not possible to estimate considering large variability in patient

characteristics, examined treatments, and different definitions of the outcomes. Published evidence of different treatment effects in aged, males, and patients with longer duration of hepatitis, large viral load, and viral genotype B should generate hypotheses for future research rather that result in valid individualized predictions of treatment benefits.

Deciding which patients should not receive treatment is difficult and necessarily made between patient and health care provider. Evidence does not indicate that therapies improve clinical outcomes but does not exclude potential effect. Furthermore, there was very limited evidence indicating which patients should or should not be treated. No RCTs evaluated treatments among carriers without chronic hepatitis. Limited evidence suggested small treatment benefits in HBeAg-negative patients with the same probability of harms independent of baseline HBeAg status. Patients with active CHB experienced off treatment benefits on selected intermediate outcomes after interferon alfa-2b, adefovir, lamivudine, or pegylated interferon alfa-2a. Absolute rates were low and indirect comparisons of absolute rates not valid.

Nucleos(t)ide analogues adefovir and lamivudine were well tolerated and adverse events were generally mild during the duration studied. Safety profiles were comparable to placebo, with the exception of significant increases in ALT and AST levels due to adevovir and increased resistance and mutation with lamivudine. Subjects with or at risk of impaired renal function may develop nephrotoxicity with chronic administration of adefovir. Pegylated interferon, alone or combined with lamivudine, was not as well tolerated as lamivudine monotherapy. A flu-like illness is commonly associated with peginterferon alfa-2a treatment. Pegylated interferon and conventional interferon therapy had comparable safety profiles. Dose modification was common.

Gaps in Evidence and Recommendations for Future Research

The greatest knowledge gap derives from the lack of large, long-term randomized trials demonstrating that interventions with antiviral agents improve all-cause mortality, liver-related mortality, hepatocellular carcinoma, and/or hepatic decompensation. Additional valid clinical outcomes could include quality of life and hospitalizations. Randomized trials did not reliably demonstrate long-term reduction in infectivity. Accurate assessments of effectiveness or decisions on whom to treat are not possible. Because individuals with baseline cirrhosis are at greatest risk for poor outcomes, they stand the most to benefit from effective therapies. Assessment of baseline and followup patient, biochemical, virological, and histological measures can then be utilized to determine if they are valid surrogates of treatment effectiveness in the studied patients. If randomized trials are judged not feasible, then accurate collection of valid epidemiologic data in clinical settings or in registry studies might be useful.

Patient characteristics and clinical markers are predictive of chronic HBV-related clinical outcomes. What remains to be addressed is the extent to which these predictors represent clinically useful therapeutic targets or disease surrogates. Observational studies that report longitudinal measurements of these predictors and collect outcome data could better identify whether change in predictor status leads to change in outcomes. There was little evidence regarding the predictive ability of liver histology besides cirrhosis. The evidence for patients with HBV infection acquired later in life is weak and involves extrapolation from studies in people with perinatally acquired infection. Biological markers to monitor the effects of drug therapies have not been evaluated in RCTs, though several genetic or immunological markers to predict virological have begun to show promise.

Recent clinical guidelines classify patients into diagnostic groups based on HBeAg status, serum HBV DNA, ALT/AST levels, and biopsy results. Future studies should measure these factors and analyze data controlling or stratifying for these variables. Future studies would benefit from creating cohorts within existing diagnostic groups: inactive carrier, chronic hepatitis HBeAg-positive, chronic hepatitis HBeAg-negative, and chronic hepatitis with cirrhosis, and presenting key findings separately for these groups. Research is needed to identify valid surrogates and to demonstrate the effect of a treatment agent on the surrogate as well as clinical endpoints. Standardized assessment and determination of clinically meaningful changes, such as adopting a uniform scoring system for liver biopsies and deciding on a definition of what constitutes clinically meaningful change, are required. Standardized laboratory assays, methods to quantify intermediate markers of interest, and thresholds of abnormality are also required. Times to assess outcomes should be standardized by investigators.

Conclusion

Adults with CHB infection are at increased risk for poorer health outcomes, though the absolute risk generally is small and requires many years to manifest. Presence of cirrhosis is the greatest risk factor leading to poor clinical outcomes. Interferons, reverse transcriptase inhibitors, and their combinations maintained short to mid-duration off-treatment improvements in selected intermediate outcomes but have not been demonstrated to improve clinical outcomes, to resolve hepatitis B infection, or sustain intermediate benefits over many years. Baseline patient and disease characteristics may modify response to treatments. Most drugs are relatively well tolerated, with few and generally mild adverse effects. Validated surrogate measures to assess treatment effectiveness do not exist. Long-term randomized controlled trials are needed to assess effects of antiviral agents on clinical outcomes and among patient subpopulation.

Evidence Report

Chapter 1. Introduction

Overview

Hepatitis B is a highly prevalent disease with 350 million chronic cases worldwide.[1] Despite immunization efforts, 6,212 incident cases of hepatitis B were diagnosed in the United States in 2004[2] and 4,713 cases in 2006.[3] An estimated 2,000 to 4,000 deaths per year are related to CHB liver diseases,[4] including liver cirrhosis and hepatocellular carcinoma.[5] The natural history of hepatitis B is variable but generally indolent for many years to decades. Up to two-thirds of adults infected with hepatitis B virus do not experience symptoms, and approximately 5 percent of acutely infected immunocompetent adults develop CHB. Demographic, clinical, and hepatitis B disease factors are believed to be associated with the development of CHB (CHB), poor prognosis among those who develop CHB, and response to therapy. These include the mode and timing of infection, gender, race/ethnicity, geographic location, comorbid conditions, including alcohol use and coinfections with hepatitis C and human immunodeficiency virus (HIV), as well as biochemical, virological, and histological intermediate measures of hepatitis B activity.

Hepatitis B treatments include nucleos(t)ide analogues categorized as L-nucleosides (lamivudine, emtricitabine, telbuvidine, and clevudine), acyclic phosphonates (adefovir and tenofovir), and cyclopentanes (entecavir). Additionally, interferons (standard interferon and peginterferon) are available. Seven antiviral agents have been approved for use in the United States (standard interferon, peginterferon, lamivudine, telbivudine, adefovir, entecavir, and tenofovir) and several others are under investigation. Antiviral drugs are used either as monotherapy or in combination. Two basic therapy approaches exist. A defined self-limited course (e.g., 4-12 months) followed by monitoring off treatment is generally used for interferon-based therapy. Long-term continuous suppressive therapy is used for other direct antiviral agents. The rationale for these different approaches is to maximize long-term loss of HBsAg, HBeAg, and HBV DNA while minimizing treatment related harms, including the development of antiviral resistance. The latter is marked by appearance of circulating hepatitis B virus with reduced sensitivity to the particular antiviral agent. Clinically this is manifested by biochemical increases in previously normalized ALT levels.

The course of CHB is typically silent and associated with few signs or symptoms of disease for many years. Therefore, the major goals of therapy have been long-term prevention of progression, development of cirrhosis, and hepatocellular carcinoma rather than immediate improvement in symptoms. Because development of clinical outcomes often does not occur for years to decades after diagnosis, most studies of therapies have used short-term intermediate biochemical, virological, and histological responses to assess treatment effectiveness. Additionally, investigators and clinicians have described these intermediate laboratory responses as surrogate measures of treatment effectiveness and substituted these measures for clinical outcome effectiveness evaluations. The primary advantage of the use of these intermediate markers is their ability to evaluate drugs more quickly and in smaller trials than would be required for the demonstration of a reduction in the risk of major clinical events.

The Clinical Research Workshop in the Liver Disease Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases,[6] the American Association for the Study of Liver Diseases,[1] the Canadian Association for the Study of the Liver, and the Association of Medical Microbiology and Infectious Disease have proposed biochemical, virologic, and histologic

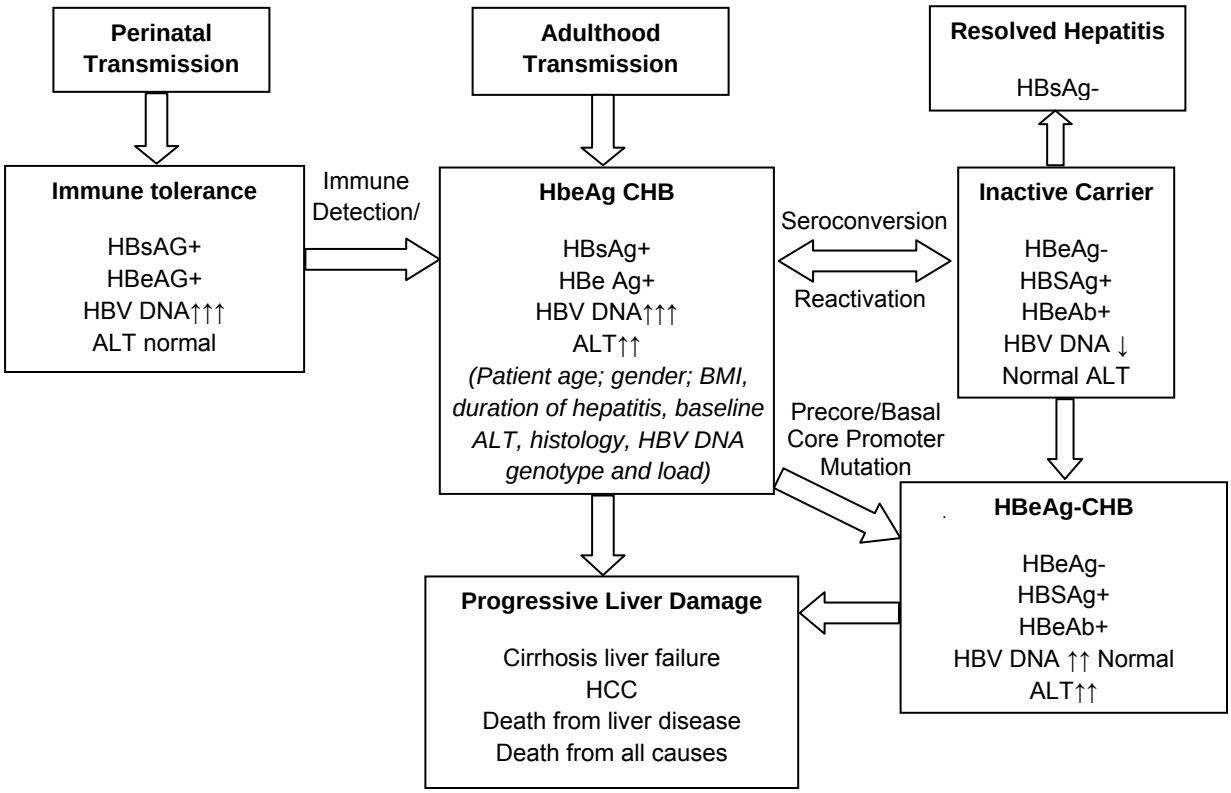
measures to determine an individual's risk for disease progression, identify candidates for treatment, and assess treatment effectiveness and harms. There is uncertainty regarding which strategy leads to improved early treatment effectiveness, development of viral resistance while on therapy, sustained off treatment effectiveness (>6 months), harms, costs, and whether treatment outcomes are influenced by patient, disease, or comorbidity factors.

Assessment of these endpoints has been categorized as initial response (measured at 6-12 months on therapy), maintained (longer term on-treatment), and sustained (at least 6 months off treatment). Frequently recommended and utilized intermediate measures have included a decrease in serum ALT levels to normal ranges, resolution of CHB based on HBsAg loss and seroconversion to antiHBsAg, liver biopsy, a decrease in serum HBV DNA to undetected levels, HBeAg loss, or seroconversion to antiHBeAg. All of these proposed endpoints have problems with measurement, standardization, and definitions of normality. For example, not all patients have elevated ALT levels, and there is no widely accepted definition of normal. Liver biopsies are invasive, potentially harmful, difficult to conduct repeatedly, and sample only a small portion of the liver. Complete virological responses are often poorly achieved or relatively short lived. Development of virological resistance and breakthrough requires frequent determinations of HBV DNA levels. Resistance may be genotypic based on detection of HBV mutations that may not be clinically significant. Of greatest importance is the lack of evidence that any intermediate outcomes serve as a true surrogate measure of treatment effectiveness for clinical outcomes. While these measures may be correlated with health outcomes in prospective reports, such a correlation does not prove surrogacy. A surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint. For an intermediate outcome to serve as a valid surrogate endpoint, it is required that the effect of the intervention on the surrogate endpoint predicts the effect on the clinical outcome. Valid surrogate endpoints must correlate with the true clinical outcome and fully capture the net effect of treatment on the clinical outcome. Reasons for failure of intermediate measures to serve as surrogates include: the surrogate may not be on the causal pathway of the disease process; of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate; the surrogate is not in the pathway of the intervention's effect or is insensitive to its effect; or the intervention has mechanisms of action independent of the disease process.

Examples of intermediary measures known to correlate with clinical outcomes and later demonstrated not to be surrogates of treatment include: use of CD4 cell counts to assess whether antiviral therapies improve survival among individuals with human immunodeficiency virus, pharmacologic suppression of ventricular arrhythmias to reduce cardiovascular-related mortality, assessment of improvement in exercise tolerance, and ejection fraction to evaluate impact of pharmacologic interventions on survival in patients with congestive heart failure and bone mineral density improvements due to fluoride to assess fracture risk. While surrogate endpoints can be useful in phase 2 trials for identifying whether a new intervention is biologically active, they are rarely, if ever, adequate substitutes for definitive clinical outcomes in phase 3 trials. We focused our primary assessment of treatment effects on clinical outcomes, including: overall and disease specific mortality and hepatocellular carcinoma. We also included cirrhosis, though many individuals with cirrhosis are asymptomatic and only detected based on study or clinically desired biopsy. Therefore, while cirrhosis is a known poor prognostic indicator, it may be better described as an intermediate, and not a clinical outcome.

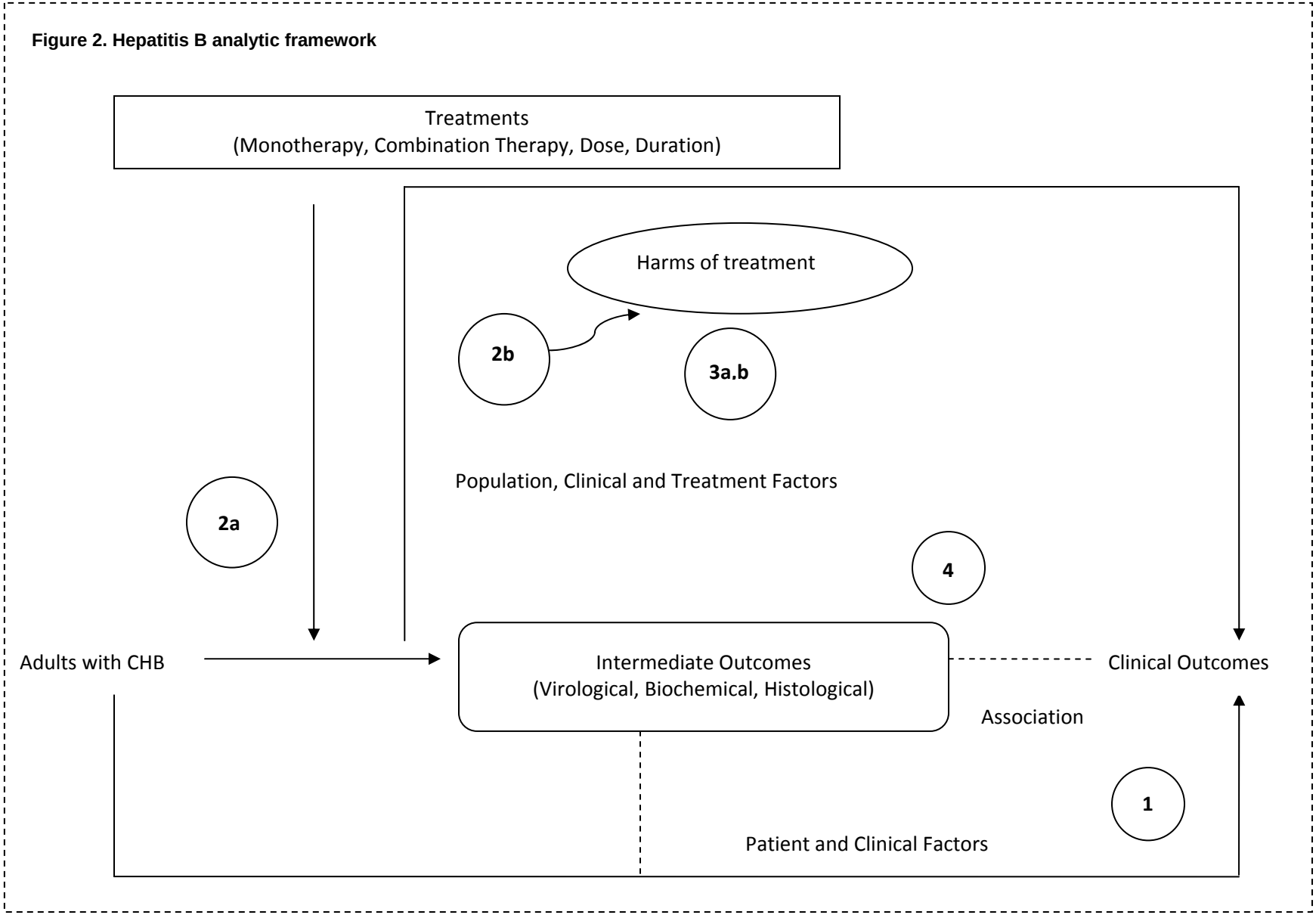
Chronic carriers of HBsAg have substantially higher rates of hepatocellular carcinoma, cirrhosis, and death than people who are not HBsAg-positive. Infection with Hepatitis B virus (HBV) can be transferred through multiple different pathways (Figure 1). Combining this individual variation with the demographic diversity within HBV-infected populations makes it difficult to predict individualized outcomes from population-based studies. Furthermore, much of the literature provides incomplete detail to characterize risk factors for progression. This holds true when evaluating observational studies to determine the long-term prognosis of CHB or when assessing outcomes from randomized treatment trials where treatment duration and followup off treatment are often limited in duration (months) yet outcomes due to CHB may require decades to manifest.

Figure 1. Classic phases in chronic Hepatitis B infection (HBeAg-positive)



Previous reviews analyzed efficacy of particular pharmacological agents for chronic HBV infection.[146,147] The aim of this report is to systematically analyze evidence of the natural history of CHB as well as treatments for adults to provide evidence for a National Institutes of Health (NIH) Consensus Conference related to Management of Chronic Hepatitis B in Adults. We emphasize treatments most relevant to clinical practice in the United States. We addressed the following NIH Consensus Conference and Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) report questions. We developed an analytic framework (Figure 2) that presents these questions in a graphical format along with the key linkages required to assess CHB natural history as well as the effectiveness and harms of treatments.

Figure 2. Hepatitis B analytic framework



Key Questions

Consensus conference question 1. Which persons with hepatitis B should be treated?

EPC question 1. What is the evidence that the following population characteristics or clinical features associated with hepatitis B are predictive of hepatocellular carcinoma, liver failure, cirrhosis, liver-related death, and all-cause mortality?

Consensus conference question 2. What are the benefits and risks of the current therapeutic options for hepatitis B with defined or continuous courses of treatment?

EPC question 2a. What is the efficacy (or effectiveness) of interferon therapy, oral therapy, and various combinations in treating hepatitis B with defined or continuous courses of treatment?

EPC question 2b. What are the known harms of interferon therapy, oral therapy, and various combinations in treating hepatitis B with defined or continuous courses of treatment?

Surrogate outcomes of interest. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels, HBV viral load, change in hepatitis B e antigen (HBeAg) status, HBsAg conversion, liver biopsy findings (necroinflammatory activity or stage of fibrosis), and drug resistance.

Clinical outcomes of interest: hepatocellular carcinoma, liver failure, cirrhosis, liver-related death, all-cause mortality.

Consensus conference question 3. Which persons with hepatitis B should be treated?

EPC question 3a. Are there differences in efficacy/effectiveness of treatments for treatment naïve vs. drug-resistant patients, HBeAg-positive vs. HBeAg-negative patients, or for other subpopulations (as defined previously)?

EPC question 3b. Is there evidence that specific subpopulations do not require treatment for hepatitis B (i.e., that the surrogate and/or clinical outcomes are equivalent or superior when not exposed to treatment?)

Consensus conference question 4. What measures are appropriate to monitor therapy and assess outcomes?

EPC question 4. What is the evidence that changes in surrogate endpoints in response to treatment are reliable predictors of long-term resolution or slowed progression of disease?
Patient Population: Adults (≥18 years of age), including elderly and members of racial/ethnic minority populations.

Chapter 2. Methods

Literature Search and Eligibility Criteria

We searched MEDLINE® via PubMed®, the Cochrane library,[12] Medwatch,[13] and United Kingdom Current Problems in Pharmacovigilance.[14] We used the European Public Assessment Report[15] to find original epidemiologic studies of adults with CHB published in English that reported mortality, incidence of hepatocellular carcinoma (HCC), or liver failure, prevalence and incidence of cirrhosis, HBeAg or HBsAg presence or seroconversion, viral load of hepatic virus B deoxyribonucleotide acid (HBV DNA), ALT levels, histological necroinflammatory and fibrosis scores,[16] and adverse events after antiviral drugs approved by the Food and Drug Administration (FDA) for CHB, including interferon alfa-2b, pegylated interferon alfa-2a, lamivudine, adefovir, entecavir, tenofovir, and telbivudine.[17] The search strategies for the four research questions are described in Appendix A[*]. Excluded references are shown in Appendix B. All work was conducted under the guidance of a Technical Expert Panel (TEP), whose members are identified in Appendix C.

Eligibility

Three investigators independently decided on the eligibility of the studies according to recommendations from the Cochrane manual for systematic reviews.[148] The algorithm to define eligibility of the studies was developed for each research question (Appendix D). We reviewed abstracts to exclude secondary data analysis, reviews, letters, comments, case reports, and clinical trials of healthy populations to prevent hepatitis B. We confirmed eligible target populations of adults with chronic hepatitis B. The full texts of the original epidemiologic studies published in English after 1989 were examined to include studies with adult patients diagnosed with CHB. Eligible outcomes were defined as overall and liver-specific mortality, incidence of hepatocellular carcinoma (HCC) or liver failure, prevalence and incidence of cirrhosis, surrogate measures of HBeAg or HBsAg presence or seroconversion, viral load of hepatic virus B deoxyribonucleotide acid (HBV DNA), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and histological necroinflammatory and fibrosis scores[16] (operational definitions in Appendix D).

For question 1, we included studies if they: (1) were original research articles; (2) reported at least one of the following: hepatocellular carcinoma, liver failure, cirrhosis, liver-related death, and all-cause mortality; (3) had at least 1 year of either prospective or retrospective followup between the measurement of predictive factors and at least one of the outcomes of interest; or (4) reported results for a hepatitis B only population. Since the focus of this report is to provide evidence most relevant for a U.S. population, all studies meeting the previous criteria were included if the study reported results from a U.S. population. Only large studies (at least 1,000 participants) of populations outside of the United States were included. For questions 2-4

[*] Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/ pdf/hepb/hepb.pdf

randomized controlled clinical trials (RCTs) of the drugs approved by the FDA for CHB, including interferon alfa-2b, pegylated interferon alfa-2a, lamivudine, adefovir, entecavir, tenofovir, and telbivudine[17] were eligible for questions 2, 3, and 4. We included publications from the multinational HBV 99-01 Study Group of pegylated interferon alfa-2b that has been intensively examined in patients with CHB but not yet approved in the United States.[18] Observational studies of more than 50 treated adults with more than 1 year followup that examined surrogate predictors of clinical outcomes were eligible for question 4.

Exclusion criteria included the following:

- Studies with target population as children and adolescents, healthy adults, adults with HCC, HIV, undergoing transplantation or chemotherapy, pregnant women, CHB populations mixed with other hepatitis patients (e.g., hepatitis C, CHB carriers, pregnant women with CHB, or individuals undergoing chemotherapy, if results were not separately provided for designated eligible cohort of CHB adults).
- Interventions of drugs not approved in the United States as of June 2008.
- Studies that reported not eligible outcomes including intra-hepatic concentrations of HBV DNA, acute pharmacokinetics measures, cardiovascular markers, or visual evoked potentials.
- Studies that evaluated cost effectiveness of different treatment options.
- Case series with small numbers of cases and no control comparison.
- Clinical trials of reverse transcriptase inhibitor that included less than 50 patients or examined active treatments for less than 24 weeks. Trials evaluating interferon for at least 12 weeks were eligible.
- Secondary data analysis with multiple reporting of the same outcomes.
- Data from randomized clinical trials that were reported ignoring randomization.

Quality Assessment and Rating the Body of Evidence

We analyzed study quality using the following criteria: subject selection, length and loss of followup, adjustment for confounding factors in observational studies and intention to treat principle in clinical trials, masking the treatment status, randomization scheme and adequacy, allocation concealment, and justification of sample sizes in RCTs.[149] The level of evidence for all studies was estimated using a subset of the U.S. Preventive Services Task Force criteria.

For all questions, evidence tables were developed identifying the purpose of the study, sample, design, independent and dependent variables, and findings (Appendix E). Baseline data were compared in different studies to test differences in the target population and unusual patterns in the data.[150,151] Standard deviations, regression coefficients, and 95 percent confidence intervals (CI) were calculated from reported event rates, means, standard errors, and sample size.[152,153] The protocol for the meta-analyses was created according to recommendations for meta-analysis of randomized controlled trials.[154,155] We assessed the level of evidence based on GRADE Working Group criteria.[156,157] We determined low level of evidence and confidence when data were from small RCTs or observational studies or from RCTs/observational studies with serious flaws in design/analysis and from post hoc subgroup analysis**,** moderate level of evidence, and confidence when a single large multinational study or several small RCTs/observational studies reported consistent effect of the same drugs or associations with factors and outcomes, and high level of evidence from multiple high quality studies in applicable patients reporting consistent sustained effects (post therapy at least 6 months).

Applicability of the population was estimated by evaluating the selection of the subjects in observational studies and clinical trials.[158] Large observational cohorts based on nationally representative samples had high applicability. Applicability of the intervention duration was high for studies with followup 1 year or more and acceptable for studies with followup of 6-12 months.[159] We evaluated baseline patient characteristics including age, gender, HBeAg status, previous treatment, and the presence of cirrhosis for generalizability.

We assumed the presence of publication bias and did not use statistical tests for bias defined as the tendency to publish positive results and to predict association when all conducted (published and unpublished) studies are analyzed.[148,160-162] We used several strategies to reduce bias, including a comprehensive literature search of published and unpublished evidence in several databases, reference lists of systematic reviews, contacts with experts for additional references they might provide, and agreement on the eligibility status by several investigators.

Data extraction. Evaluations of the studies and data extraction were performed independently by five researchers. The data abstraction forms are shown in Appendix F. Errors in data extractions were assessed by a comparison with the established ranges for each variable and the data charts with the original articles.[148] Any discrepancies were detected and discussed. We abstracted the number of events among treatment groups to calculate rates, relative risk, odds ratios, and absolute risk differences (ARD).[152] We abstracted the number randomized to each treatment group as the denominator to calculate estimates applying intention to treat principle.[152] Means and standard deviations of continuous variables were abstracted to calculate mean differences with a 95 percent CI. We abstracted the time when the outcomes were assessed as weeks from randomization and the time of followup post treatments. We defined sustained response as 6 months or more post therapy. We extracted author reported adjustments for patient age, race, gender, and comorbidities. We prioritized clinical outcomes in the assessment of treatment benefits and harms. Sustained resolved hepatitis B was considered the next most relevant outcome.

Data synthesis. For questions 2 and 3 we summarized the results of individual studies in evidence tables to analyze differences in the outcomes among treatment groups. The definitions of the outcomes are presented below:

Clinical outcomes (clinical events) included death from all causes, liver related death, HCC or liver failure, and incidence of cirrhosis.

Intermediate outcomes.

- *Complete response (resolved hepatitis B)* included HBsAg loss or seroconversion in combination with undetectable HBV DNA and normal ALT.
- *Biochemical outcomes* included changes in ALT levels, the rates of ALT normalization, and flare of hepatitis B as intermittent elevations of aminotransferase activity to more than ten times the upper limit of normal and more than twice the baseline value.
- *Virological outcomes* included HBsAg clearance or seroconversion, HBeAg clearance in a person who was previously HBeAg-positive, HBeAg seroconversion defined as loss of HBeAg and detection of antiHBeAg in a person who was previously HBeAg-positive and antiHBeAg-negative, viral load of HBV DNA, and the rates of HBV DNA loss or reduction.
- *Histological outcomes* included histological scores of inflammation or fibrosis and the rates of improvement in necroinflammatory scores without worsening in fibrosis scores.
- *Resistance* was defined as worsening of histological scores or persistent HBV DNA load, or rates of genetic mutations.

- *Relapse* was defined as reappearance of HBV DNA or active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B.
- *Harm effects* included any adverse effects, serious adverse events, discontinuation of treatment, or decrease in dose independent of author's judgments of causality between drug therapies and events.

For question 3 we synthesized the results from subgroup analyses when the authors reported outcomes among patients according to age, gender, body mass index (BMI), baseline ALT, viral load, HBeAg status, pretreatment history, or histological activity. We synthesized the evidence of effect measure modification when authors compared the effects of baseline patient characteristics on the effects of the drug therapies. We compared the effects of the same drugs on different patient populations across the RCTs that included patients with only positive or negative HBeAg status.

Pooling criteria included the same operational definitions of outcomes and the same risk factors or clinical interventions.[155] Meta-analysis was used to assess the consistency of the association between treatments and outcomes with random effects models.[163] We conducted analyses separately for clinical, biochemical, virological, and histological outcomes and for relative risk and absolute risk differences. Assumptions underlying meta-analysis included valid measurements of the outcomes and similarity in study and target populations.

We tested consistency in the results comparing the direction and strength of the association. Chi squared tests were used to assess heterogeneity.[164,165] Significant heterogeneity means the effects of interventions on the outcomes were not consistent in the studies. We explored heterogeneity with meta-regression and sensitivity analysis and reported the results from random effects models. We analyzed whether duration of treatments or followup, doses of the drugs, proportion of the patients with HBeAg-positive baseline status, proportion of the patients with baseline cirrhosis, or control rates of the outcomes could explain heterogeneity between studies. Calculations were performed using STATA software at the 95 percent confidence level.[166] We calculated the number needed to treat and the number of the events attributable to the treatments per 1,000 treated.[167]

Chapter 3. Results

Consensus Conference Question 1
What is the Natural History of Hepatitis B?

EPC Question 1. What is the evidence that population characteristics (age, age at infection, geographic location, race/ethnicity, gender, positive family history) or clinical features (presence of coinfections, HBV viral load, change in HBeAg status, genotype, nonalcoholic, fatty liver disease, alcohol consumption, AST/ALT level, liver biopsy finding) associated with hepatitis B are predictive of hepatocellular carcinoma, liver failure, cirrhosis, liver-related death, and all-cause mortality?

Objectives. We outlined the evidence to which the above mentioned population characteristics and clinical features predict HCC, liver failure, cirrhosis, liver-related death, and all-cause mortality in people with hepatitis B.

Description of study characteristics. Our search strategy identified 614 articles from abstracts or full articles that were obtained to determine study eligibility. Additionally we included six articles that were found through hand-searching other articles or identified by members of our TEP. Each article was read by one of three extractors and included for further review if the article either appeared to meet the inclusion criteria or if inclusion was uncertain. In cases where inclusion was not obvious, consensus by the other reviewers was used to decide.

A total of 41 articles met inclusion criteria (Appendix E* Figure 1).[19-59] These articles include populations from the United States, Argentina, Australia, Canada, China, Europe, Japan, Korea, and Taiwan.

Studies from the United States are over-represented; although the majority of research has occurred outside the Unites States, our review includes 14 publications representing eight unique populations within the United States. Appendix E Table 1 provides the descriptive characteristics in terms of the country, study design, number of patients, participant characteristics, length of followup, and outcomes assessed for each of the included studies. Table 1 provides a summary of the key risk factors and outcomes assessed, a semiquantitative estimate of risk magnitude (small <2-fold, moderate 2-5-fold, and strong ≥5-fold increased risk) and a statement regarding our confidence in the effect (inconclusive, low, medium, high) based on strength of evidence. Definitions for the ratings of magnitude and confidence are included in Table 1.We believe that the data available do not allow for more accurate quantitative risk estimates due to multiple patient and disease characteristics likely to affect prognosis.

Absolute risk of hepatocellular carcinoma, liver failure, cirrhosis, liver-related death, and all-cause mortality. Chronic carriers of HBsAg have substantially higher rates of HCC, cirrhosis, and death than people who are not HBsAg-positive.[21,24,30,39,45] Figure 1 shows that infection with

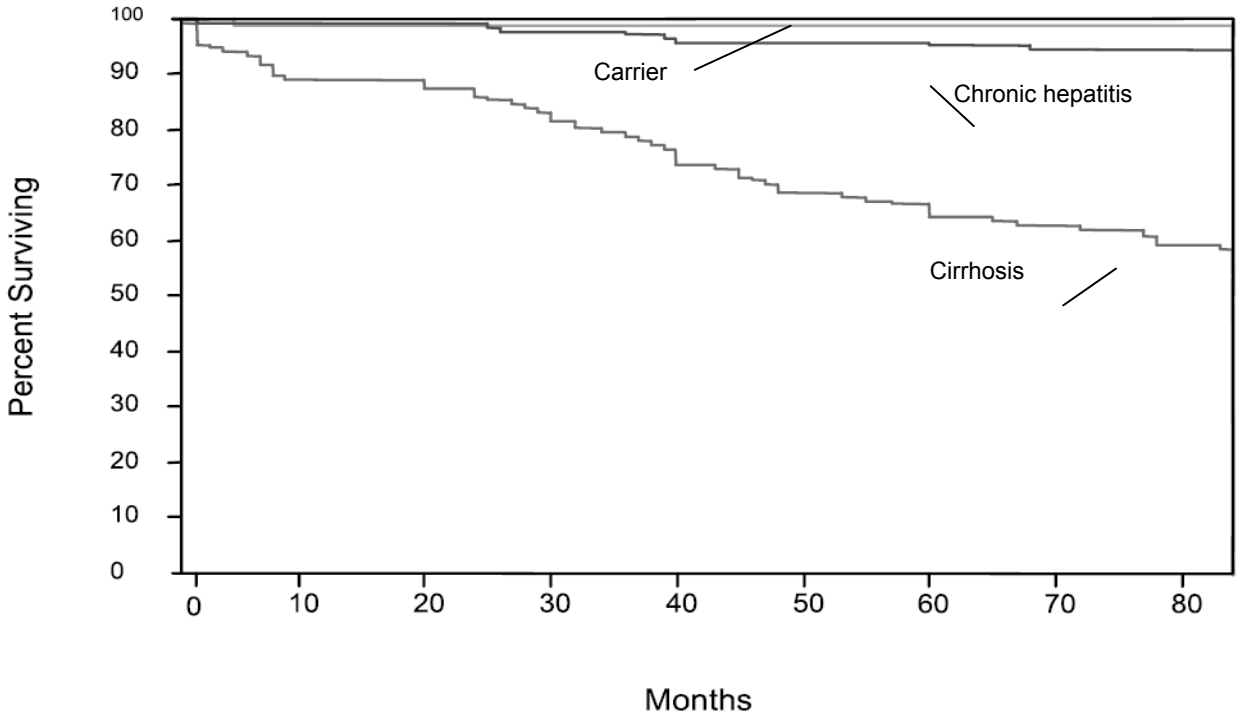
* Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/ pdf/hepb/hepb.pdf

HBV can transition through multiple different pathways. Each pathway has differing degrees of risk for clinical outcomes. It is difficult to report the results of a population-based study in a way that captures each individual's fluctuations in disease severity and risk. This is particularly true during the longer-term followup for the studies that make up this review (at least 1 year and up to decades of followup). Therefore, while we briefly describe the absolute rate differences in HCC, cirrhosis and death among different HBsAg patient groups, the majority of this review will focus on the relative risk differences due to various patient and clinical characteristics.

Prior reports from Asia have estimated that the annual incidence of HCC is only 0.1 percent in asymptomatic HBsAg individuals, 1 percent in patients with CHB, but increases to 3-10 percent in patients with cirrhosis.[60] In this same report, patients with CHB developed cirrhosis at a rate of 2 percent per year.

Reports from the United States have also shown similarly large differences in clinical event rates across diagnostic groups such as inactive HBsAg carriers, CHB without cirrhosis and CHB with cirrhosis. In a large U.S. cohort study of 400 chronic HBsAg patients (70 percent born in Asia and 24 percent born in North America), followed for over 7 years, results were reported by strata of inactive HBsAg carriers, CHB without cirrhosis, and CHB with cirrhosis (Figure 3).[48] Among the 110 inactive carriers with an average age of 41 (standard deviation [SD]±16) years (who had no symptoms or signs of chronic liver disease, normal liver tests, and normal platelet counts) none developed HCC or died of a liver-related disease and only one died of any cause. Among the 151 patients with CHB but no cirrhosis (elevated serum aminotransferase levels and biopsy determined histologic grades of 1-3 and a stage of 1-3), 6 percent developed HCC and died from it, while another 2 percent died from nonliver related causes. Among those with CHB and cirrhosis, nearly 16 percent were diagnosed with HCC, and a total of 42 percent died during followup (all from liver-related causes).

Figure 3. Survival by hepatitis status, modified from Tong, 2006[48]



Population characteristics.

Age and age at infection. Age is a complex variable to assess with respect to its relationship between HBV infection and risk of clinically important outcomes. For most clinically important outcomes increased age is related to higher risk of clinical events irrespective of HBV. However, with regard to age of infection, it is well known that individuals with earlier age of infection are more susceptible to chronic HBV infections and less likely to experience HBsAg loss. An example of the effect of age at infection is shown in a convenience study of U.S. military personnel exposed to a HBV contaminated yellow fever vaccine. Researchers noticed a very low rate of HCC-related mortality and hypothesized that immunocompetent adults rarely become carriers or go on to experience serious health consequences after a single exposure to HBV.[40] Therefore, people who get exposed to HBV early in life will likely have worse outcomes than those exposed later in life. However, for any one individual the likelihood for events such as HCC, cirrhosis, liver failure, and death increases with age. So, ideally two pieces of information should be used to calculate risk: current age and age of infection. These two pieces of information provide estimates for whether or not an individual was exposed early on in life, the duration of chronic exposure, and increased risk of events due to older age. Unfortunately, we were unable to find studies that clearly identified the age of participants exposure, and few reported any information on duration of exposure. So the results we provide below with respect to the relationship between age and clinical outcomes should be interpreted with the knowledge that these results are confounded by age of exposure and duration of exposure effects that were unmeasured or just unreported.

One additional factor that might be confounding age-related associations is that selection into a study might be different depending on the age of the participant. A large study of HCC cases in Hong Kong found that younger cases (≤40 years of age) were more likely to present with more pain, hepatomegaly, and more advanced stage with frequent pulmonary metastasis than older HCC cases (>40 years of age).[32] While the survival rate (6.6 versus 8.3 months, p=0.77) was similar for younger versus older HCC cases, this study makes clear that assessing differences in death rate by age should take severity of disease at diagnosis into account.

Overall, age does appear to be associated with poorer outcomes. In studies that have controlled for other potential confounders such as disease severity, age is often found to increase the risk of poor outcomes. Among a U.S. case control study of HCC in HBsAg-positive individuals (70 percent born in Asia), each 1 year increase was associated with 5 percent relative increased odds of HCC (odds ratio [OR], 1.05, 1.02; 1.08).[49] Similarly, among Alaska Native people each 1 year increase in age increased the rate of HCC by 4 percent (hazard ratio [HR], 95 percent CI 1.04, 1.0; 1.07).[37] Some of the largest and best controlled non-U.S. studies have also confirmed the finding of age and poor outcomes, particularly for HCC. Even after controlling for differences in gender, cirrhosis status, HBV genotype, and HBV viral load, a large prospective study from Hong Kong found that each year of age increased the relative rate of HCC by 8 percent (95 percent CI 5-11 percent).[22] The Taiwanese REVEAL Study also found increased relative rates of HCC per year of age to be 6-11 percent depending on the severity of HBV.[23] The relative rates for cirrhosis also increased in the REVEAL study by approximately 3-5 percent per year of age.[29]

In conclusion, increased age of the patient is associated with poorer long-term clinical outcomes due to CHB. Limited evidence suggested medium confidence of a small effect on HCC and cirrhosis and low confidence of a moderate effect on mortality outcomes. There is inconclusive evidence regarding the extent to which this association between age and clinical

outcomes is explained by duration of infection, age of infection, comorbidities in older individuals and other factors that tend to be different between older and younger patients.

Gender. Males are much more likely to have chronic HBV than females; and the rate of clinical outcomes among those with HBV in terms of HCC,[20,22,24,25,30] cirrhosis,[29] and death[24,27,41,48,56] are consistently several fold higher in males than in females. Actual magnitudes of effect ranged from 1.5-7.6 fold higher rates of outcomes in men than in women, with most studies reporting at least 2-3 fold differences, even after adjusting for many important potential confounders such as age, severity of liver disease, and other health related factors. Results tended to be somewhat stronger for HCC than death.

In conclusion, there is high confidence that males on average have increased rates of death and HCC and medium confidence of an increased rate of cirrhosis. The magnitude of effect is on average greater than 2-fold in men compared to women for all of these outcomes. It is unclear what the mechanism is for this substantial effect by gender.

Geographic location, race/ethnicity. HBV infection is endemic in several locations around the world, including portions of Asia, Africa, and also among Alaska Natives in the United States. While geographic location is important in terms of exposure to HBV infection, we found little evidence that would allow us to separate out the effects of geographic location of birth and race/ethnicity. Geographic regions have different portions of early HBV transmission and different distributions of HBV genotypes. Further complicating geographic differences in outcomes related to HBV are the economic and health systems resources available in different regions.

Among a U.S. case control study of HCC in HBsAg-positive individuals, Asians did not have a significantly increased rate of HCC compared to non-Asians (OR, 95 percent CI 1.6, 0.6; 4.2). However, the power to detect clinically meaningful differences was limited and this number was not adjusted for known differences in age at infection or other key characteristics.[49] Two studies also reported geographic/ethnic differences in Alaska Native populations.[35,37]

In conclusion, there is high confidence that certain geographic locations are associated with increased HBV infection. Among people with CHB it is inconclusive that geographic location or race/ethnicity contribute meaningfully for the prediction of clinical outcomes.

Positive family history. Few studies reported information about the effect of positive family history and outcomes such as HCC, cirrhosis, and liver-related death. It is nearly impossible to sort out any independent effect for family history outside of the effects already mentioned based on age of infection and patient's geographic location or race/ethnicity.

One study from Haimen City, China, reported 2.3 fold ($p < 0.001$) greater odds of positive family history of HCC among cases of HCC compared to controls.[28,34] This study did not report results specific for HBsAg-positive subjects, but it did claim the results were similar between HBsAg-positive and negative subjects. Another study from Taiwan found that HCC cases were at 2.8 fold greater odds of having a family history of HCC compared to controls.[54] Neither study was able to adequately control for shared environmental factors between family members, but both studies do suggest that propensity for HCC might have a heritable component.

In conclusion, a positive family history of HCC is associated with a moderate increased risk of HCC (low confidence), but the extent this increased risk is independent of age of infection and duration of disease is unclear.

Clinical features.

Presence of coinfections: Human immunodeficiency virus (HIV), Hepatitis C virus (HCV), Hepatitis delta virus (HDV). Coinfection with HIV, HCV or HDV has been found to be associated with poorer clinical outcomes. However, the number of studies reporting this issue for any one type of coinfection is small, and associations are not consistent across different types of coinfection, so there is a low level confidence in the magnitude of these associations.[19,31,43,44]

Among HIV patients in Europe, Argentina, and Israel, HBV coinfection increased all-cause and liver-related death rates 1.5 and 3.6 times, respectively, above that of HIV infection alone.[31] Thio and colleagues[44] found that among the large U.S. Multicenter AIDS Cohort Study (MACS) of 5,293 men who had sex with men, HIV status dramatically increased the rate of liver-related mortality in men positive for HBsAg. The liver-related mortality rate was 14.2 per 1,000 person years, which was approximately ten-fold higher than men with only HBsAg or HIV alone. However, the MACS study does not provide evidence on the extent to which the dramatically higher rate of liver-related death is due to more severe hepatitis B disease in the men with coinfection with HIV.

Among Japanese blood donors positive for HBV, those with coinfection with HCV had a 3-fold increase in HCC independent of age, sex, and ALT level.[43] However, a study by Amin and colleagues from Australia found similar rates of HCC in people with both HBV and HCV compared to those with HBV alone.[20]

In a U.S. study of 231 developmentally disabled patients with chronic HBsAg-positive status living in institutional facilities, 65 patients were also antiHDV-positive.[19] In multivariable models, patients positive for antiHDV were nearly 12 times (95 percent CI 1.4; 97.8) more likely to die of liver-related causes, but all-cause mortality was not significantly increased. The evidence for this association is weak because there were only eight liver-related deaths and it is uncertain how generalizable the results from an institution are to other environments.

In conclusion, estimates regarding coinfection and clinical outcomes could only be made with low confidence due to the paucity or inconsistency of the data. Coinfection with either HIV or HDV was associated with strongly increased liver-related mortality. Coinfection with HCV was associated with moderately increased HCC risk.

HBV viral load. Higher HBV viral load has been consistently shown to be associated with poorer clinical outcomes, particularly when comparing very low or undetectable levels of DNA to levels above 10^5 or 10^6 copies/mL. However, having low or undetectable DNA does not eliminate the risk of clinical outcomes.[52] Furthermore, much less well known is the extent to which reductions in viral load lead to improvements in clinical outcomes.

The evidence for the association between HBV viral load and clinical outcomes was primarily from several large studies in Taiwan[23,29,52,54] and China.[22,25] However there were two articles from the United States that also found increased HCC cases[49] and increased non-HCC liver-related death in those with high viral loads.[48]

The Taiwan REVEAL Study found that in multivariable models adjusted for age, gender, smoking, alcohol use, HBeAg status, ALT level, and cirrhosis the risk of HCC began increasing slightly for people with $>10^4$ to $<10^5$ copies/mL and the risk of HCC was around 6-fold higher for people with viral loads above 10^5 or $>10^6$ compared to people with undetectable viral loads.[23] This same study reported a similar association between viral load and risk of cirrhosis.[29] Additional reports from this study have also shown a strongly increased rate of liver-related mortality, that in turn leads to a modest (approximately 2-fold) multivariable adjusted increased all-cause death rate in those with HBV DNA $\geq 10^5$ compared to those with HBV DNA $<10^5$.[58]

There was no significant increase in the nonliver related death rate for those with elevated HBV DNA level. Another study from Taiwan found a similar HCC association with some increase in risk beginning above 10^4 copies/mL and a substantial 7-fold increase in risk above 10^6 copies/mL.[54,59] HCC death and chronic liver disease death have also been reported in a study from China to follow a similar trend.[25]

In the REVEAL study the risk for HCC appeared to increase more steeply along the viral load gradient for groups with lower baseline risk of clinical outcomes.[23] For example, among the subset of people with normal ALT levels, no liver cirrhosis and negative for HBeAg there was a 4.5-fold increased risk at $>10^4$ to $<10^5$ copies/mL and a greater than 11 fold increased risk above $>10^5$ copies/mL compared to people with normal ALT levels, no liver cirrhosis, negative for HBeAg and no detectable HBV DNA. It is likely that this steeper gradient of relative risk is driven largely by the much lower absolute rate of HCC in the low risk reference group. In a study from Hong Kong where the "low risk" HBV viral load group was defined more broadly as having levels $<10^{4.5}$ copies/mL and the "high risk" group was define as $>10^{6.5}$ copies/mL, only around a 2-fold increase in rate of HCC was found, after accounting for age, gender, cirrhosis, and albumin (additional adjustment for HBV genotype did not substantially alter the association).[22] Another study from Taiwan also found that among people positive for HBsAg and negative for HBeAg, HCC cases were much more likely than controls to have elevated DNA; however, the greatest absolute proportion of both cases and controls had undetectable HBV DNA.[52]

Results from the United States are consistent with the results from Asian countries, showing an increased rate of HCC and liver-related death across a gradient of HBV viral load.[48,49] In one U.S. study of 101 HCC cases of HBsAg-positive individuals, increased viral load was strongly associated with increased likelihood of HCC; however, none of the chronic inactive HBV controls had viral loads in the "high viral load group" ($>10^6$ copies/mL), so the magnitude of effect due to "high viral load" could not be estimated.[49] Another U.S. cohort study from the same group of researchers found that among 400 chronic HBsAg patients high baseline HBV DNA viral load significantly increased the odds of nonHCC related liver death by nearly 5-fold (OR, 95 percent CI 4.7, 1.2; 20.4) independent of age and gender.[48]

In conclusion, increased HBV DNA viral load is strongly associated with increased HCC (high confidence) and liver-related mortality (high confidence) even after accounting for baseline cirrhosis, HBeAg status, and ALT levels. However, there was only low confidence of a small to moderate association with all cause mortality. We also found a strong association between HBV viral load and cirrhosis (medium confidence). We found no evidence from these large observational studies regarding whether reduction in HBV DNA viral load is associated with better outcomes.

HBV genotype. Evidence for the impact of HBV genotypes on clinical outcomes for HBV is limited. It is clear that the prevalence of different genotypes varies substantially by geographic location, but more research is needed to determine the extent to which HBV genotype modifies the natural history of HBV related outcomes. What is available indicates that there likely are some differences in at least HCC rates according to genotype. Among a U.S. case control study of HCC in HBsAg-positive individuals, patients with HBV genotype C had 4-fold greater odds of HCC compared to other genotypes (genotypes A, B, and D). However, this association remained strong but was not statistically significant after accounting for age, gender, and basal core and precore mutations (OR 3.3, 95 percent CI 0.9; 12.1).[49] A large study from Taiwan found similar associations of 3- 6-fold increased risk of HCC among people with the C genotype only

compared to people with the B genotype only.[57,59] People with both B and C genotypes were at an intermediate risk.[59] The results from this study remained statistically significant and only modestly attenuated following multiple adjustment. In a large study from Hong Kong the HBV C genotype was associated with only a modest 1.5-fold (95 percent CI 1.2; 2.0) increased rate of HCC compared to genotype B after accounting for age, gender, cirrhosis, viral DNA load, and albumin.[22] Finally, among Alaska Native people the odds of HCC were 4.7 times greater in patients with the A genotype (95 percent CI 1.4; 16.0) and 11.7 times greater in patients with the F genotype (95 percent CI 5.4; 25.4) compared to those with the D genotype.[33]

In conclusion, HBV genotypes may be associated with differing risk of clinical outcomes. Genotype C moderately increases risk of HCC compared to genotypes A, B, and D (high confidence), and genotypes A (moderate effect) and F (strong effect) may increase risk compared to D (low confidence).

HBsAg loss. Only one study was identified that reported HBsAg loss and clinical outcomes, and this study had low power to detect meaningful differences in risk.[53] In a large Taiwanese study of asymptomatic carriers at baseline followed for an average of 7 years, those with HBsAg loss had a 40 percent reduction in risk of cirrhosis, but this was not statistically significant (95 percent CI 79 percent reduction ranging to a 64 percent increase in risk of cirrhosis), after adjusting for age, HBeAg status and AST/ALT levels.[53]

In conclusion, HBsAg loss may be associated with a reduction in risk of cirrhosis (low confidence). There is no evidence whether or not HBsAg loss is associated with other clinical outcomes.

HBeAg status. HBeAg-negative status in a population study tends to be a marker of inactive carrier status, particularly when ALT levels are normal and HBV viral load is low (Figure 1). However, HBeAg-negative CHB can also occur (it is indicated by elevated HBV DNA and ALT). Therefore, it becomes more difficult to interpret the association between HBeAg status and outcomes without also using ALT and HBV DNA levels to help to classify people into either inactive carrier status or HBeAg-negative status. Since it is well known that inactive carriers have lower rates of clinical outcomes than those with either HBeAg-positive or negative chronic active hepatitis, the most interesting research questions may be to determine the impact of HBeAg status in people with active hepatitis and the effect of HBeAg reversion on clinical outcomes. Unfortunately, we found few studies that classified people into groups of chronic inactive hepatitis and chronic active hepatitis and then looked at the effect of HBeAg within those groups.

While several studies have reported a consistently higher rate of outcomes among people who are HBeAg-positive compared to HBeAg-negative,[23,29,37,53,57,59] we were unable to assess the effect of the HBeAg independent of its role as a marker of chronic active versus chronic inactive hepatitis. One study in Taiwan found the incidence rate for HCC was 3.6 times higher in HBsAg-positive people who were also HBeAg-positive compared to those who were HBeAg-negative.[52] From the REVEAL study in Taiwan this increased risk of HCC (HR 2.6, 95 percent CI 1.6; 4.2) and cirrhosis (RR 1.7, 95 percent CI 1.3; 2.9), for HBeAg-positive people persisted following adjustment for age, gender, HBV viral load, and ALT level.[23,29] A third large Taiwanese study also reported 2-3-fold increased risk of HCC among people with HBeAg-negative CHB.[57,59]

Among Alaska Natives, reversion to HBeAg positivity or multiple switches in HBeAg status was associated with increased risk for hepatocellular carcinoma (HR 2.6, 95 percent CI 1.3; 5.4), after adjustment for potential confounders.[37] Another U.S. study by Tong and colleagues that

classified all patients into "inactive carriers," "chronic hepatitis," or "cirrhotic," found that patients who were positive for HBeAg at baseline had similar rates of HCC and all cause death as patients antiHBeAg at baseline.[47]

In conclusion, HBeAg-positive status is associated with moderately increased HCC (medium confidence) and small increases in cirrhosis (medium confidence) independent of other disease factors such as HBV viral load and ALT level.

Basal core promoter (T1762/A1764) or precore mutation (A1896). Only a few recent studies have attempted to look at the extent to which basal core promoter (BCP) mutations and precore (PC) mutations impact clinical outcomes.[26,33,48,49,57] This is one area where much of the information came from U.S. based studies.

Among Alaska Natives there was no significant association between either BCP or PC mutations and HCC. However, the basal core mutations did vary significantly by HBV genotype.[33] Among a U.S. case control study of HCC in HBsAg-positive individuals, the A1896 PC mutation was associated with a nearly 4-fold increase in HCC and the T1762/A1764 mutation was associated with an 11-fold increase in HCC compared to wild types for both of these factors, independent of age, gender, race, and HBV genotype.[49] In a U.S. cohort study of 400 chronic HBsAg patients the odds of developing HCC were 2.9 times greater (95 percent CI 1.2; 7.6) for those with the BCP mutation and 4.2 times greater (95 percent CI 1.5; 19.6) for those with the A1896 PC mutation compared to those with wild type basal and PC mutations, respectively.[48] In a large study out of China the HCC death rate was 1.40 (95 percent CI 1.06; 1.85) times greater in those with 1762T/A1764 BCP mutations compared to other HBsAg-positive subjects.[26] Likewise a large study from Taiwan found a 1.92-fold (95 percent CI 1.14; 3.25) increased risk of HCC, independent of HBV genotype, ALT level and HBeAg status.

In conclusion, the BCP mutations (T1762/A1764) and the PC mutation (A1896) are associated with moderately increased HCC rates and BCP is associated with increased liver-related death rates (low confidence).

Cirrhosis. Cirrhosis has been shown to be a consistently strong predictor of HCC development and death in many studies. It has been reported for decades even within the United States that survival is greatly reduced in patients with cirrhosis compared to patients without cirrhosis.[47,51] As early as 1984 Weissberg and colleagues were reporting that the 5-year survival rate among patients with CHB could range from 97 percent in patient without cirrhosis to 55 percent in patients with chronic active hepatitis and cirrhosis.[51] In a study by Tong and colleagues, biopsy determined cirrhosis was associated with a 3.6-fold (95 percent CI 1.6; 8.9) increased odds of developing HCC independent of age, serum albumin, and baseline platelets. In the same study, the independent association was even stronger for all-cause death and nonHCC liver-related death (OR 14.2, 95 percent CI 3.4; 111.8 and 7.3, 95 percent CI 1.3; 69.56 respectively).

The findings from U.S. studies are consistent with the large studies from Taiwan and China which have consistently reported much higher rates of HCC and death in cirrhotic individuals.[22,23,53] Rates are often nearly 10-fold greater in people with cirrhosis even after adjustment for other markers of disease severity such as elevated ALT or HBV viral load. Few large studies had biopsies in all of their patients and instead relied on ultrasound detected cirrhosis which still strongly predicted increased rates of clinical outcomes.

In conclusion, cirrhosis is a strong predictor of HCC (high confidence) and liver-related death (medium confidence).

Nonalcoholic fatty liver disease. No studies were identified that reported the impact of nonalcoholic fatty liver disease on clinical outcomes in people with chronic HBV.

Alcohol consumption. Alcohol consumption was not frequently reported as an important factor in models predicting clinical outcomes from HBV. Studies that did include measures of alcohol consumption tended to use variables that indicate any consumption or years of consumption and did not try to isolate people with heavy alcohol consumption. The association between alcohol consumption and clinical outcomes reported in the identified studies appeared modest at best with effect sizes around 1.5-fold increased risk of HCC. In a large Taiwanese study of over 2,000 people, alcohol consumption and duration of alcohol use were only weakly associated with HCC development. Compared to people who never drank alcohol, those who drank for over 20 years only had a 1.33-fold increased risk of HCC (95 percent CI 0.75; 2.43) adjusting for age, family history of HCC, HCV status, baseline liver function, ethnicity, and education.[50] However, there did appear to be a potential interaction with smoking status such that those with increased alcohol and smoking use had elevated HCC.[53] Similarly, size associations were reported in two other studies of 1.5 and 1.6-fold increased risk of HCC in those who consumed about two drinks per day in one study[30] or reported any alcohol consumption in the other study.[23]

While modest consumption of alcohol does not appear to be a strong predictor of clinical outcomes related to HBV, cirrhosis was a consistently strong predictor of HCC and death. So while the studies identified did not break out causes of cirrhosis, it might be reasonable to assume that heavy drinking that leads to liver cirrhosis may be an important factor in clinical outcomes, even if modest drinking is not.

In conclusion, moderate alcohol consumption in people chronically infected with HBV appeared to be a weak predictor of increased HCC. There is low confidence in this association. Little evidence exists regarding the association between heavy alcohol use and clinical outcomes in people with chronic HBV.

AST and ALT levels. Few studies reported associations between elevated aminotransferase levels and clinical outcomes. Those that did tended to report increased risk of outcomes. This increased risk may be in part explained by other factors. Among a large Taiwanese study of asymptomatic carriers at baseline followed an average of 7 years, those with either elevated AST or ALT levels had a 3.1-fold (95 percent CI 1.0; 10.0) increased risk of HCC and a 3.7 fold (95 percent CI 2.3; 6.0) increased rate of cirrhosis, independent of age, HBeAg status, and baseline cirrhosis (for the HCC results).[53] Another study from Taiwan, also found a similar association with HCC 2.5-fold (95 percent CI 1.1; 4.3).[57] Also from Taiwan, the REVEAL study reported an unadjusted 4-fold increased risk of HCC with ALT levels >45 U/L, but after adjusting for age, gender, smoking, alcohol, HBeAg, cirrhosis, and HBV viral load the association was completely attenuated (HR 1.1, 95 percent CI 0.7; 1.7).[23] In the same study, the association between elevated ALT and cirrhosis remained significant but only modest in strength after multiple adjustment (HR 1.5, 95 percent CI 1.1; 2.1).[29]

In conclusion, ALT is moderately associated with increased risk of HCC (high confidence) and weakly associated with cirrhosis (low confidence). These associations appear to be largely explained by accounting for baseline cirrhosis, HBeAg status, and HBV viral load (low confidence).

Table 1. Factors associated with increased risk of selected outcomes in adults with chronic hepatitis B

Risk Factor	All cause Mortality	Liver Mortality	Hepatocellular Carcinoma	Cirrhosis
Increased Age (~10 years)	3 studies[32,51,56] Low confidence Moderate effect	1 study[48] Low confidence Moderate effect	6 studies[22,23,47-49,53] Medium confidence Small effect	2 studies[29,53] Medium confidence Small effect
Male	4 studies[24,47,48,56] High confidence Moderate effect	4 studies[24,27,41,47] High confidence Moderate effect	8 studies[20,22-24,30,42,46,49] High confidence Moderate effect	1 study[29] Medium confidence Moderate effect
Geographic location and Asian race/ethnicity, early age of infection			3 studies[35,48,49] Inconclusive	
Family history of hepatocellular carcinoma			3 studies[28,34,54] Low confidence Moderate effect	
Nonalcoholic fatty liver disease				
Modest alcohol consumption (drinkers average ~1 or fewer drinks per day)			5 studies[23,28,30,50,53] Low confidence Small effect	1 study[29] Inconclusive
Heavy alcohol consumption				
Cirrhosis (present vs. absent various types of detection)		2 studies[47,48] Medium confidence Strong effect	5 studies[22,23,46,48,53] High confidence Strong effect	N/A
Genotype C (vs. other [mostly A, B, D])			6 studies[22,33,49,55,57,59] High confidence Moderate effect	
Genotype F (vs. mostly A D)			1 study[33] Low confidence Strong effect	
Precore mutation (A1896)			3 studies[33,48,49] Low confidence Moderate effect	
Basal core promoter mutation (T1762/A1764)		1 study[26] Low confidence Small effect	4 studies[33,48,49,57] Low confidence Moderate effect	
High HBV DNA load (<10^4 copies mL, >10^5)	1 study[57] Low confidence Small to moderate effect	3 studies[25,48,58] High confidence Strong effect	6 studies[22,23,49,52,59,168] High confidence Strong effect	1 study[29] Medium confidence Strong effect
HBsAg loss				1 study[53] Low confidence Small effect

Risk Factor	All cause Mortality	Liver Mortality	Hepatocellular Carcinoma	Cirrhosis
HBeAg-positive status			8 studies[23,37,48,52,53,55,57,59] Medium confidence Moderate effect	2 studies[29,53] Medium confidence Small effect
Coinfection with HCV			2 studies[20,43] Low confidence Moderate effect	
Coinfection with HIV	2 studies[19,31] Low confidence Small effect	3 studies[19,31,44] Low confidence Strong effect		
Coinfection with HDV	2 studies[19,31] Inconclusive	3 studies[19,31,44] Low confidence Strong effect		
Elevated ALT level (>45 U/L)			3 studies[23,53,57] High confidence Moderate effect	2 studies[29,53] Medium confidence Small effect

Studies with references providing data for each outcome according to risk factor; level of confidence in estimate based on quality, quantity and consistency of evidence for the estimate of the relative risk magnitude is rated as “Inconclusive” (evidence insufficient to permit estimation of effect), “Low” (further research is likely to change the estimate), “Medium” (further research may change the estimate), “High” (further research is very unlikely to change the estimate); blank cells indicate no evidence available or does not apply. Magnitude of relative risk increase (RR) due to each factor for each outcome is estimated according to ranges from studies as “Small” (RR=1-2), “Moderate” (RR=2-5); and strong (RR=5 or greater)

Consensus Conference Question 2
What are the Benefits and Risks of the Current Therapeutic Options for Hepatitis B with Defined or Continuous Courses of Treatment?

EPC Question 2a. What is the efficacy (or effectiveness) of antiviral therapy in treating adults with chronic hepatitis B?

Characteristics of included studies. Ninety-three articles (Appendix E Figure 1)[10,61-145,169-175] represented 60 unique randomized trials of interferon alfa-2b,[61-92] peginterferon alfa-2a,[93-97] adefovir,[10,110-120] peginterferon alfa-2b,[98-109] entecavir,[121-126] lamivudine,[64,67,95,96,119,127-142] or telbivudine.[120,127,143,144] Studies enrolled between 20 and 1,367 patients (Table 2). Males constituted 78 percent of enrollees. Study duration lasted 69 weeks (range 17-208) with treatment duration averaging 44±22 weeks, and followup off the treatment 98±158 weeks for studies that reported outcomes during followup off treatment (Appendix E. Table 2). Nearly all enrollees were Asian (64 percent) or white (30 percent) ethnicity/race. The estimated mean or median duration of infection was reported in eight studies and ranged from about 2-6 years. However, the individual patient duration of infection ranged from 6 months to 20 years.[61,63,66,69,81,83,84,86,87,90]

Studies enrolled predominately HBeAg-positive individuals. Fifty-four reports included more than 98 percent of HBeAg-positive patients.[61,62,64,65,67-70,72,73,75,77,78,80,83-88,90,92,94,96,98-109,112,113,116,119,120,122,126,127,129-131,134-136,138,140,145] Eleven reports described outcomes in HBeAg-negative patients.[10,71,74,76,79,81,91,93,95,110,111,142] Other authors reported outcomes without differentiating between HBeAg-positive and negative patients (Appendix E, Table 2).

In 16 reports investigators reported outcomes for individuals who were naïve to antiviral drugs patients.[68,72,75,76,85,90,94,106-108,115,120,122,126,136,139] Seven reports enrolled patients independent of previous treatment status or tested new drugs on patients resistant to previous treatments.[67,77,92,118,119,125,141] Cirrhosis was assessed at baseline in 32 studies[61-64,67,73,74,77,80-83,85,88,91,92,94-96,99,103-105,110,121,122,132,135,136,138,139,142] and was noted in 21 percent these enrollees. Authors reported HBV genotype in 13 studies.[94,96,99,104,107,109,114,121,122,124,125,139,143] Genotype C was the most common (42 percent).

Sixteen of 93 articles reported mortality, liver related death, hepatocellular carcinoma, hepatic decompensation, or cirrhosis (Appendix E Table 3).[83,85,86,90,91,96,106,107,111,121,122,124-126,132,141] The largest study enrolled 814 HBeAg-positive patients and lasted 72 weeks.[96] Few events were reported in these studies. None were of sufficient size or duration to adequately assess the effect of treatments on these outcomes. (Appendix E. Table 4).

Clinical outcomes Only 16 RCT reported on clinical outcomes: (mortality [13]; hepatocellular carcinoma [4]; hepatic decompensation [3]; or cirrhosis [2]). None were of sufficient size or duration or were designed to assess clinical outcomes. A small number of clinical events and studies compared different drugs and patients, generally precluding pooling. Investigators primarily designed studies to examine the effects of antiviral therapies alone or in combination compared to other antiviral therapies (or placebo) on intermediary biochemical, virological, or histological outcomes. Most studies assessed these as short-mid-term outcomes during the course of treatment or at treatment conclusion (typically 1 year or less). Sustained

efficacy of these intermediary outcomes was reported in the minority of studies and when reported typically was less than 1 year off treatment. The majority of RCTs that reported clinical outcomes described zero or a small number of clinical events (Appendix E Table 4). The longest study duration reporting mortality or cirrhosis (treatment + followup) was less than 3 years and the longest study assessing mortality was 130 weeks (Table 3, Appendix E Figure 2).

Mortality. Thirteen studies assessed mortality (Table 3).[70,83,86,90,96,106,111,121,122,124-126,132] The longest study lasted 130 weeks and enrolled 651 HBeAg-positive patients.[132] No study reported a statistically significant improvement in mortality due to any treatment, though few deaths occurred. Studies were not designed or powered to assess statistically significant differences. Medications evaluated included lamivudine,[132] entecavir,[121,122,124-126] interferon alpha 2b,[70,86,90] peginterferon alfa-2a,[96] peginterferon alfa-2b,[106] and adefovir.[111] Studies enrolled only HBeAg-positive[70,83,86,90,96,106,126] or HBeAg-negative patients;[111,121] some reported proportions of patients with baseline cirrhosis.[83,96,121,122,125,132] One multicenter, double-blind RCTs of 651 Chinese patients (58 percent HBeAg-positive, 61 percent with cirrhosis, median ALT=69.3 U/L, median HBV DNA=14.9 mEq/mL), failed to demonstrate a statistically significant effect of lamivudine for 130 weeks versus placebo on liver related death or all-cause mortality (RR=2.47, 95 percent CI 0.12; 51.25).[132] Very few deaths occurred (none in the control group) (Table 3).

The largest study was a multi-arm trial that involved 814 HBeAg-positive patients, lasted 72 weeks, and was conducted at 67 sites in Asia, Australia, Europe, and North and South America. Authors reported no difference in mortality between combination peginterferon alfa-2a combined with lamivudine compared to either lamivudine or peginterferon alone during 48 weeks of treatment and 24 weeks of treatment free followup.[96] However, very few deaths occurred in any of the groups **(**Appendix E Figure 3). Several reports compared entecavir to lamivudine in a total of 2,476 subjects.[121,122,124-126] One included HBeAg-negative patients only,[121] three enrolled treatment naïve,[121,122,126] two included lamivudine resistant patients,[124,125] and three reported baseline cirrhosis.[121,122,125] Treatment duration lasted from 48-96 weeks and reported followup off therapy was 0-24 weeks. There were no significant differences in mortality at the end of treatment or after additional followup off treatment in any of the studies or in pooled analysis. However, only 0.5 percent of participants died (five in the entecavir group and eight in the lamivudine group), precluding accurate assessment of relative effectiveness of entecavir versus lamivudine on long-term mortality in these patients.

The remaining studies were small and short term. They assessed use of corticosteroids or different doses or duration of therapy. None demonstrated a mortality difference between treatment approaches. One small RCT from Egypt of 40 HBeAg-positive patients (40 percent with cirrhosis) found no difference in mortality after 16 weeks of interferon alfa-2b compared to placebo and 48-64 weeks of followup.[83] Interferon alfa-2b with corticosteroid pretreatment compared to symptomatic therapy without antiviral drugs failed to reduce mortality in a small RCT of 20 HBeAg-positive South African patients.[70] Steroid withdrawal and low dose of interferon alfa-2b for 24 weeks in 56 HBeAg-positive patients did not reduce mortality rates (ARD -0.11 95 percent CI -0.27; 0.06).[86] Two RCTs[86,90] of interferon alfa-2b did not find a dose-response effect on mortality among HBeAg-positive patients.[86,90]

Dose or duration of the therapy did not affect mortality. Prolongation of adefovir administration did not reduce mortality in 125 HBeAg-negative Greek patients.[111] Entecavir in different doses did not decrease mortality in patients with lamivudine resistant hepatitis.[124]

In conclusion, antiviral medications did not reduce mortality versus placebo, compared to other antiviral medications, or in combination with corticosteroids regardless of HBeAg or cirrhosis status. Studies reporting mortality evaluated different patient populations and drug combinations, thus generally precluding pooling. Level of evidence and confidence in effect estimate is low. Studies assessing mortality had inadequate size and duration to detect significant differences.

Cirrhosis. Cirrhosis was assessed in two small relatively short-term studies of interferon alfa-2b (Appendix E Figure 4.) Compared to placebo, interferon alfa-2b at 16 weeks of therapy and at 48-64 weeks of followup did not reduce incident cirrhosis (1/20 versus 2/20; ARD -0.05, 95 percent CI -0.21; 0.11) in 40 HBeAg-positive patients (40 percent with baseline histologically confirmed cirrhosis).[83] The study did not have power to detect differences in incident cirrhosis.[176] The French Multicenter Group examined interferon alfa-2b alone and with simultaneous prednisone for 24 weeks and reported no significant difference (ARD -0.06, 95 percent CI -0.24; 0.11) in histologically confirmed cirrhosis at the end of therapy and at 24 weeks of followup (3/31 versus 4/25).[85]

In conclusion, sparse data suggest no effects of interferon alfa-2b alone or in combination with steroids on short-term incident cirrhosis. The long-term effects of interferon alfa-2b alone or in combination with steroids on clinical outcomes are unknown. No data were available for other antiviral drugs. Overall level of evidence and confidence in effect estimate is low.

Hepatic decompensation. Hepatic decompensation was reported in three studies;[122,126,141] one small RCT compared lamivudine to placebo[141] and two assessed outcomes after 52-96 weeks of entecavir versus lamivudine administration.[122,126] Studies reported very few cases of hepatic decompensation. Eighty weeks of lamivudine treatment did not affect the development of hepatic decompensation in 74 Korean patients with lamivudine-resistant mutant CHB (ARD 0.05, 95 percent CI -0.11; 0.22).[141] The Benefits of Entecavir for Hepatitis B Liver Disease (BEHoLD) study evaluated 715 HBeAg-positive patients of which 8 percent had cirrhosis at baseline.[122] An American study[126] also assessed 709 HBeAg-positive patients, though they did not report the number of subjects with cirrhosis at baseline. Neither found a difference in hepatic decompensation between entecavir compared to lamivudine.[122,126] There were only two cases reported both in the lamivudine group.

In conclusion, there is insufficient evidence regarding the relative effects of entecavir versus lamivudine in preventing hepatic decompensation over 1-2 years among HBeAg-positive patients. Effects of other antiviral drugs or in different patient populations are unknown.

Hepatocellular carcinoma was reported in four studies. None demonstrated a statistically significant difference. Two studies compared placebo to lamivudine[132] or interferon alfa-2b.[91] One compared the addition of corticosteroids to interferon alfa-2b versus interferon monotherapy,[85] and one examined the effects of prolonged adefovir therapy.[111] Incidence of hepatocellular carcinoma did not differ between lamivudine (130 weeks, 17/436) and placebo (16/215) in a multicenter study of 651 Asian patients (58 percent HBeAg-positive) with confirmed cirrhosis (61 percent) or advanced fibrosis (ARD -0.04, 95 percent CI -0.07; 0.00).[132] A further analysis that adjusted for country, sex, baseline ALT level, Child-Pugh score, and Ishak fibrosis score found a borderline significant effect (HR 0.49, 95 percent CI 0.25; 0.99, p=0.047 borderline significant).[132]

Interferon alfa-2b for 96 weeks compared to placebo failed to prevent hepatocellular carcinoma in 42 HBeAg-negative Italian patients.[91]

The French Multicenter Group did not find protective effects of adding corticosteroids to interferon alfa-2b compared to interferon alone at the end of 24 weeks of therapy and at 24 weeks of followup in treatment naïve HBeAg-positive patients with CHB (ARD -0.02, 95 percent CI -0.28; 0.24).[85]

In conclusion, study number, design, and duration were inadequate to accurately assess the impact of treatments on hepatocellular cancer. Limited low level evidence from one multinational RCT suggested that 130 weeks of lamivudine may reduce the incidence of hepatocellular carcinoma in Asian adults with hepatitis B and cirrhosis or advanced fibrosis. Results come from a single trial that noted no significant differences in crude rates and reported a nonstatistically significant increase in all-cause mortality with lamivudine. Protective effects on HCC with lamivudine were significant only after adjustment for baseline variables and after excluding five individuals who developed hepatocellular cancer within the first year of the study. Interferon alfa-2b monotherapy was not protective in a single small short-term study reporting very few events (low confidence). Addition of corticosteroids to alfa interferon was not superior to alfa interferon alone in a single, small short-term study with few events (low confidence). There are no data evaluating other antiviral agents.

Virological outcomes (Appendix E Tables 4 and 5). HBsAg clearance is one of the diagnostic criteria proposed to define complete response and resolved hepatitis B (the American Association for the Study of Liver Diseases).[1] Other parameters include undetectable HBV DNA, normal ALT, and presence of antiHBsAg in patients with previous known history of acute or CHB (the American Association for the Study of Liver Diseases).[1] HBsAg-positive patients can transmit infection to others. Therefore, sustained HBsAg clearance after drug administration benefits not only individual patients but prevents transmission of hepatitis B virus to others. Short-term effects reported in RCTs among patients "on treatment" might be generalizable to clinical settings if these treatments could be continued indefinitely. Six studies[10,67,70,83,84,91] compared active drugs to placebo at the end of the treatments, ten studies[61,67,83,87,91,136,139] evaluated sustained HBsAg clearance, and ten studies[67,69,71,84,99,111,119,122,126] examined sustained comparative effectiveness between antiviral treatments on sustained HBsAg loss (Appendix E Table 5).

From six studies that compared active drugs with placebo or no treatment,[10,67,70,83,84,91] only one RCT of 169 HBeAg-positive patients found a significant increase in HBsAg loss (ARD 0.12, 95 percent CI 0.02; 0.23) at the end of 24 weeks administration of interferon alfa-2b, 5MU/day[84] (Appendix E Figure 5). The same study reported a similar significant increase in HBsAg loss after interferon alfa-2b with corticosteroid (ARD 0.11, 95 percent CI 0.02; 0.21). Pooled analysis of two RCTs that compared steroid pretreatment followed by interferon alfa-2b to no antiviral drugs found a significant increase in HBsAg loss at the end of the treatments (pooled ARD 0.11, 95 percent CI 0.02; 0.20).[70,84]

All treatments failed to increase rates of post-treatment HBsAg loss at followup off drug administration (range 8-48 weeks off drug) (Appendix E Figure 6).[61,67,83,87,91,136,139]

Comparative effectiveness of interferon and reverse transcriptase inhibitors on HBsAg loss at the end of the drug administration did not differ in any of the ten RCTs that examined the association.[67,69,71,84,99,111,119,122,126]

Entecavir and lamivudine resulted in similar rates of HBsAg loss and seroconversion.[122,126] Combination of interferon alfa-2b with lamivudine did not increase HBsAg loss compared to lamivudine alone in HBeAg-positive[67] and negative patients.[71]

Adefovir combined with lamivudine resulted in the same rates of HBsAg loss as adefovir or lamivudine monotherapy.[119] Longer treatment with adefovir for 240 weeks resulted in worse

rates of HBsAg clearance compared to 114 weeks (ARD -0.05, 95 percent CI -0.09; -0.01).[111] (Appendix E Figure 7).

Comparative effectiveness of interferon and reverse transcriptase inhibitors on HBsAg loss or seroconversion to antiHBsAg at followup off the drug administration did not differ in any of the 12 RCTs that examined the association[63,66,67,74,76,80,85,88,90,98,99,109] (Appendix E Figure 8). Duration of followup off treatment ranged from 16-48 weeks; therefore, outcomes at longer duration off treatment are not known. Four RCTs examined the effects of interferon alfa-2b on HBsAg loss combined with other criteria of resolved hepatitis B including loss of HBV DNA and HBeAg and normalization of ALT[73,82,89,91] (Appendix E Figure 9). Trials included patients who were HBeAg-positive (N=113),[73] HBeAg-negative (N=42),[91] or both positive and negative for HBeAg (N=58).[82,89] The proportion of patients with baseline cirrhosis varied from 5 percent[82] to 17 percent.[91] Interferon alone and with corticosteroid pretreatment failed to increase rates of resolution of hepatitis B as assessed by the combined outcomes of HBV DNA, HBeAg, and HBsAg clearance and normalization of ALT levels.

In conclusion, interferon alfa-2b alone and with steroid pretreatment increased HBsAg loss by about 10-15 percent at the end of drug administration (moderate level of evidence). However, sustained effects of interferon alfa-2b on HBsAg loss beyond 48 weeks off treatment have not been examined. Additionally, interferon alfa-2b failed to increase rates of several criteria of resolved hepatitis B. The effects of other drugs and their combinations on composite criteria of resolved hepatitis B including HBsAg loss have not been investigated. Comparative effectiveness of evaluated active treatments on short-term intermediate outcomes (loss of HBsAg) was similar at the end of the therapy and at short-mid duration followup off treatment in the populations studied (moderate evidence).

HBV DNA clearance (Appendix E Tables 4 and 5) is associated with a favorable prognosis, though little longitudinal data is available in persons with HBV DNA levels.[1,5] Undetectable levels of HBV DNA in combination with HBeAg and HBsAg loss determine resolved hepatitis. A value of 20,000 IU/mL is an arbitrary threshold defining active hepatitis or inactive HBsAg carrier state.[1]

Studies obtained assays with different sensitivity to detect HBV DNA. Viral load was measured using polymerase chain reaction assay,[63,74,87,90,110,113,117,119-123,126,127,129,139,143] reverse transcription polymerase chain reaction assay,[107,124] or solution hybridization assay.[62,66-69,71,72,75,77,84-86,136,145] Obtained assay methods had different detection limits and units to measure viral load: <200 copies/mL,[117] <300 copies/mL,[113,121,122,126] <400 copies/mL,[96,102,116] <500 copies/mL,[117] <1,000 log copies/ml,[10,111] <3 log10 copies/mL,[143] <1.6pg/mL,[131,140] <2.5 pg/mL,[142] <3 pg/mL,[62,67] or <6pg/mL.[77] We explored heterogeneity in drug effects across the studies using the assay to measure HBV DNA loss and did not convert units of cut offs.

We reviewed 43 studies that examined HBV DNA clearance after interferon and reverse transcriptase inhibitors.[10,57,62,63,66-69,71,72,75,77,80,85-88,90,92,96,106,107,110-113,117,119-124,126,127,129,131,133,136,137,139,142,145] Twenty-eight publications included HBeAg-positive.[63,65,68,69,72,75,77,80,84-88,90,92,96,102,106,107,112,119,120,126,127,129,131,136,140] Five reports assessed HBeAg-negative patients;[10,71,74,110,111] the rest of the studies included patients with chronic active hepatitis B independent of HBeAg baseline status. Twenty trials examined the effects of interferon alfa-2b,[62,63,65-69,71,72,74,75,77,80,84-88,90,92] one trial examined peginterferon alfa-2a,[96] eight publications reported HBV DNA loss after adefovir,[10,110-113,117,119,120] five articles[121-124,126] examined the effects of entecavir on HBV DNA clearance, and 39 analyzed the effects of lamivudine.[57,62,63,67,68,71,72,74,75,77,96,102,106,107,119,121-124,126,127,129,131,133,136,137,139,140,142,143,145]

Effects of drugs on HBV DNA clearance at the end of the treatment. Adefovir administration for 48-96 weeks increased rates of HBV DNA loss compared to placebo at the end of treatment in four reports[10,110,112,113] with a consistent across-the-studies increase in relative risk (pooled RR 20.41, 95 percent CI 6.79; 61.32). The pooled absolute risk difference was significant (pooled ARD 0.38, 95 percent CI 0.23; 0.53) but there was evidence of statistical heterogeneity between studies that could not be explained by control rate of HBV DNA clearance, length of treatments, or baseline HBeAg status (metaregression p value >0.05) (Appendix E Figure 10).

Interferon alfa-2b for 16 weeks compared to no antiviral treatment [69] (ARD 0.45, 95 percent CI 0.22; 0.68) increased HBV DNA loss in HBeAg-positive patients. The same RCT of HBeAg-positive patients reported a significant increase in HBV DNA loss after 16 weeks of interferon alfa-2b combined with corticosteroid (ARD 0.25, 95 percent CI 0.04; 0.46).[69]

Lamivudine for 12-104 weeks compared to placebo or usual care[67,129,131,133,136,139,145] increased HBV DNA clearance with consistent across-the-studies relative risk (pooled RR 3.79, 95 percent CI 2.71; 5.30). The pooled absolute risk difference was significant (pooled ARD 0.48, 95 percent CI 0.31; 0.66), but inconsistent, with evidence of statistical heterogeneity that could not be explained by length of treatment or control rate of HBV DNA loss (metaregression p value >0.05). The effects of baseline HBeAg status, assay to measure viral load, or the proportion of patients with baseline cirrhosis, could not explain variability in the results. A valid metaregression was not possible because not all studies reported this information.

Interferon alfa-2b combined with lamivudine for 52 weeks compared to placebo[67] increased the rate of undetectable HBV DNA (<3pg/mL—a measure used to define resolved hepatitis B) (ARD 0.48, 95 percent CI 0.33; 0.63) with random differences (ARD 0.05, 95 percent CI -0.09; 0.18) in sustained HBV DNA response (no two consecutive detectable HBV DNA on treatment) in predominantly HBeAg-positive patients (98 percent).

Comparative effects of antiviral drugs of HBV DNA clearance at the end of treatment was mixed across RCTs (Table 5). Entecavir demonstrated greater HBV DNA clearance compared to lamivudine;[121-123,126] however, the effect was not consistent across studies in either multiplicative scale (pooled RR 1.64, 95 percent CI 1.22; 2.22) or absolute risk differences (0.23, 95 percent CI 0.11; 0.35). Rates in the control group and the dose of entecavir could not explain heterogeneity across the studies. Pooled analysis suggested that effects in HBV DNA clearance became significant after more than 1 year of treatment (ARD 0.30, 95 percent CI 0.16; 0.44 at >1 year of active treatment) with no significant differences at 6 months of active treatment (ARD 0.09, 95 percent CI -0.04; 0.21; metaregression p-value 0.04).

Telbivudine resulted in greater rates of HBV DNA loss compared to adefovir at 24 (ARD 0.28, 95 percent CI 0.12; 0.44) but not 52 weeks of treatment[120] in a multinational study of 135 HBeAg-positive, naïve to antiviral drugs patients. Only one drug demonstrated a significant dose response increase in rates of HBV DNA loss, 100-300 mg of lamivudine resulted in greater viral clearance compared to 25-100 mg (pooled ARD 0.21, 95 percent CI 0.10; 0.31).[133,137,145] The length of treatment was not associated with greater response increase in HBV DNA loss.[131] Larger doses or duration of administration of adefovir did not result in larger viral clearance.[10,111-113,120] Only one RCT of adefovir (Adefovir Dipivoxil 437 Study Group) reported greater HBV DNA loss after 30 versus 10 mg (ARD 0.18, 95 percent CI 0.08; 0.27).[112] Entecavir did not show a dose response association with HBV DNA loss in a single 24-week, double-blind, multicenter, phase II clinical trial.[123] Limited evidence suggested that lamivudine was less effective than adefovir (ARD -0.26, 95 percent CI -0.47; -0.06) in patients with lamivudine-resistant CHB[119] and less effective than telbivudine in HBeAg-positive patients with

compensated (upper limit of normal for serum ALT was 48 U/L for men and 37 U/L for women) CHB (ARD -0.30, 95 percent CI -0.55; -0.04).[127]

Combined therapy of adefovir with lamivudine resulted in increased HBV DNA clearance compared to lamivudine alone[117,119] (pooled ARD 0.25, 95 percent CI 0.10; 0.39) but not compared to adefovir alone.[119] Interferon alfa-2b combined with lamivudine resulted in the same HBV DNA loss when compared to interferon alfa-2b alone.[62] Longer administration of interferon alfa-2b + lamivudine for 20 weeks did not increase HBV DNA loss compared to pretreatment with interferon alfa-2b followed by lamivudine.[92] Combined interferon alfa-2b with lamivudine therapy failed to increase viral clearance compared to lamivudine alone (pooled ARD 0.03, 95 percent CI -0.11; 0.17).[62,63,67,71,74,75,77] Comparative effects of other antiviral drugs was similar at the end of the treatment (Appendix E Table 5).

Effects of drugs on HBV DNA clearance at followup off treatment (Table 5). Limited evidence suggests that antiviral drugs and their combinations sustain HBV DNA clearance at followup off therapy ranging from 18-24 weeks (Appendix E Figure 11). Interferon alfa-2b at 8-24 weeks of followup increased HBV DNA loss compared to placebo or no antiviral therapy (pooled ARD 0.44, 95 percent CI 0.27; 0.60);[69,87] however, the effects were attenuated at longer followup at 48 weeks off the therapy (pooled ARD of three studies 0.28, 95 percent CI -0.04; 0.60)[69,84,87] (Appendix E Table 5). Limited evidence from one RCT suggests sustained effects of lamivudine on HBV DNA loss at 24 weeks of followup after 96 weeks of drug administration (ARD 0.08, 95 percent CI 0.01; 0.15).[139] One large RCT, reported a significant benefit from adefovir administration in HBeAg-negative patients that was sustained at 18 weeks off treatment (ARD 0.59, 95 percent CI 0.46; 0.72).[10] Entecavir provided similar HBV DNA loss compared to lamivudine at 24 weeks of followup.[122] Sustained effects of the drugs that demonstrated significant difference at the end of the treatment have not been investigated or were not significant (Appendix E Table 5).

In conclusion, lamivudine and adefovir resulted in HBV DNA clearance that was large in magnitude and maintained for periods up to 24 weeks after the treatment in patients with CHB (moderate to high evidence). Interferon alfa-2b resulted in off treatment HBV DNA loss for 8-24 weeks, the effect was attenuated at longer followup off the treatment (low evidence). Entecavir and adefovir were more effective than lamivudine at the end of the treatment (low). However, sustained differences off the treatments were not significant (entecavir) or have not been examined in RCTs. HBV DNA clearance was greater after combined therapy of adefovir and lamivudine compared to lamivudine alone at the end of the treatment (low to moderate). Long-term sustained effect off therapies has not been examined.

Effects of drugs on HBeAg clearance at the end of treatment (Table 5 and Appendix E Tables 4 and 5). Thirty-five included studies reported HBeAg loss at the end of antiviral drug treatment in patients with positive baseline HBeAg status.[57,61,62,64,66,67,69,72,75,80,83,86-88,92,94,96,98,99,102,106,109,112,113,117,119,120,122-125,127,136,140,143] Limited evidence from one small RCT[83] suggested that interferon alfa-2b increased HBeAg loss compared to no antiviral treatments (ARD 0.55, 95 percent CI 0.29; 0.81) Lamivudine for 52 weeks compared to placebo increased HBeAg loss in three of four RCTs (pooled ARD 0.13, 95 percent CI 0.04; 0.22), but the effect size was not consistent across the studies.[64,67,136,140] (Appendix E Figure 12). One short-term RCT of 122 Chinese patients found random changes in HBeAg loss after 12 weeks of drug administration.[140] Adefovir for 48-52 weeks compared to placebo resulted in increased rates of HBeAg loss (pooled ARD 0.11, 95 percent CI 0.06; 0.16).[112,113] Neither dose[112] nor duration of treatment of adefovir increased HBeAg loss.[113] No differences in HBeAg clearance were reported after three

doses of entecavir (0.01; 0.1; or 0.5 g) administered for 24 weeks.[123] Longer treatment duration with interferon alfa-2b did not have any effect on HBeAg loss.[66]

Comparative effects of monotherapies was significant only for peginterferon alfa-2a when compared to lamivudine in one large RCT of 814 patients (Peginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group, ARD 0.08, 95 percent CI 0.01; 0.16).[96] Adefovir followed by telbivudine resulted in the same rates of HBeAg loss compared to adefovir alone.[120] Entecavir did not increase HBeAg loss compared to lamivudine[122,123,125] at the end of 24-63 weeks of therapy. Comparative effects of evaluated combined therapies was similar (Appendix E Table 5). Adefovir combined with lamivudine for 48-52 weeks increased HBeAg loss compared to lamivudine alone in two RCTs (pooled ARD 0.12, 95 percent CI 0.03; 0.21).[117,119]

Effects of drugs on HBeAg clearance at followup off the treatment (Table 5). Significant HBeAg clearance at followup off treatments was demonstrated for interferon alfa-2b (pooled RR 2.52, 95 percent CI 1.55; 4.1)[64,83,87] (Appendix E Figure 13). An increase in absolute risk of HBeAg loss was significant (pooled ARD 0.28, 95 percent CI 0.07; 0.50) but not consistent across RCTs. In patients receiving 52 weeks of lamivudine, HBeAg loss was greater at 16 weeks off therapy than patients receiving placebo (pooled ARD 0.15, 95 percent CI 0.05; 0.24).[67,136] HBeAg loss at 24 weeks off treatment was greater after peginterferon alfa-2a compared to lamivudine therapy in one large RCT (ARD 0.13, 95 percent CI 0.05; 0.20).[96] However, this study did not find a significant difference in HBeAg clearance after combination of peginterferon alfa-2a with lamivudine when compared to peginterferon alfa-2a alone or lamivudine alone. The HBeAg loss did not demonstrate a dose response association with peginterferon alfa-2a at followup.[94] Interferon alfa-2b combined with corticosteroid compared to interferon alfa-2b alone,[80,86,88] interferon alfa-2b combined with lamivudine compared to placebo,[64,67] interferon alfa-2b alone,[62,64] or lamivudine alone[62,64,67,72,75] did not result in greater off treatment HBeAg clearance. Interferon alfa-2b and lamivudine provided similar off-treatment HBeAg loss.[62,64]

Effects of drugs on HBeAg seroconversion at the end of treatment (Table 5). HBeAg seroconversion was reported in 36 studies.[10,57,62-64,66-68,75,80,83,88,91,94,96,99,106,109,111-113,117,119,120,122-127,133,136,140,141,143,145] At the end of the treatments, lamivudine increased HBeAg seroconversion with consistent results across the studies (pooled RR 1.69, 95 percent CI 1.05; 2.74)[64,67,136,140,141,145] (Appendix E Figure 13); however, the effect size was not consistent (i.e., significant heterogeneity in effects across studies) in absolute risk scale (pooled ARD 0.05, 95 percent CI 0.01; 0.1, heterogeneity p value <0.05). The rate in the placebo group and duration of treatments could not explain the heterogeneity in absolute rates. Adefovir for 48-52 weeks compared to placebo resulted in increased rates of HBeAg seroconversion without dose response association (ARD 0.05, 95 percent CI 0.01; 0.09)[112,113] (Appendix E Figure 14).

E*ffects of drugs on HBeAg seroconversion at followup off the treatment* (Table 5). Interferon alfa-2b[64,83] increased rates of HBeAg seroconversion versus placebo at 28-64 weeks of followup (ARD 0.12, 95 percent CI 0.03; 0.21). Lamivudine monotherapy failed to maintain HBeAg seroconversion at 16 weeks of followup.[67,136] Interferon alfa-2b combined with lamivudine demonstrated inconsistent effects on HBeAg seroconversion at 6-28 weeks of followup.[64,67] Pooled analysis of individual patient data from four RCTs found a significant increase in HBeAg seroconversion after combined therapy with interferon alfa-2b and lamivudine. (0.13, 95 percent CI 0.05; 0.21).[64] Interferon alfa-2b combined with lamivudine did not result in better sustained HBeAg seroconversion compared to interferon alfa-2b alone.[62,64,68] Limited evidence from one RCT of HBeAg-positive untreated patients suggested an increase in HBeAg seroconversion at 56 weeks off therapy (ARD 0.31, 95 percent CI 0.1; 0.63).[68] Telbivudine compared to adefovir for

24-52 weeks increased HBeAg seroconversion in relative terms (RR 6.03, 95 percent CI 2.20; 16.52) but had random differences in absolute rates.[120] Peginterferon alfa-2a increased HBeAg seroconversion at 24 weeks of followup compared to lamivudine (ARD 0.13, 95 percent CI 0.06; 0.20).[96] Peginterferon alfa-2a combined with lamivudine resulted in greater HBeAg seroconversion compared to lamivudine alone (ARD 0.08, 95 percent CI 0.01; 0.15) but not peginterferon alfa-2a alone (ARD-0.05, 95 percent CI -0.12; 0.03).[96] Combined treatments of peginterferon alfa-2b with for 60 weeks increased HBeAg seroconversion compared to lamivudine alone (ARD 0.32, 95 percent CI 0.14; 0.50).[106] All other comparisons demonstrated random differences between compared treatments.

In conclusion, monotherapy with interferon alfa-2b and peginterferon alfa-2a increased off treatment HBeAg loss and seroconversion compared to placebo (moderate evidence and confidence). Lamivudine monotherapy increased rates of HBeAg loss at the end of the treatments and at followup (moderate to high) but did not maintain sustained HBeAg seroconversion (low). Limited low level evidence suggested that peginterferon alfa-2a increased HBeAg loss and seroconversion at followup. Combined therapy with lamivudine was more effective than lamivudine alone (low level of evidence and confidence).

Combined virologic and biochemical outcomes including HBV DNA loss, HBeAg clearance and seroconversion, and ALT normalization (Appendix E Table 4) were investigated in eight RCTs at the end of treatment[75,81,84,91,122,126,127,139] and in 13 RCTs at followup off treatment[61,73,75,81,82,85,87,89,91,106,122,125,139] (Table 4).

Effects of drugs on combined outcomes at the end of treatment. Interferon alfa-2b for 24 weeks with steroid pretreatment compared to no treatment with antiviral drugs increased rates of HBV DNA and HBeAg clearance (ARD 0.29, 95 percent CI 0.13; 0.46) in one RCT of 169 patients[84] (Appendix E Figure 15). This study demonstrated an increase in HBV DNA and HBeAg clearance after 24 weeks of interferon alfa-2b administered at a dose of 35 MU/week (ARD 0.30, 95 percent CI 0.13; 0.46) but not 7 MU/week (ARD 0.10, 95 percent CI -0.04; 0.24).[84] HBV DNA and HBeAg loss after interferon alfa-2b (35 MU/week) were larger compared to 7 MU/week (ARD 0.20, 95 percent CI 0.01; 0.38).[84] Interferon alfa-2b for 16-96 weeks compared to no antiviral treatment increased rates of HBV DNA loss and normalization of ALT (pooled ARD 0.36, 95 percent CI 0.20; 0.51) in HBeAg-positive[81] and HBeAg-negative patients.[91] Lamivudine for 96 weeks compared to placebo increased HBV DNA loss and ALT normalization (ARD 0.46, 95 percent CI 0.32; 0.59) in HBeAg-negative Chinese patients.[139]

Comparative effects of interferon alfa-2b, 35 MU/week with steroid pretreatment on negative HBV DNA and HBeAg was larger compared to interferon, 7 MU/week alone.[84] Interferon alfa-2b combined with lamivudine did not improve HBV DNA and HBeAg clearance and seroconversion compared to lamivudine alone.[75] Entecavir or telbivudine did not improve combined outcomes at the end of monotherapy or in combination with lamivudine.[126,127]

Effects of drugs on combined outcomes at followup off treatment. Interferon alfa-2b increased rates of negative HBV DNA and HBeAg at 24-144 weeks off treatment with consistent results in relative terms (pooled RR 2.96, 95 percent CI 1.40; 6.25) (Appendix E Figure 13).[61,73,87,91] Significant heterogeneity in absolute risk difference was observed (pooled ARD 0.22, 95 percent CI 0.08; 0.36) and could not be explained by differences across studies in control rate of the outcome or duration of treatments and followup (Appendix E Figure 16). Interferon alfa-2b compared to no treatment increased rates of negative HBV DNA, HBeAg loss, and normal ALT at 40 weeks of followup off treatments (ARD 0.27, 95 percent, 0.10; 0.43).[82] Interferon alfa-2b compared to no treatment increased rates of negative HBV DNA and normalization of ALT

(pooled ARD 0.28, 95 percent CI 0.14; 0.42).[81,91] Interferon alfa-2b combined with lamivudine compared to lamivudine alone increased HBV DNA and HBeAg clearance and seroconversion (ARD 0.21, 95 percent CI 0.06; 0.35) in 75 treatment naïve patients.[75]

In conclusion, administration of interferon alfa-2b alone and in combination with lamivudine resulted in off treatment response in combined biochemical and virological outcomes in patients with HBeAg-positive CHB that was large in magnitude. Lamivudine alone increased rates of HBV and HBeAg loss at the end of the treatments but not at followup. The long-term effects of adefovir and telbivudine on combined outcomes have not been evaluated in RCTs.

Histological outcomes (Table 5)**.** We analyzed histologic outcomes including changes in total, fibrosis, or necroinflammatory scores to assess effects of treatments on development of cirrhosis[177,178] (Appendix E Tables 4 and 5). Liver biopsy is invasive and is associated with complications including pain, bleeding, infection, and rarely death.[179,180] Histological results were not available in all subjects of the studies for unknown reasons. We analyzed the results among all randomized patients applying intention to treat principle.

Histological outcomes at the end of the therapy were reported in 22 publications[10,63,67,68,75,77,91,99,107,110-112,121,122,125,130,135,136,139,145] and at followup off therapy in five studies (Appendix E. Table 5).[62,83,95,96,99]

Effects of drugs on histological outcomes at the end of treatment. Adefovir for 48-96 weeks improved necroinflammatory scores (decrease of at least two points in the Knodell necroinflammatory scores) compared to placebo (pooled ARD 0.26, 95 percent CI 0.17; 0.34) (Appendix E Figure 17).[10,110,112] An improvement in fibrosis scores after adefovir administration was significant (pooled ARD 0.20, 95 percent CI 0.14; 0.26) but did not demonstrate dose response association.[110,112] Lamivudine administration for 48-96 weeks improved necroinflammatory scores (decrease of at least two points in necroinflammatory scores) in all RCTs[130,136,139,145] (pooled RR 2.09, 95 percent CI 1.60; 2.74). The effect on absolute risk was significant (pooled ARD 0.25, 95 percent CI 0.13; 0.38) but inconsistent across the studies (Appendix E. Table 5).[130,136,139,145] Control rate of outcomes, duration of the treatment, a proportion of HBeAg-positive patients at baseline, and a proportion of untreated patients could not explain heterogeneity between studies. Entecavir compared to lamivudine improved necroinflammatory scores (ARD 0.14, 95 percent CI 0.04; 0.24) but without dose response association.[121,122,125] Interferon alfa-2b combined with lamivudine for 48 weeks improved HAI scores compared to interferon alone (ARD 0.54, 95 percent CI 0.2; 0.79) in one RCT of 48 untreated HBeAg-positive Turkish patients.[68]

Effects of drugs on histological outcomes at followup off treatment. Histological improvement in necroinflammatory scores at 24 weeks of followup off treatment (ARD 0.12, 95 percent CI 0.02; 0.22) was reported in only one RCT[95] after a 48 week administration of peginterferon alfa-2a compared to lamivudine in 552 HBeAg-negative patients.[95]

In conclusion, low-moderate quality evidence suggested improvement in histological scores at the end of monotherapy with adefovir or lamivudine. Off treatment improvement was reported only in HBeAg-negative patients after treatment with peginterferon alfa-2a compared to lamivudine. A higher level of certainty is not possible because reporting is from a relatively small number of short term, small studies, there is inconsistency in findings, and there are limitations in using liver biopsy findings to accurately assess overall histological changes due to treatments. The histological improvement in necroinflammatory scores reported with peginterferon compared to lamivudine was from only one study and at 24 weeks off therapy.

Normalization of ALT at the end of drug administration was reported in 35 publications[10,62,66,67,74-76,90,92,95,96,99,107,110-113,117,119-127,131,136,138-141,143,145] and at followup off treatments in 24 studies[10,61-63,66,68,72,74-76,80,84,87,88,90,94-96,99,102,109,113,126,139] (Appendix E. Tables 4 and 5).

Effects of drugs on ALT normalization at the end of treatment (Table 5). Adefovir for 48-96 weeks increased rates of ALT normalization compared to placebo in all RCTs (pooled RR 2.97, 95 percent CI 2.38; 3.69).[10,110,112,113] However, the studies reported inconsistent differences in absolute rates of the outcome; such statistical heterogeneity in absolute risk difference (ARD 0.40, 95 percent CI 0.30; 0.49) could not be explained by the dose of adefovir, control rate, duration of the treatment, or the proportion of HBeAg-positive patients (Appendix E. Figure 18). Longer treatment with adefovir was associated with a decreased rate of ALT normalization (poled ARD -0.06, 95 percent CI -0.12; -0.01) without does response association.[10,111-113,120]

Lamivudine for 12-96 weeks increased ALT normalization with consistent effect size in relative risk compared to placebo or no antiviral treatment (pooled RR 2.42, 95 percent CI 1.94; 3.01).[67,131,136,139-141,145] Heterogeneity in pooled absolute risk (pooled ARD 0.22, 95 percent CI 0.13; 0.31) could not be explained by the length of treatment, control rate, or the proportion of HBeAg-positive patients. Comparative effectiveness of entecavir on ALT normalization was greater compared to lamivudine with significant heterogeneity in relative (pooled RR 1.62, 95 percent CI 1.28; 2.06) and absolute risk (pooled ARD 0.22, 95 percent CI 0.11; 0.32).[90,121-126] Heterogeneity could not be explained by the dose of entecavir, the duration of treatments, or the proportion of HBeAg-positive patients. The effect of entecavir on absolute risk of ALT normalization was lower in RCTs with higher rates of outcomes after lamivudine administration (meta-regression p value=0.005).

Lamivudine was less effective compared to adefovir (ARD -0.42, 95 percent CI -0.67; -0.18) in 38 American adults with compensated liver disease (Child-Pugh-Turcotte score <7) and lamivudine-resistant hepatitis B virus;[119] however, lamivudine administration for 48 weeks was more effective in normalizing ALT compared to peginterferon alfa-2a in HBeAg-positive and negative patients (the Peginterferon Alfa-2a Chronic Hepatitis B Study Group, pooled RR for Peginterferon alfa-2a versus lamivudine 0.57, 95 percent CI 0.46;0.70).[95,96] The absolute risk difference for peginterferon alfa-2a versus lamivudine was larger (ARD -0.36, 95 percent CI -0.45; -0.26) in HBeAg-negative patients[95] than in HBeAg-positive patients (ARD -0.23, 95 percent CI -0.31; -0.15)[96] (pooled ARD -0.29, 95 percent CI -0.42; -0.17). The same study reported that monotherapy with lamivudine resulted in greater ALT normalization compared to combined treatment (pooled ARD for peginterferon alfa-2a + lamivudine versus lamivudine -0.20, 95 percent CI -0.29; -0.10).[95,96] In contrast, a combination of lamivudine with adefovir compared to monotherapy with lamivudine increased the rate of ALT normalization in lamivudine-resistant patients with compensated CHB (pooled ARD 0.32 95 percent CI 0.13; 0.52).[117,119]

Effects of drugs on ALT normalization at followup off treatment. ALT normalization at followup off treatments was greater after adefovir administration compared to placebo (pooled ARD 0.26, 95 percent CI 0.19; 0.33) in HBeAg-negative patients (the Adefovir Dipivoxil 438 Study Group)[10] as well as in HBeAg-positive Chinese patients (Appendix E. Figure 19).[113] Lamivudine for 96 weeks compared to placebo increased rates of ALT normalization at 24 weeks of followup off treatment (ARD 0.21, 95 percent CI 0.04; 0.38) in 139 HBeAg-negative Chinese patients.[139] Interferon alfa-2b at doses 35 MU/week but not 7 MU/week compared to no antiviral treatment increased rates of ALT normalization at 8-24 weeks of followup (pooled

ARD 0.31, 95 percent CI 0.17; 0.44).[84,87] Interferon alfa-2b with steroid pretreatment increased ALT normalization compared to no antiviral drugs (ARD 0.25, 95 percent CI 0.06; 0.43)[84] and random differences compared to interferon alfa-2b alone.[80,84,88] In contrast with the superior effectiveness of lamivudine at the end of the treatment, sustained ALT normalization at 24 weeks of followup was greater after peginterferon alfa-2a compared to lamivudine (pooled ARD 0.13, 95 percent CI 0.07; 0.20)[95,96] and after combined therapy of peginterferon alfa-2a with lamivudine compared to lamivudine alone (pooled ARD 0.13, 95 percent CI 0.06; 0.19).[95,96]

In conclusion, adefovir and lamivudine monotherapy resulted in ALT normalization that was maintained for up to 24 weeks. Longer term effects are not known. Entecavir and adefovir were more effective than lamivudine at the end of the treatment, while sustained differences have not been investigated. Peginterferon alfa-2b alone and combined with lamivudine normalized ALT at followup off the treatments when compared to lamivudine alone.

Relapse was defined as reappearance or increase in viral load[63,71,74,79,113,115,121,126,127,131] or increase in HBV DNA and ALT levels[107] at the end of active treatments or at followup off therapies[61,72,75,81,84,85,91,106,122] (Appendix E. Tables 4 and 5). Lamivudine administration for 60 weeks compared to 48 weeks increased rates of virological relapse in one RCT of 348 HBeAg-positive Chinese patients.[131] Entecavir administration for 52 weeks resulted in lower rates of viral relapse at 24 weeks of followup off treatments compared to lamivudine (ARD -0.16, 95 percent CI -0.20; -0.12) in 709 HBeAg-positive naïve to nucleoside analogue patients (participants in BEHoLD Study Group).[122]

Antiviral resistance (Table 5) was detected by the development of resistant HBV YMDD mutations (genotypic resistance) at the end of the treatments with reverse transcriptase inhibitors[63,67,74-76,79,110,111,115,117,131,132 96,99,107] or at followup off the therapies[10,62] (Appendix E. Tables 4 and 5). Lamivudine administration for 52-130 weeks increased the rates of YMDD mutation compared to placebo by 43 percent (pooled ARD 0.43, 95 percent CI 0.38; 0.48).[67,132] Longer treatments for 60 weeks versus 48 weeks resulted in larger rates of mixed (ARD 0.06, 95 percent CI 0.01; 0.11) and pure YMDD mutation (ARD 0.03, 95 percent CI 0.00; 0.06).[131] Adefovir versus placebo increased rates of emerging amino acid substitutions in the HBV-RT domain and rates of rt221Y amino acid substitution but not rt134D; rt219A; rt91I; rt134N; rt54H; rt145M substitutions.[110,115] Longer treatments for 240 versus 114 weeks increased rates of adefovir resistant mutations;[111] however, combined therapy with adefovir plus lamivudine reduced the rates of YMDD compared to monotherapy with lamivudine (ARD -0.33, 95 percent CI -0.50; -0.17) in 135 patients with CHB and YMDD mutant HBV[117] with random differences in wild type mutations. Interferon alfa-2b combined with lamivudine reduced rates of mutation compared to lamivudine alone with significant heterogeneity in relative (pooled RR 0.42, 95 percent CI 0.16; 1.09) and absolute risk (pooled ARD -0.18, 95 percent CI -0.35; -0.01).[63,67,74-76,79] Heterogeneity could not be explained by the dose of interferon alfa-2b, length of treatment, or the proportion of HBeAg-positive patients at baseline. Lamivudine combined with interferon alfa-2b did not increase mutation rates compared to placebo in HBeAg-positive patients who had failed previous interferon therapy.[67] Peginterferon alfa-2a with lamivudine compared to peginterferon alfa-2a alone increased the rate of mutation (ARD 0.03, 95 percent CI 0.01; 0.06) in the patients participating in the Peginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group.[96] The same study reported reduced rates of mutations when peginterferon alfa-2a (ARD -0.25, 95 percent CI -0.31; -0.20) or peginterferon alfa-2a combined with lamivudine (ARD -0.22, 95 percent CI -0.28; -0.16) were compared to lamivudine monotherapy.[96]At followup off treatments, interferon alfa-2b monotherapy (ARD -0.23, 95 percent CI -0.33; -0.14) or combined with

lamivudine (ARD -0.23, 95 percent CI -0.32; -0.14) resulted in lower rates of mutations compared to lamivudine alone.[62]

In conclusion, limited evidence from a single trial suggested that a prolongation of lamivudine administration increased virological relapse in HBeAg-positive patients. Viral relapse post treatment was lower after entecavir compared to lamivudine in patients HBeAg-positive and naïve to nucleoside analogue. Lamivudine and adefovir increased the incidence of resistant HBV YMDD mutations, while combined therapy with interferon resulted in lower rate of mutation at the end of therapy and at followup. The effect on clinical outcomes including hepatocellular carcinoma and mortality is not known.

Effects of antiviral drugs on examined nonclinical outcomes at followup off treatments. Interferon alfa-2b resulted in sustained HBV DNA and HBeAg clearance and seroconversion and ALT normalization (Figure 4). A combination of interferon alfa-2b with steroid pretreatment or lamivudine did not maintain sustained HBV DNA and HBeAg loss at followup (Figure 5).

Adefovir administration provided sustained ALT normalization and HBV DNA clearance without evidence of genotypic resistance (Figure 6). Lamivudine resulted in sustained HBV DNA and HBeAg clearance and ALT normalization. Entecavir compared to lamivudine reduced the rates of virological relapse at followup off therapy (Figure 7).

Interferon alfa-2b combined with lamivudine compared to lamivudine sustained HBV DNA and HBeAg clearance and seroconversion and reduced rates HBV DNA mutations (Figure 8).

Pegylated interferon alfa-2a was more effective compared to lamivudine in HBV DNA and HBeAg clearance and seroconversion and ALT normalization as well as in improved necroinflammatory scores (Figure 9). Combined therapy of pegylated interferon alfa-2a with lamivudine resulted in better sustained HBV DNA and HBeAg clearance and seroconversion and ALT normalization when compared to lamivudine alone but with random changes when compared to pegylated interferon alfa-2a alone (Figure 10).

Levels of viral load, biochemical, or histologic outcomes were evaluated in 27 publications after active and control treatments at the end of the therapy and at followup off therapy (Appendix E Table 6).[10,63,68,70,71,75,79,85,86,95,96,101,105,110,112,117,119-122,124,125,127,128,134,145] Adefovir compared to placebo reduced serum HBV DNA levels by -1.65 log copies/ml (95 percent CI -2.08; -1.22) at 18 weeks of followup in HBeAg-negative patients (Adefovir Dipivoxil 438 Study Group).[10] Telbivudine administration decreased viral load compared to adefovir at 28 weeks of followup (mean difference -0.84 log10 copies/ml 95 percent CI -1.49; -.19).[120] Examined drugs failed to maintain sustained reduction in ALT level at followup.[10,75,86] Necroinflammatory and fibrosis scores did not differ at followup off the treatments with interferon alfa-2b followed by steroid administration compared to interferon alfa-2b alone.[85,86]

In conclusion, measures of viral load, ALT levels, and histological scores at followup off the antiviral medications were evaluated in few studies without consistent differences between compared treatments.

EPC Question 2b. What are the known harms associated with treatments of hepatitis B?

Literature search and review strategy. RCTs were identified through an Ovid MEDLINE® search, using the search terms used to assess efficacy. Additional harms data were obtained from the FDA website and industry prescribing information. We excluded interferon trials that did not report type of interferon (2a or 2b) from the adverse events and lab abnormalities analyses.[75,77,181]

To address question 3 regarding particular patient populations that should not be treated, we describe whether adverse events and withdrawals varied by patient and/or disease characteristics and whether these seemed to be at high enough frequency or severity to preclude treatment.

Adverse events after nucleotide analogues (Appendix E Tables 4 and 7).

Adefovir monotherapy. Two randomized, double-blind, placebo-controlled trials (N=700), one enrolling HBeAg-positive[95] and one HBeAg-negative chronic hepatitis subjects[110] evaluated orally administered adefovir, an adenosine nucleotide analogue. Adefovir 10 mg/day was generally well tolerated, with rates of study withdrawal, adverse events, severe (Grade 3 or 4) adverse events, and adverse events leading to discontinuation similar to placebo over the 48 week study durations. Approximately 8 percent of both groups did not complete treatment for any reason. Fewer than 2 percent of all subjects had an adverse event leading to the discontinuation of study intervention (Table 6). In the trial with HBeAg-negative subjects, none of the serious adverse events were considered to be treatment-related.[110] Most adverse events were generally mild to moderate in severity, with pharyngitis (23 percent versus 30 percent placebo) and flu-like syndrome (14 percent versus 19 percent placebo) the most commonly reported. Pooled analyses of the two RCTs from the prescribing information insert reported the most common events related to treatment were asthenia and headache, 13 and 9 percent versus 14 and 10 percent for placebo (www.fda.gov/medwatch/safety/2006/Oct_PIs/Hepsera_PPI.pdf). Long-term therapy (49-96 weeks) found adverse event similar in frequency and severity to those reported through week 48.[10] Adverse event rates were comparable between nucleoside analogues lamivudine,[119] telbivudine,[120] and combination adefovir and lamivudine therapy (high level of evidence).

Lamivudine monotherapy versus placebo. Several placebo-controlled RCTs evaluated the efficacy and safety of orally administered lamivudine (generally 100 mg/day) over 1 to 2 years.[136,139,145] Similar to adefovir, lamivudine was generally well tolerated with no adverse events significantly greater than placebo. Fewer subjects randomized to placebo were likely to complete treatment compared to lamivudine, 13 percent versus 9 percent (ARD -1 percent, 95 percent CI -7; 4) in two trials[139,145] and 18 percent versus 8 percent (ARD -10 percent, 95 percent CI -21; 1) in one trial enrolling subjects refractory to interferon.[67] These differences were not statistically significant. The most common events were upper respiratory tract infections or symptoms, asthenia, abdominal pain, and headache. Overall, adverse events were similar between lamivudine and placebo in one study that enrolled subjects with advanced liver disease (histologically confirmed cirrhosis or advance fibrosis) with the exception of a greater incidence of diarrhea in the placebo group and cough in the lamivudine group over a median duration of treatment of 32 months.[132] Rate of serious adverse events was slightly higher among the placebo

group (18 percent) compared to the lamivudine group (12 percent), with an ARD of -5 percent (95 percent CI -11; 1). There were two deaths during therapy in the lamivudine group, one from lymphoma and one drowning due to a myocardial infarction (high level of evidence).

Lamivudine monotherapy versus peginterferon-alfa-2a monotherapy. Two RCTs, one with HBeAg-positive and one HBeAg-negative subjects, compared lamivudine 100 mg/day (n=456) to subcutaneously administered peginterferon-alfa-2a 180 µg/week monotherapy (n=453).[95,96] Subjects were treated for 48 weeks and then followed up for an additional 24 weeks. Significantly more subjects assigned lamivudine discontinued treatment compared to the subjects assigned peginterferon-alfa-2a, 16 percent to 10 percent (RR 1.57, 95 percent CI 1.10; 2.22). However, more subjects treated with peginterferon alfa-2a were more likely to withdraw from a study due to an adverse event, 5 percent compared to <1 percent.(ARD -5 percent, 95 percent CI -10; 1). Dose modification due to an adverse event was required for 7 percent of peginterferon alfa-2a subjects and none of the lamivudine group. Most adverse events were significantly more frequent with peginterferon alfa-2a therapy. An initial flu-like illness was commonly associated with peginterferon alfa-2a treatment, noted by pyrexia, fatigue, myalgia, and headache. Approximately 18 percent of peginterferon alfa-2a subjects reported hair loss compared to 2 percent of lamivudine subjects. Anorexia was reported in 16 percent of peginterferon alfa-2a subjects. Events attributed solely to peginterferon alfa-2a included rigors and an injection-site reaction (due to the subcutaneously administration). Depression was reported in 5 percent and 2 percent of peginterferon alfa-2a and lamivudine subjects, respectively, (RR 0.31, 95 percent CI 0.10; 0.93). One subject receiving lamivudine developed hepatic decompensation after cessation of therapy and died.[96] There was one death in the peginterferon-alfa-2a group.[95] This subject had developed thrombotic thrombocytopenic purpura (moderate level of evidence).

Lamivudine monotherapy versus combination peginterferon alfa-2a and lamivudine therapy. Combined peginterferon alfa-2a and lamivudine had a similar adverse event profile as peginterferon alfa-2a when compared to lamivudine monotherapy in two trials reporting.[95,96] More lamivudine subjects did not complete treatment but combination subjects were more likely to discontinue treatment due to an adverse event. Fifty-three percent of lamivudine subjects reported any adverse event compared to 88 percent of the combination subjects (ARD -35 percent, 95 percent CI -41; -29). Nearly 11 percent of the combination group required dose modification due to an adverse event, slightly higher than peginterferon monotherapy. The higher frequency of flu-like symptoms (pyrexia, fatigue, myalgia, and headache) was also observed with combination therapy compared to lamivudine as well as significantly greater incidences of hair loss (22 percent versus 2 percent), anorexia (13 percent versus 2 percent), and depression (6 percent versus 2 percent). There were three deaths in the combination group during the treatment period.[96] These deaths were reported as accidental and unrelated to the study drug (low to moderate level of evidence).

Lamivudine monotherapy versus combination peginterferon alfa-2b and lamivudine therapy. One trial assessed combination peginterferon alfa-2b (1.5 µg/kg of body weight per week up to 100 µg) and lamivudine therapy (n=50) compared to lamivudine monotherapy (n=50) over 52 weeks.[107] Combination therapy resulted in higher frequencies of transient flu-like adverse events, hair loss, and anorexia. Four subjects assigned combination therapy had serious adverse events, including one case of bipolar disorder requiring antidepressant treatment and one case of a severe local reaction. Peginterferon treatment was stopped for all cases.

Lamivudine monotherapy versus combination conventional interferon alfa-2b and lamivudine therapy. Six trials evaluated conventional interferon alfa-2b combined with

lamivudine.[62,63,67,71,72,74] Adverse event data were provided primarily by three of the studies.[62,63,67] Combined therapy had a similar safety profile to the pegylated formulation, with high frequencies of pyrexia, headache, fatigue, and myalgia compared to lamivudine monotherapy. Similar to the pegylated formulation, there were significantly higher incidences of alopecia (30-40 percent versus <1-10 percent) and anorexia (19-40 percent versus <1-5 percent) compared to lamivudine monotherapy in two RCTs reporting.[62,67] The trial with subjects refractory to interferon reported a significantly lower incidence of depression in the monotherapy group compared to combined therapy, 3 percent to 18 percent (ARD -15 percent, 95 percent CI -25; -5)[67] (moderate level of evidence).

*Telbivudine monotherapy***.** The GLOBE study evaluated orally administered L-nucleoside analog telbivudine 600 mg/day (n=683) against lamivudine 100 mg/day (n=687) in both HBeAg-positive and negative chronic hepatitis subjects over 52 weeks[143] (www.fda.gov/cder/foi/label/2006/022011lbl.pdf). Compared to lamivudine, significantly fewer subjects receiving telbivudine withdrew from treatment or were noted to have a serious (Grade 3 or 4) adverse event. Less than 1 percent of subjects in both groups discontinued treatment due to an adverse event. One case of myopathy presumed to be treatment-related occurred in the telbivudine group. Comparable to adefovir and lamivudine, telbivudine is generally well tolerated; most adverse events are typically mild to moderate in severity. Incidences of adverse events were low in both groups (www.fda.gov/cder/foi/label/2006/022011lbl.pdf). In the trial versus adefovir, no serious adverse events were reported and no subject withdrew from therapy due to an adverse event[120] (low level of evidence).

Adverse events after acyclic guanosine derivative.

*Entecavir monotherapy***.** Two RCTs enrolling nucleoside-naive subjects compared entecavir 0.5 mg/day, an acyclic guanosine derivative was to lamivudine 100 mg/day.[121,122] One trial enrolled HBeAg-positive subjects,[122] and the other HBeAg-negative subjects.[121] All subjects in both trials had not received treatment with a nucleoside analogue. Mean exposure to therapy was 56 to 75 weeks for entecavir and 56 to 75 weeks for lamivudine. Numbers of subjects not completing treatment, reporting any or serious adverse events were similar between treatments. More subjects in the lamivudine group were likely to discontinue treatment due to an adverse event. Rates of individual adverse events were not reported in the trials, but the most frequent events cited included headache, upper respiratory tract infection, upper abdominal pain, nasopharyngitis, dyspepsia, fatigue, back pain, arthralgia, diarrhea, insomnia, cough, and nausea. These events were noted to be mostly mild to moderate. There were four deaths considered unrelated to study therapy, two in both treatment groups. A slightly higher percentage of subjects randomized to lamivudine reported any Grade 2 to 4 adverse event through two years, 18 percent versus 15 percent for entecavir (Bristol Myer package insert). Pooled analysis of two studies enrolling subjects refractory to lamivudine found rates of any Grade 2 to 4 adverse events were similar between the entecavir 1 mg dose group and lamivudine group, 22 percent and 23 percent, respectively (Bristol Myer package insert). Three deaths were reported in one trial enrolling lamivudine-refractory subjects, none were deemed related to the study medication by the investigator[125] (low to moderate evidence).

Adverse events after interferons.

Pegylated interferon alfa-2a versus lamivudine monotherapy and combination therapy (see above).

Combination of peginterferon alfa-2a and lamivudine therapy versus peginterferon alfa-2a monotherapy. Combined peginterferon alfa-2a and lamivudine had a similar safety profile and

withdrawal rates compared with peginterferon alfa-2a monotherapy.[95,96] The most common treatment-related adverse events in both groups included flu-like symptoms (pyrexia, fatigue, myalgia, and headache). Depression was reported by 6 percent (n=16) of the monotherapy group and 5 percent (n=13) of the combination group in one study enrolling HBeAg-positive subjects.[96] Four subjects died during the study periods, one in the peginterferon alfa-2a group[95] and three in the combined therapy group[96] (low to moderate evidence).

Combination of pegylated interferon alfa-2b and lamivudine therapy versus pegylated interferon monotherapy. One 52 week (26 week followup period) trial enrolling 307 subjects evaluated combined pegylated interferon alfa-2b 100 µg/week and lamivudine therapy in comparison to pegylated interferon alfa-2b monotherapy.[99] Approximately one-fourth of all subjects did not complete treatment. Between 7 and 8 percent discontinued treatment due to an adverse event. Overall, rates of adverse events were comparable between groups and the most common events were flu-like symptoms. There were 32 serious adverse events reported for both treatment arms. Seventeen events were likely to be attributed to therapy and included hepatitis flare (4), depression (3), severe neutropenia (3), and one case each of psychosis, seizures, pancreatitis, anxiety, dizziness, diarrhea, and syncope. All serious adverse events were reversible after treatment cessation. A study which followed these subjects an additional 26 weeks concluded that the most important predictors of dose reduction or study withdrawal were pre-existing cirrhosis and neutropenia[103] (low level of evidence).

Pegylated interferon alfa-2b versus interferon alfa-2. One Chinese trial (N=230) compared pegylated interferon alfa-2b 1.0 µg/kg/week monotherapy to interferon alfa-2b 3 MU/week monotherapy.[109] Significantly more subjects receiving conventional interferon did not complete treatment and followup compared to the pegylated interferon group, 17 percent versus 6 percent (ARD -11 percent, 95 percent CI -19; -3). Seventy-five percent of patients in each group reported drug-related adverse events, mainly flulike symptoms and fever. Adverse events lead to four subjects (4 percent) in the conventional interferon group to discontinue treatment.

Conventional interferon alfa-2b and lamivudine. One trial of interferon nonresponders to interferon compared 24 weeks of combined interferon alfa-2b 10 MU/week and lamivudine therapy (n=63) versus 52 weeks of placebo (n=56).[67] The percentages of subjects not completing treatment were comparable. There were significantly more flu-like adverse events observed with interferon therapy in the combined group. A multinational trial comparing combined therapy (n=76) to interferon monotherapy (n=70) found rates of adverse events were similar between groups with the exception of headache, which had significantly higher incidence in the combined group (93 percent to 67 percent, ARD 26 percent, 95 percent CI 14; 39).[62] A Turkish study of 49 subjects reported a significantly higher incidence of mouth dryness in the combined therapy group (76 percent) compared to the interferon monotherapy group (33 percent) (ARD 57 percent, 95 percent CI 33; 81).[68]

Interferon alfa-2b. Several RCTs compared different regimens of interferon alfa-2b therapy to no treatment. The trials reported that treatment was generally well-tolerated, but most subjects developed transient mild flu-like symptoms. In addition, Chung (N=65) reported anorexia/nausea in 22 percent of all subjects.[66] Janssen noted dose reduction was required in 12 percent of subjects in the "Prolonged Treatment" group due to depression, fatigue, hair loss, and headache[61] (low to moderate evidence).

Laboratory abnormalities/toxicities after nucleotide analogues. (Appendix E Tables 4 and 8).

Adefovir. In a pooled analysis of two trials, similar incidences of Grade 3 or 4 laboratory abnormalities were observed for adefovir and placebo with the exception of significant increases in ALT and AST levels (www.fda.gov/medwatch/safety/2006/Oct_PIs/Hepsera_PPI.pdf). Over 40 percent of placebo subjects had ALT levels more than five times the upper limit of normal (ULN) in the placebo group compared to 20 percent of the adefovir 10 mg group (RR 0.49, 95 percent CI 0.37; 0.65). AST levels greater than five times the ULN were observed in 23 percent and 8 percent of the placebo and adefovir subjects, respectively. An increase in serum creatinine ≥0.3 mg/dL from the baseline level was observed in 4 percent of adefovir subjects versus 2 percent of placebo subjects with adequate renal function at week 48 of treatment. No subject developed an increase ≥0.5 mg/dL at week 48. After extended adefovir treatment of an additional 48 weeks, two subjects had increases in serum creatinine ≥0.5 mg/dL from baseline, leading to discontinued treatment in one subject.[10] A black box warning from the prescribing information states subjects with or at risk of impaired renal function may develop nephrotoxicity with chronic administration of adefovir (www.fda.gov/medwatch/safety/2006/Oct_PIs/Hepsera_PPI.pdf). An analysis of renal safety utilizing the study population of the trial by Marcellin[95] found a greater occurrence of Grade 1 and 2 hematuria and proteinuria in the adefovir 30 mg group compared to placebo.[116] In the trial versus telbivudine, one adefovir subject had an elevated serum creatinine level that returned to normal range after switching to telbivudine after study cessation.[120] Grade 3 or 4 neutropenia was reported for one subject in each treatment arm. Each case resolved without dose reduction or treatment interruption. In one 48 week trial of lamivudine-refractory subjects, there were seven Grade 3 events (37 percent) compared to two Grade 3 and 4 events (10 percent) in the combined adefovir/lamivudine group[119] (moderate to high evidence).

Lamivudine versus placebo. A one year placebo-controlled trial of 385 Chinese subjects reported 10 subjects had abnormal liver function tests considered to be of major clinical concern, five in the lamivudine group (2 percent; four received 100 mg and one 25 mg) versus five in the placebo group (7 percent) (RR 0.26, 95 percent CI 0.08; 0.86).[145] A trial of 143 American subjects found the frequency of Grade 3 or 4 lab abnormalities similar between lamivudine and placebo during the course of treatment.[136] However, 25 percent of lamivudine subjects had an ALT level at least three times the baseline level (Grade 3 or 4 abnormality) compared to eight percent of placebo subjects during the 16 week post-treatment period (p=0.01). In subjects with advanced liver disease, 12 percent of subjects receiving lamivudine had elevations in serum ALT at least three times the level at baseline compared to one-fourth of the subjects receiving placebo (ARD -13 percent, 95 percent CI -20; -7)[132] (moderate evidence).

Lamivudine versus peginterferon alfa-2a monotherapy. Comparable to the adverse event profile, rates of lab abnormalities were significantly higher in the peginterferon alfa-2a monotherapy group compared to lamivudine. In a pooled analysis of two RCTs (N=901), dose modification was required for 46 percent of peginterferon alfa-2a recipients versus none of the lamivudine recipients (ARD -46 percent, 95 percent CI -51; -42.[95,96] Approximately 37 percent (95 percent CI 32; 41) of peginterferon alfa-2a subjects required dose medication due to a lab abnormality (79 percent of all dose modifications), with neutropenia and thrombocytopenia cited as the most common causes (moderate evidence).

Lamivudine versus combination peginterferon alfa-2a and lamivudine therapy. Combined peginterferon alfa-2a and lamivudine had a similar lab abnormality profile as peginterferon alfa-2a monotherapy in two trials reporting (N=903).[95,96] No subject assigned lamivudine required dose modification, while 47 percent of combined therapy subjects need alterations in the therapy regimen (ARD -47 percent, 95 percent CI -52; -43). Lab abnormalities accounted for 78 percent of all dose modifications, primarily due to neutropenia, thrombocytopenia and elevated ALT (moderate evidence).

Lamivudine versus combination peginterferon alfa-2b and lamivudine therapy. One Chinese trial randomizing 100 subjects assessed combination peginterferon alfa-2b and lamivudine therapy (n=50) compared to lamivudine monotherapy (n=50) over at least 78 weeks.[107] Dose reduction was required for five (10 percent) pegylated interferon subjects due to anemia (one patient), neutropenia (three patients), and/or thrombocytopenia (four patients). One combined therapy subject had peginterferon withheld for two doses due to a severe hepatic flare-up. No lamivudine subject required a reduction of dose. There were no significant differences in the incidence of lab abnormalities between groups (low evidence).

Lamivudine versus combination conventional interferon alfa-2b and lamivudine therapy. Several trials evaluated conventional interferon alfa-2b combined with lamivudine compared to lamivudine monotherapy. One Italian trial (N=151) with a study duration of 100 weeks found no significance in rates of lab abnormalities between groups.[63] One trial of interferon-refractory subjects noted similar frequencies of lab abnormalities between groups.[67] Elevated ALT (≥2 times the baseline level) was significantly greater in the combined therapy group (n=63) during primary treatment, 48 percent versus 26 percent for the lamivudine group (n=119) (ARD -22 percent, 95 percent CI -36; -7). Incidence of neutropenia was also significantly greater among subjects assigned combined therapy, 16 percent versus 1 percent of lamivudine recipients. A Turkish trial (N=80) reported four cases of neutropenia occurred with combined therapy.[71] Two cases each required temporary and permanent dose modification, respectively. Thrombocytopenia occurred in 11 cases (28 percent) in the combined therapy group versus three subjects in the lamivudine group (8 percent) (ARD -20 percent, 95 percent CI -36; -4) (moderate to high evidence and confidence).

Telbivudine. Significantly greater incidences in creatine kinase (CK) elevations were associated with telbivudine therapy compared to therapy with lamivudine. Data from the 52 week GLOBE trial showed 68 percent of telbivudine recipients (n=680) had a Grade 1-4 CK elevation compared to 39 percent of lamivudine subjects (n=687) (ARD 29 percent (95 percent CI 24; 34) product monograph (www.fda.gov/cder/foi/label/2006/022011lbl.pdf). Grade 3-4 CK elevations were reported for 7.5 and 3 percent of the telbivudine and lamivudine subjects, respectively. CK elevations decreased spontaneously to Grade 2 or lower in two-thirds of the telbivudine recipients and approximately three-fourths of the lamivudine subjects by the next clinical visit.[143] In the telbivudine group, two subjects required discontinuation and three subjects required interruption of treatment due to CK toxicity product monograph (www.fda.gov/cder/foi/label/2006/022011lbl.pdf). There were higher frequencies of Grade 3-4 elevations in ALT and aspartate aminotransferase (AST) in the lamivudine group compared to the telbivudine group. ALT levels greater than three times the baseline level occurred in 6 percent of the lamivudine-assigned subjects versus 3 percent of the telbivudine subjects (RR 0.59, 95 percent CI 0.36; 0.95).[143] Analysis of categories of ALT flares (≥2 times the baseline level) after 24 weeks of treatment found ALT flares were more

likely to occur with lamivudine therapy (5 percent) than telbivudine (1 percent) product monograph (www.fda.gov/cder/foi/label/2006/022011lbl.pdf) (low to moderate evidence).

Laboratory abnormalities/toxicities after acyclic guanosine derivative.

Entecavir monotherapy. Elevations in ALT occurred more frequently in the lamivudine group (n=668) compared to the entecavir group (n=679), particularly during post-treatment.[121,122] During the 24 week followup period, ALT flares (ALT >2 times the baseline level and >5 times the ULN) occurred in 24 percent and 9 percent of the lamivudine and entecavir groups, respectively (absolute risk difference -14 percent, 95 percent CI -21; -6). Elevations in ALT were also observed more frequently in the lamivudine group compared to entecavir 1 mg in a pooled analysis of two trials assessing lamivudine-refractory subjects through 2 years of study duration (N=373) [Patient information sheet, (Bristol Myers Squibb http://www.fda.gov/medwatch/safety/2007/Baraclude_PI_jul2407.pdf)]. ALT flares >5 times the ULN occurred in 24 percent of subjects assigned lamivudine versus 12 percent assigned entecavir (ARD -12 percent, 95 percent CI -20; -4). AST levels >5 times the ULN were also significantly greater in the lamivudine group (17 percent) compared to the entecavir group (5 percent) (ARD -12 percent, 95 percent CI -18; -6) (moderate evidence).

Laboratory abnormalities/toxicities after interferons.

Pegylated interferon alfa-2a versus lamivudine monotherapy and combination therapy (see above).

Combination peginterferon alfa-2a and lamivudine therapy versus peginterferon alfa-2a monotherapy. Combined peginterferon alfa-2a and lamivudine therapy and peginterferon alfa-2a monotherapy had similar laboratory abnormality profiles.[95,96] Over 45 percent of both groups required dose modification. Nearly 80 percent of dose modifications were due to a lab abnormality, mainly neutropenia and thrombocytopenia. Elevated ALT levels occurred more frequently in the monotherapy group, 9 percent versus 4 percent (ARD -5 percent, 95 percent CI -10; 0)[95] (low to moderate evidence).

Combination pegylated interferon alfa-2b and lamivudine therapy versus pegylated interferon monotherapy. No significant differences in dose modifications were reported between the treatment groups, and nearly 70 percent remained on full-dose treatment at the end of therapy.[99] Frequencies of hematologic events, neutropenia (21-26 percent) and thrombocytopenia (11-13 percent), were also similar in the combined and monotherapy groups (low evidence).

Pegylated interferon alfa-2b versus interferon alfa-2. The trial by Zhao (N=230) reported four subjects (6 percent) in the conventional interferon group with elevated ALT levels and /or increased bilirubin levels discontinued treatment.[109] No subjects in the pegylated group discontinued therapy due to a lab abnormality (low evidence).

Conventional interferon alfa-2b and lamivudine. In a trial evaluating subjects refractory to interferon treatment, frequencies of abnormal ALT or AST, abnormal enzymes and neutropenia were not significantly different from combined conventional interferon alfa-2b and lamivudine therapy (n=63) versus placebo (n=56) through the 68 treatments and followup duration.[67] During the 52 week treatment period, 48 percent of combined therapy subjects had ALT levels at least two times the baseline level compared to 20 percent of placebo subjects (absolute risk difference 28 percent, 95 percent CI 12; 440. The Schalm trial found hepatic flares (ALT levels at least 500 IU/L and greater than two times the baseline level) were observed more frequently in the interferon monotherapy group (11 percent; 8/70 subjects) compared to combined therapy (0 percent; 0/75 subjects) during the 24 week treatment period.[62] There was no difference in the incidence of flares during the 40-week post-treatment period (low evidence).

Interferon alfa-2b. Few of the small studies comparing different regimens of interferon alfa-2b therapy or to no treatment reported lab abnormalities. Low incidences (up to 6 percent) of thrombocytopenia and neutropenia were observed in three trials[61,66,81] (low evidence).

Table 2. Treatments of hepatitis B: Overview of randomized controlled trials

Study Characteristic	Percent or Mean (Range)	Number of Subjects	Number of Trials Reporting
All studies (# subjects)	20-1,367	11,144	59
Weighted mean age	37 (24-58)	7,884	40
Gender, male (%)	78	8,408 / 10,721	58
Race, Asian (%)	64 (0-100)	5,097 / 7,954	27
Race, White (%)	30 (0-98)	2,219 / 7,954	
Race, Black (%)	1 (0-24)	111 / 7,954	
Race, Other (%)	5 (0-8)	184 / 5,380	
e Antigen-positive (%)	81 (2-100)	7,453 / 9,160	48
e antigen-negative (%)	64 (19-100)	2,828 / 4,434	17
Mean ALT level (IU/L)	139 (77-284)	6,917	33
Median ALT level (IU/L)	Range 56-170	1,327	7
Study duration (weeks), therapy and followup combined	69 (17-208)	10,606	56
Treatment naive	*All subjects*	2,388	13
Treatment resistant	*All subjects*	1,241	11
Study withdrawals (%)	7 (0-35)	712 / 10,199	50
Withdrawals due to adverse events (%)	3 (0-16)	199 / 7,697	36
Cirrhosis (%)	21 (5-65)	1,258 / 6,047	31
Studies ≥1 biopsy	*All subjects*	8,466	43
HBV genotype			
A	13 (0-34)	609 / 4,800	11
B	19 (0-32)	913 / 4,800	
C	42 (15-100)	2,002 / 4,800	
D	19 (0-46)	906 / 4,800	

Table 3. Effects of drug therapies for chronic hepatitis B on clinical outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/Subjects Enrolled	Estimates (95% CI) *Dose Response Heterogeneity: p Value/ I Squared, %	Level of Evidence/Comments
Liver related death				
Lamivudine vs. placebo[132]	130/0	1/651	0.00 (-0.01; 0.01) (RD)	Low. Sparse data (0 events in both groups) No effect of LAM on liver related death
Mortality				
Lamivudine vs. placebo[132]	130/0	1/651	0.00 (-0.01; 0.01) (RD)	Low. Sparse data (0 events in control group) No effect of LAM on mortality
Interferon alfa-2b vs. placebo[83]	16/48-64	1/40	NS at the end of treatment and after followup	Low. Sparse data (small N of events) No effect of Interferon alfa 2 B on mortality
Adefovir dipivoxil[111]	114 vs. 240/0	1/125	0.33 (0.01; 8.10) (RR)	Low. Sparse data (0 events at second time point, no formal control) Length of adefovir therapy did not affect mortality
Entecavir[124]	48/0	1/89	NS among all compared doses No *	Low. Sparse data (small number of events) No dose response effect on mortality
Entecavir vs. lamivudine[121,122,124-126]	48-96/0-28	5/2476	NS in all studies -0.003 (-0.008;0.002) (RD) 0.7/0%	Low. Sparse data (small N of events) No differences between entecavir vs. lamivudine on mortality
Interferon alfa 2b+corticosteroid vs. interferon alfa 2b[86]	24/0	1/37	-0.11 (-0.27; 0.06) (RD)	Low. Sparse data (0 events in active group) No differences of pretreatment with steroid and interferon alfa-2b vs. interferon alfa-2b on mortality
Interferon alfa 2b+corticosteroid vs. symptomatic treatment[70]	24/48	1/20	-0.10 (-0.34; 0.14) (RD)	Low. Sparse data (0 events in active group) No differences of pretreatment with steroid and interferon alfa-2b on mortality
Interferon alfa 2b[86,90]	24-48/0-24	2/76	NS among all compared doses No *	Low. Sparse data (0 events in active group) No dose response effect on mortality
Peginterferon alfa-2a+placebo vs. lamivudine[96]	48/8	1/543	0.00 (-0.01; 0.01) (RD)	Low. Sparse data (0 events in both groups) No differences between peginterferon alfa-2a and lamivudine on mortality
Peginterferon alfa-2a+lamivudine vs. lamivudine[96]	48/8	1/543	0.01 (0.00; 0.03) (RD)	Low. Sparse data (0 events in control group) No differences between peginterferon alfa-2a combined with lamivudine vs. lamivudine alone on mortality
Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a[96]	48/8	1/543	0.01 (0.00; 0.03) (RD)	Low. Sparse data (0 events in control group) No differences between peginterferon alfa-2a combined with lamivudine vs. peginterferon alfa-2a alone on mortality

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/Subjects Enrolled	Estimates (95% CI) *Dose Response Heterogeneity: p Value/ I Squared, %	Level of Evidence/Comments
Peginterferon alfa-2b+lamivudine vs. amivudine[106]	50-60/56-64	1/100	0.02 (-0.03; 0.07) (RD)	Low. Sparse data (0 events in control group) No differences between peginterferon alfa-2b combined with lamivudine vs. lamivudine on mortality
Incident cirrhosis				
Interferon alfa-2b vs. no treatment[83]	16/48-64	1/40	-0.05 (-0.21; 0.11) (RD)	Low. Sparse data (small number of events) No effect of interferon alfa-2b on cirrhosis
Interferon alfa 2b+corticosteroid vs. interferon alfa 2b[85]	24/24	1/56	-0.06 (-0.24; 0.11) (RD)	Low. Sparse data (small number of events) No differences of pretreatment with steroid and interferon alfa-2b on incidence of cirrhosis
Hepatic decompensation				
Lamivudine vs. placebo[141]	80/0	1/74	0.05 (-0.11; 0.22) (RD)	Low. Sparse data (small number of events) No effect of lamivudine on liver decompensation
Lamivudine vs. no treatment[141]	80/0	1/74	0.00 (-0.12; 0.12) (RD)	Low. Sparse data (small number of events) No effect of lamivudine on severe liver decompensation
Peginterferon alfa-2b+lamivudine vs. lamivudine[106]	52-60/57-72	1/100	0.00 (-0.04; 0.04) (RD)	Low. Sparse data (0 events in both groups) No differences between combined peginterferon alfa-2b with lamivudine vs. lamivudine alone on liver decompensation
Entecavir vs. lamivudine[122,126]	52-96/0-24	2/709	NS after different treatment duration	Low. Sparse data (0 events in active group) No differences between entecavir vs. lamivudine on liver decompensation
HCC				
Lamivudine vs. placebo[132]	130/0	1/651	-0.04 (-0.07; 0.00) (RD)	Low. Significant protective effects of active drug after adjustment for country, sex, baseline Alanine aminotransferase level, Child-Pugh score, and Ishak fibrosis score (HR = **0.49, 95% CI 0.25; 0.99)** No effect of lamivudine on HCC
Interferon alfa-2b vs. placebo[91]	96/0	1/42	0.05 (-0.07; 0.17) (RD)	Low. Sparse data (0 events in control group) No effect of Interferon alfa-2b on HCC
Adefovir dipivoxil[111]	114 vs. 240/0	1/250	0.03 (-0.01; 0.07) (RD)	Low. Sparse data (small number of events at first time point, no formal control) Length of adefovir therapy did not affect HCC
Interferon Alfa 2b+corticosteroid vs. interferon alfa 2b[85]	24/24	1/56	-0.02 (-0.28; 0.24) (RD)	Low. No difference on active hepatitis between interferon alfa-2b with pretreatment using corticosteroid vs. interferon alfa-2b

Bold - significant association at 95% confidence level; RD - absolute risk difference; RR - relative risk

Table 4. Effects of drug therapies for chronic hepatitis B on combined outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/Subjects Enrolled	Estimates (95% CI) *Dose Response Heterogeneity: p Value/ I Squared, %	Level of Evidence/Comments
Combined outcomes (virological, histological, biochemical) at end of treatment				
Interferon alfa 2b+ prednisone vs. no treatment[84]	24/0	1/87	**0.29 (0.13; 0.46)** (RD)	Low. Interferon alfa 2b+ prednisone vs. no treatment increased rates of negative HBV DNA and HBeAg
Interferon alfa-2b vs. no treatment[84]	24/0	1/84	**0.30 (0.13; 0.46)** (RD 35MU/week) 0.10 (-0.04; 0.24) (RD 7MU/week)	Low. Interferon alfa-2b vs. no treatment increased rates of negative HBV DNA and HBeAg after 35 but not 7 MU/week
Lamivudine vs. placebo[139]	96/0	1/136	**0.46 (0.32; 0.59)** (RD)	Low. Lamivudine vs. placebo increased rates of negative HBV DNA, normal ALT
Interferon alfa-2b vs. no treatment[81,91]	16-96/0	2/92	**0.36 (0.20; 0.51)** (RD) 0.473/0%	Low. Interferon alfa-2b vs. no treatment increased rates of negative HBV DNA and normal ALT
Entecavir vs. lamivudine[126]	52-96/0	2/1418	0.03 (-0.01; 0.08) (RD) 0.49/0%	Moderate. No differences between entecavir vs. lamivudine on negative HBV DNA and HBeAg
Interferon alfa-2b +lamivudine vs. lamivudine[75]	52/0	1/75	0.13 (-0.05; 0.31) (RD)	Low. No differences between interferon alfa-2b +lamivudine vs. lamivudine alone on loss of HBV DNA+HBeAg seroconversion+HBeAg loss
Lamivudine vs. telbivudine[127]	52/0	1/63	-0.06 (-0.30; 0.19) (RD)	Low. No differences between lamivudine vs. telbivudine on loss of HBV DNA+HBeAg loss
Peginterferon alfa-2b+lamivudine vs. lamivudine[107]	60/0	1/100	**0.32 (0.14; 0.50)** (RD)	Low. Peginterferon alfa-2b+lamivudine vs. lamivudine increased rate of loss of HBV DNA+HBsAg seroconversion
Telbivudine+lamivudine vs. lamivudine[127]	52/0	1/60	-0.07 (-0.30; 0.16) (RD)	Low. No differences between telbivudine+lamivudine vs. lamivudine alone on loss of HBV DNA and HBeAg
Telbivudine+lamivudine vs. telbivudine[127]	52/0	1/85	-0.12 (-0.31; 0.06) (RD)	Low. No differences between telbivudine+lamivudine vs. telbivudine on loss of HBVDNA and HBeAg
Entecavir vs. lamivudine[122,126]	52-96	2/1418	0.03 (-0.01; 0.08) (RD) 0.49/0%	High. No differences between entecavir vs. lamivudine on negative HBV DNA and HBeAg
Interferon alfa 2b, 5MU/day vs. interferon alfa 2b, 1MU/day[84]	24/0	1/82	**0.20 (0.01; 0.38)** (RD)*	Low. Interferon alfa-2b in dose 35MU/week increased HBV DNA and HBeAg loss compared to 7MU/week
Interferon alfa 2b+lamivudine vs. lamivudine,100[75]	52/0	1/75	0.13 (-0.05; 0.31) (RD)	Low. No differences between interferon alfa-2b+lamivudine vs. lamivudine on loss of HBV DNA+HBeAg seroconversion+HBeAg loss
Interferon alfa 2b, 5MU/day+ prednisolone. interferon alfa 2b, 1MU/day[84]	24/0	1/85	**0.19 (0.01; 0.38)** (RD)	Low. Interferon alfa 2b, 35MU/week+pretreatment with prednisone vs. interferon alfa-2b alone, 7MU/ week increased rate of loss of HBV DNA+HBeAg loss
Lamivudine vs. telbivudine[127]	52/0	1/63	-0.06 (-0.30; 0.19) (RD)	Low. No differences between lamivudine vs. telbivudine on loss of HBV DNA+HBeAg loss
Peginterferon alfa-2b + lamivudine,	60/0	1/100	**0.32 (0.14; 0.50)** (RD)	Low. Peginterferon alfa-2b+lamivudine vs. lamivudine

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/Subjects Enrolled	Estimates (95% CI) *Dose Response Heterogeneity: p Value/ I Squared, %	Level of Evidence/Comments
vs. lamivudine[107]				increased rate of loss of HBV DNA+HBsAg seroconversion
Telbivudine+lamivudine vs. lamivudine[127]	52/0	1/60	-0.07 (-0.30; 0.16) (RD)	Low. No differences between telbivudine +lamivudine vs. lamivudine on loss of HBV DNA and HBeAg
Telbivudine+lamivudine vs. telbivudine[127]	52/0	1/85	-0.12 (-0.31; 0.06) (RD)	Low. No differences between telbivudine+lamivudine vs. telbivudine on loss of HBV DNA and HBeAg
Combined outcomes (virological, histological, biochemical) end of followup				
Interferon alfa 2b+prednisone vs. no treatment[73]	24/24	1/76	0.00 (-0.05; 0.05) (RD)	Low. Sparse data (0 events). Interferon alfa 2b+prednisone compared to no treatment did not increase HBV DNA, HBsAg, and HBeAg loss
Interferon alfa-2b vs. no treatment[61,73,87,91]	16-96/24-144	4/282	**0.22 (0.08; 0.36)** (RD) 0.042/63.4%	Moderate. Interferon alfa-2b vs. no treatment increased rates of negative HBV DNA+HBeAg with consistent results in multiplicative scale
			2.96 (1.40; 6.25) (RR) 0.313/16%	Control rate or duration of treatment and followup could not explain statistical heterogeneity in absolute rate
Lamivudine vs. placebo[139]	96/24	1/136	0.07 (-0.08; 0.21) (RD)	Low. Lamivudine vs. placebo did not increase loss of HBV DNA and HBeAg at time of followup
Interferon alfa-2b vs. no treatment[82,89]	16-96/24-48	2/116	0.03 (-0.03; 0.10) (RD) 1/0%	Moderate. Interferon alfa-2b did not increase rate of negative HBV DNA, normal ALT, HBsAg and HBeAg loss
Interferon alfa-2b vs. no treatment[82]	16/40	1/58	0.19 (-0.01; 0.39) (RD)	Low. Interferon alfa-2b vs. no treatment did not increase rates of negative HBV DNA and HBeAg seroconversion
Interferon alfa-2b vs. no treatment[89]	16/40	1/58	0.16 (-0.04; 0.35) (RD)	Low. Interferon alfa-2b vs. no treatment did not increase rates of negative HBV DNA, HBeAg loss
Interferon alfa-2b vs. no treatment[82]	16/40	1/58	**0.27 (0.10; 0.43)** (RD)	Low. Interferon alfa-2b vs. no treatment increased rated of negative HBV DNA, HBeAg loss and normal ALT
Interferon alfa-2b vs. no treatment[81,91]	16-96/40-144	2/92	**0.28 (0.14; 0.42)** (RD) 0.968/0%	Low. Sparse data (small number of events) Interferon alfa-2b vs. no treatment increased rates of negative HBV DNA and normal ALT
Entecavir vs. lamivudine[122,125]	52-63/76-87	2/995	Random differences in all comparisons	Moderate. Entecavir, 0.50 or 0.1mg vs. lamivudine did not increase rate of HBV DNA and HBeAg loss
Interferon alfa 2b+prednisone vs. interferon alfa 2b[73,85]	24/48	1/56	-0.17 (-0.42; 0.07) (RD)	Low. Interferon alfa-2b+pretreatment with prednisone vs. interferon alfa-2b alone did not increase rates of HBV DNA loss, HBeAg loss and seroconversion
	24/48	1/79	0.07(-0.10;0.24)(RD)	

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/Subjects Enrolled	Estimates (95% CI) *Dose Response Heterogeneity: p Value/ I Squared, %	Level of Evidence/Comments
Interferon alfa-2b+lamivudine vs. lamivudine[75]	52/75	1/75	**0.21 (0.06; 0.35)** (RD)	Low. Interferon alfa 2b+lamivudine vs. lamivudine alone increased rates of loss of HBVDNA+ HBeAg seroconversion+HBeAg loss
Peginterferon alfa-2b+lamivudine vs. lamivudine[106]	60/24	1/100	**0.20 (0.05; 0.35)** (RD)	Low. Peginterferon alfa-2+lamivudine vs. lamivudine alone increased rates of los of HBV DNA+HBeAg loss at two time points of followup
	60/40	1/100	0.12 (-0.01; 0.25) (RD)	
	60/57	1/100	**0.20 (0.05; 0.35)** (RD)	

Table 5. Absolute risk difference in tested nonclinical outcomes after antiviral drugs for chronic hepatitis B in adults

Comparison	HBsAg [RCTs/Patients]	HBeAg [RCTs/Patients]	HBV DNA Clearance [RCTs/Patients]	Histology Improved [RCTs/Patients]	ALT Normal [RCTs/Patients]	Relapse/Mutation [RCTs/Patients]
Adefovir vs. placebo	SC: NS [1/120] L	Loss: 0.11 (0.06; 0.16) [2/995] M SC: 0.05 (0.01; 0.09) [2/700] H	0.38 (0.23; 0.53) [4/1002] H *20.41 (6.79; 61.32) [4/1002]* 0.59 (0.46; 0.72)* [1/120] L	Fibrosis: 0.20 (0.14; 0.26) [2/699] M Necroinflammation scores: 0.26 (0.17; 0.34) [3/819] H	0.40 (0.30; 0.49) [5/1342] *2.97 (2.38; 3.69)* H 0.26 (0.19; 0.33)* [2/600] M	NS [2/1055] L NS* [1/140] L
LAM vs. placebo	Loss: NS [1/175] L NS* [3/1068] L	Loss:0.13 (0.04; 0.22) [4/1349] M 0.15 (0.05; 0.24)* [2/318] M SC: 0.05 (0.001; 0.10) [6/1638] H *1.70 (1.05; 2.74)* NS * [2/318] L	0.48 (0.31; 0.66) [7/1305] *3.79 (2.71; 5.30)* H 0.08 (0.00; 0.15)* [1/136] L	Necroinflammation: *2.09 (1.60; 2.74)* M 0.25 (0.13; 0.38) [4/580] M	0.22 (0.13; 0.31) [7/1602] *2.42 (1.94; 3.01)* M 0.21 (0.04; 0.38)* [1/136] L	YMDD mutation: 0.43 (0.38; 0.48) [2/826] H
Adefovir + LAM vs. LAM	Loss: NS [1/39] L	Loss: 0.12 (0.03; 0.21) [2/134] M SC: NS [2/134] L	0.25 (0.10; 0.39) [2/134] L		0.32 (0.13; 0.52) [2/13] M	YMDD:-0.33 (-0.50; -0.17) [1/95] L Wild type mutation: NS [1/95] L
Adefovir+ LAM vs. adefovir	Loss: NS [1/39] L	Loss: NS [1/39] L SC: NS[1/39] L	NS:[1/39] L		NS [1/39] L	
Entecavir vs. LAM	Loss: NS [2/1117] M SC: NS [1/408] L	Loss: NS [3/1112] L SC: NS [3/1185] M	0.23 (0.11; 0.35) [4/1636] *1.64 (1.22; 2.22)* L/M NS*1/709] L	Necroinflammation: 0.14 (0.04; 0.24) [3/1633] M Fibrosis: NS [2/995] M	0.22 (0.11; 0.32) [6/2423] *1.62 (1.28; 2.06)* H	NS [0/1347] L -0.16 (-0.20; -0.12)* [1/709] L
LAM vs. adefovir		Loss: NS [1/38] L SC:NS [1/38] L	-0.26 (-0.47; -0.06) [1/38] L		-0.42 (-0.67; -0.18) [1/38] L	
LAM vs. telbivudine		Loss: NS [1/63] L SC: NS [1/63] L	-0.30 (-0.55; -0.04) [1/63] L		NS [1/85] L	NS [1/63] L
Telbivudine vs. adefovir		Loss: NS [1/135] L SC: *6.03 (2.20; 16.52) [1/136]* L	0.28 (0.12; 0.44) [1/136] L		NS [1/135] L	
Telbivudine+LAM vs. LAM		Loss: NS[1/60] L SC: NS [1/60] L	NS [1/60] L		NS [1/101] L	NS [1/60] L
Telbivudine+LAM vs. telbivudine		Loss: NS [1/85] L SC: NS [1/85] L	NS [1/85] L		NS [1/101] L	NS [1/85] L
Interferon alfa-2b vs. placebo	Loss: NS [3/166] M NS* [4/247] L SC: NS* [2/82] L	Loss: 0.55 (0.29; 0.81) [1/40] L *2.52 (1.55; 4.10)* 0.28 (0.07; 0.50)* [3/351] M	0.45 (0.22; 0.68) [1/34] L 0.44 (0.27; 0.60)* [3/168] L	Total scores: NS* [1/40] L HAI scores:0.24 (0.00; 0.48) [1/72] L	0.31 (0.17; 0.44)* [2/131] M	Relapse: NS* [5/378] H

Table 5. Absolute risk difference in tested nonclinical outcomes after antiviral drugs for chronic hepatitis B in adults (continued)

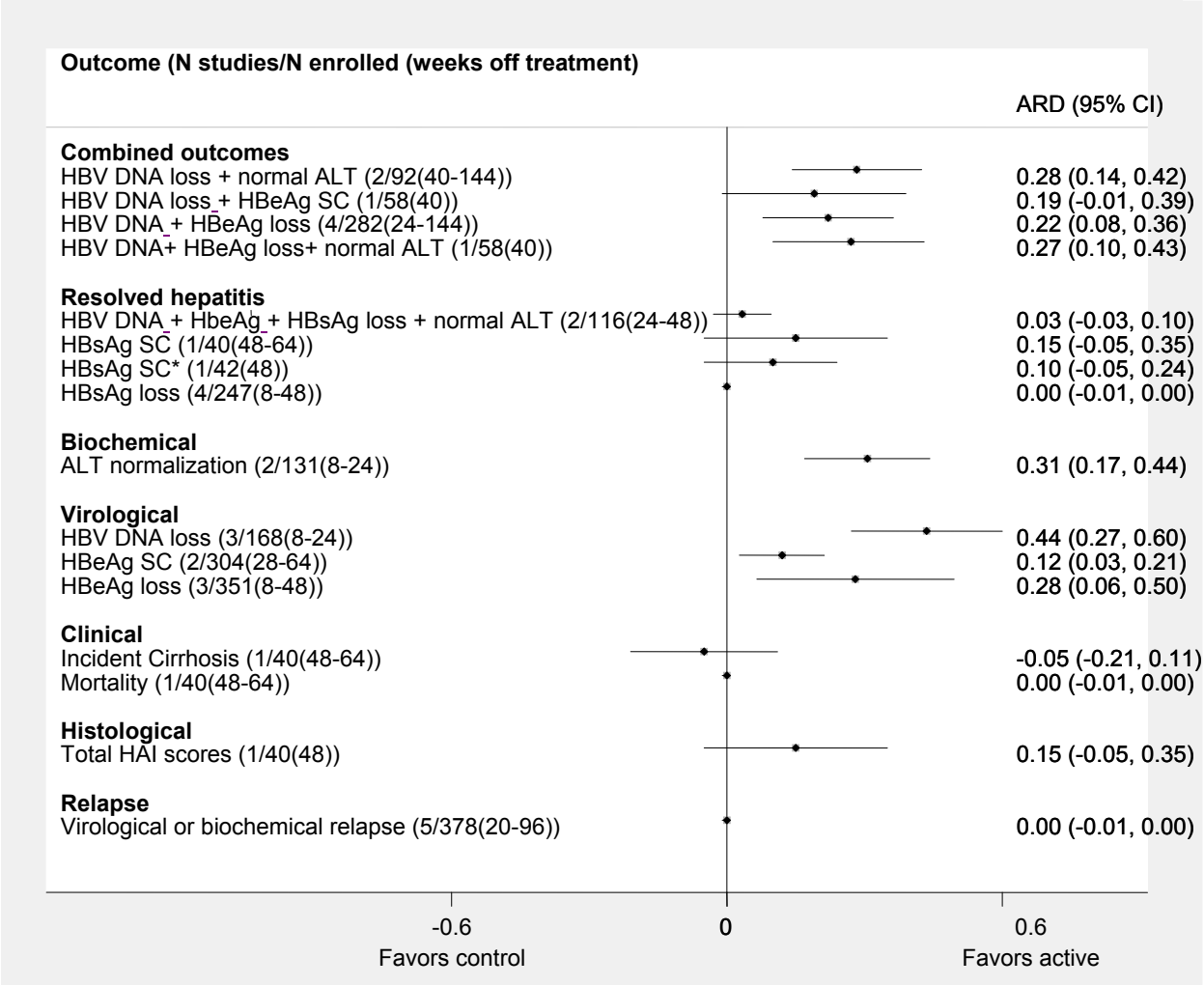
Comparison	HBsAg [RCTs/Patients]	HBeAg [RCTs/Patients]	HBV DNA Clearance [RCTs/Patients]	Histology Improved [RCTs/Patients]	ALT Normal [RCTs/Patients]	Relapse/Mutation [RCTs/Patients]
		SC:NS [1/40] L 0.12 (0.03; 0.21) * [2/304] M				
Interferon alfa-2b+lamivudine vs. placebo	Loss: 0.06 (0.00; 0.13) [1/119] L NS* [1/119] L	Loss: NS [1/118] L NS* [2/450] M SC: NS [1/119] L NS* [2/450] L	0.48 (0.33; 0.63) [1/119] L NS* [1/119] L	HAI scores NS [1/119] L	NS [1/119] L	YMDD mutation NS [1/118] L
Interferon alfa-2b+ corticosteroid vs. no treatment	Loss: 0.11 (0.02; 0.20) [2/103] M		0.25 (0.04; 0.46) [1/34] L NS* [2/121] M		0.25 (0.06; 0.43)* [1/87] L	Relapse NS* [1/87] L
Interferon alfa-2b vs. LAM		Loss: NS [1/151] L NS* [2/625] M SC: NS[1/151] L NS* [3/776] M	NS [1/76] L NS* [1/151] L	Knodell scores: NS* [1/151] L	NS [1/151] L NS* [2/151] L	YMDD mutation -0.23 (-0.33; -0.14)* [1/151] L
Interferon Alfa 2b+ LAM vs. interferon alfa-2b		Loss: NS [1/144] L NS* [2/347] M SC: NS [1/144] L NS* [3/482] L	NS [1/144] L NS* [2/278] L	HAI scores 0.54 (0.28; 0.79) [1/48] L Knodell scores NS* [1/144] L	NS [1/144] L NS* [2/192] L	YMDD mutation NS* [1/144] L
Interferon alfa-2b+ LAM vs. LAM	Loss: NS [2/262] L NS* [3/495] L	Loss: NS [3/414] M NS* [5/1167] M SC: NS [4/565] H NS* [3/490] M	NS [7/786] H NS* [4/365] M	HAI scores NS [3/327] M necroinflammation NS [2/389] L Knodell scores NS* [1/157] L	NS [5/626] M NS* [6/751] M	Relapse: NS [4/326] H NS* [2/158] L YMDD mutation: -0.18 (-0.35; -0.01) [6/721] M *0.42 (0.16; 1.09) M* -0.23 (-0.32; -0.14)* [1/157] L
Interferon alfa-2b+ corticosteroid vs. IFN alfa-2b	Loss: NS [2/125] M NS* [3/141] L	Loss: NS [2/77] L NS* [3/122] L SC: NS* [2/85] L	NS [2/77] L NS* [6/322] H		NS* [3/170] M	Relapse: NS* [2/141] L
Peginterferon alfa-2a vs. LAM		Loss: 0.08 (0.01; 0.16) M 0.13 (0.05; 0.20)* [1/543] M SC: NS [1/543] L 0.13 (0.06; 0.20) [1/814]* M	-0.15 (-0.22; -0.07) [1/543] M 0.09 (0.04; 0.14) [1/543]* L	Necroinflammation 0.12 (0.02; 0.22) [1/552]* L Fibrosis: NS* [1/552] L HAI: NS [2/1366]* M	-0.29 (-0.42; -0.17) [2/905] *0.57 (0.46; 0.70)* [2/905] M 0.13 (0.07; 0.20)* [2/905] H	YMDD mutation -0.25 (-0.31; -0.20) [1/543] L
Peginterferon alfa-2a+LAM vs. LAM		Loss: NS [1/543] L 0.07 (0.00; 0.15)* [1/543] M SC: NS [1/543] L 0.08 (0.01; 0.15) *[1/814] L	0.29 (0.21; 0.37) [1/543] M 0.09 (0.04; 0.13) [1/543]* L	Total scores: NS [2/1366]* H	-0.20 (-0.29; -0.10) [2/905] H 0.13 (0.06; 0.19) [2/905]* H	YMDD mutation -0.22 (-0.28; -0.16) [1/543] L

Table 5. Absolute risk difference in tested nonclinical outcomes after antiviral drugs for chronic hepatitis B in adults (continued)

Comparison	HBsAg [RCTs/Patients]	HBeAg [RCTs/Patients]	HBV DNA Clearance [RCTs/Patients]	Histology Improved [RCTs/Patients]	ALT Normal [RCTs/Patients]	Relapse/Mutation [RCTs/Patients]
Peginterferon alfa-2a+LAM vs. peginterferon alfa-2a		Loss: NS [1/542] L NS [1/542]* M SC: NS [1/542] L NS [1/814]* L	0.44 (0.36; 0.51) [1/542] M NS[1/542]* L	Total scores: NS [1/96]* L	NS [1/542] L NS [1/542]* L	YMDD mutation: 0.03 (0.01; 0.06) [1/542] L
Peginterferon alfa-2b vs. interferon alfa-2b	SC: NS* [1/230]	Loss: 0.10 (0.00; 0.21) [1/230]* L			NS [1/230]* L	
Peginterferon alfa-2b+LAM vs. LAM	Negative HBVDNA+ HBsAg SC 0.32 (0.14; 0.50) [1/100]	Loss: 0.34 (0.16; 0.52) [1/100] M SC: 0.32 (0.14; 0.50) [1/100] L NS: [1/100]* L	NS [1/100] L NS [1/100]* L	HAI scores NS: [1/100] L	NS [1/100] L	NS: [1/100]* L YMDD mutation: NS [1/100] L
Peginterferon alfa-2b+LAM vs. peginterferon alfa-2b	Loss: NS [1/307]	Loss: 0.12 (0.01; 0.22) [1/307] M NS [2/614]* M SC: NS [1/307]L NS: [1/307]* L		fibrosis scores: NS [1/307]* L necroinflammation scores: NS [1/307] L	0.14 (0.03; 0.24) [1/307] L NS [1/307]* L	YMDD mutation: 0.09 (0.04; 0.14) [1/307] L

SC = seroconversion; NS = not significant; italic = relative risk; * = outcomes off treatments; LAM = lamivudine
Level of evidence: L = low; M = moderate; H = high

Figure 4. Off treatment effectiveness of monotherapy with interferon compared to no treatment (results from individual studies and pooled analysis with random effects model)



* compared to placebo

Figure 5. Off treatment effectiveness of combined therapy with interferon compared to placebo (results from individual studies and pooled analysis with random effects model)

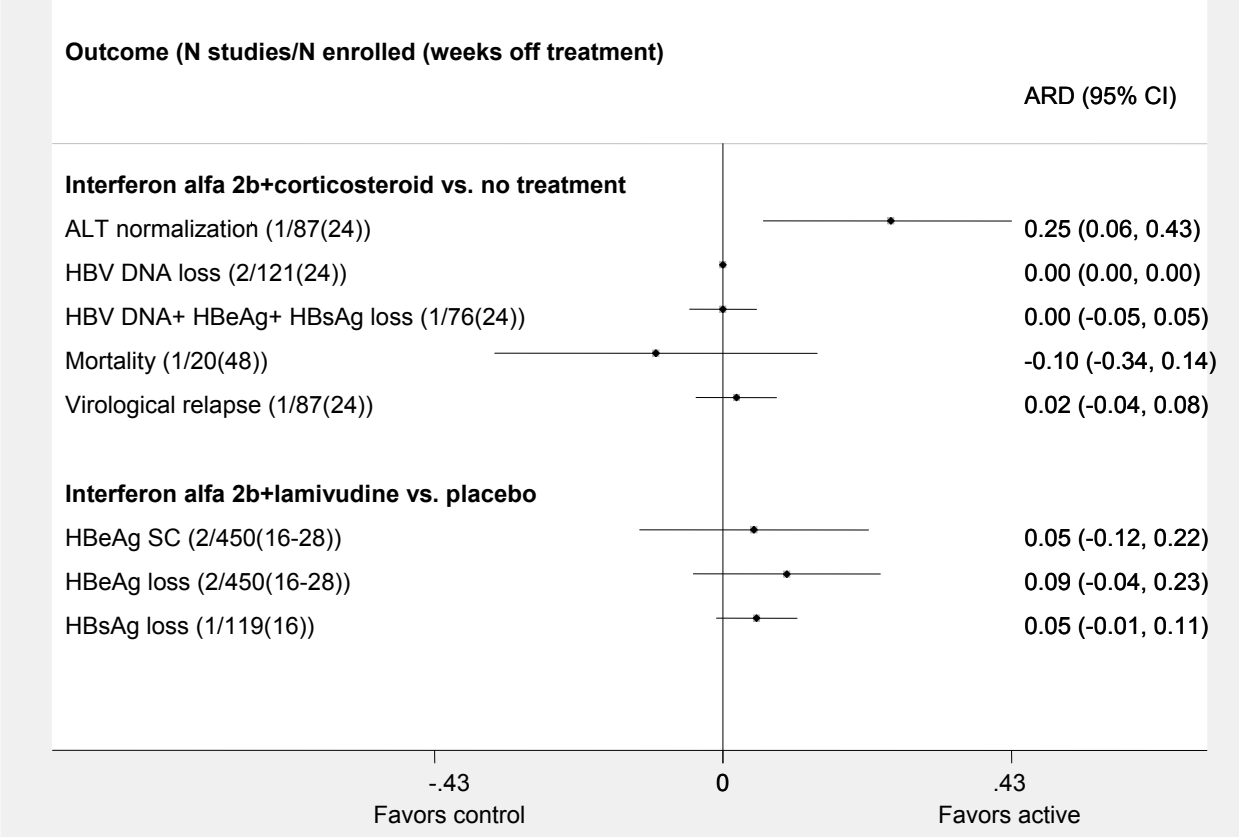


Figure 6. Off treatment effectiveness of reverse transcriptase inhibitors compared to placebo (results from individual studies and pooled analysis with random effects model)

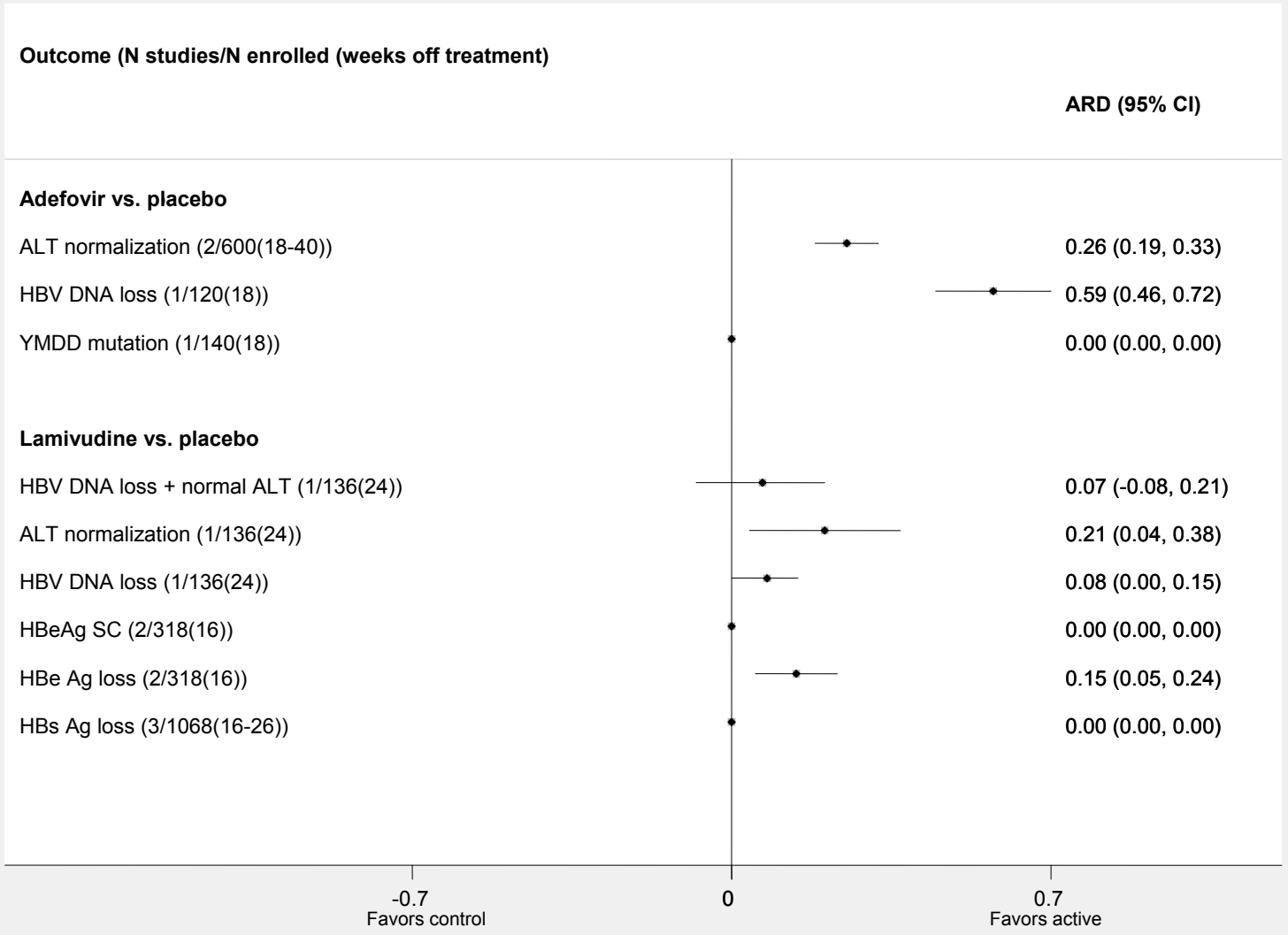


Figure 7. Off treatment comparative effectiveness of monotherapy with interferon or reverse transcriptase inhibitors (results from individual studies and pooled analysis with random effects model)

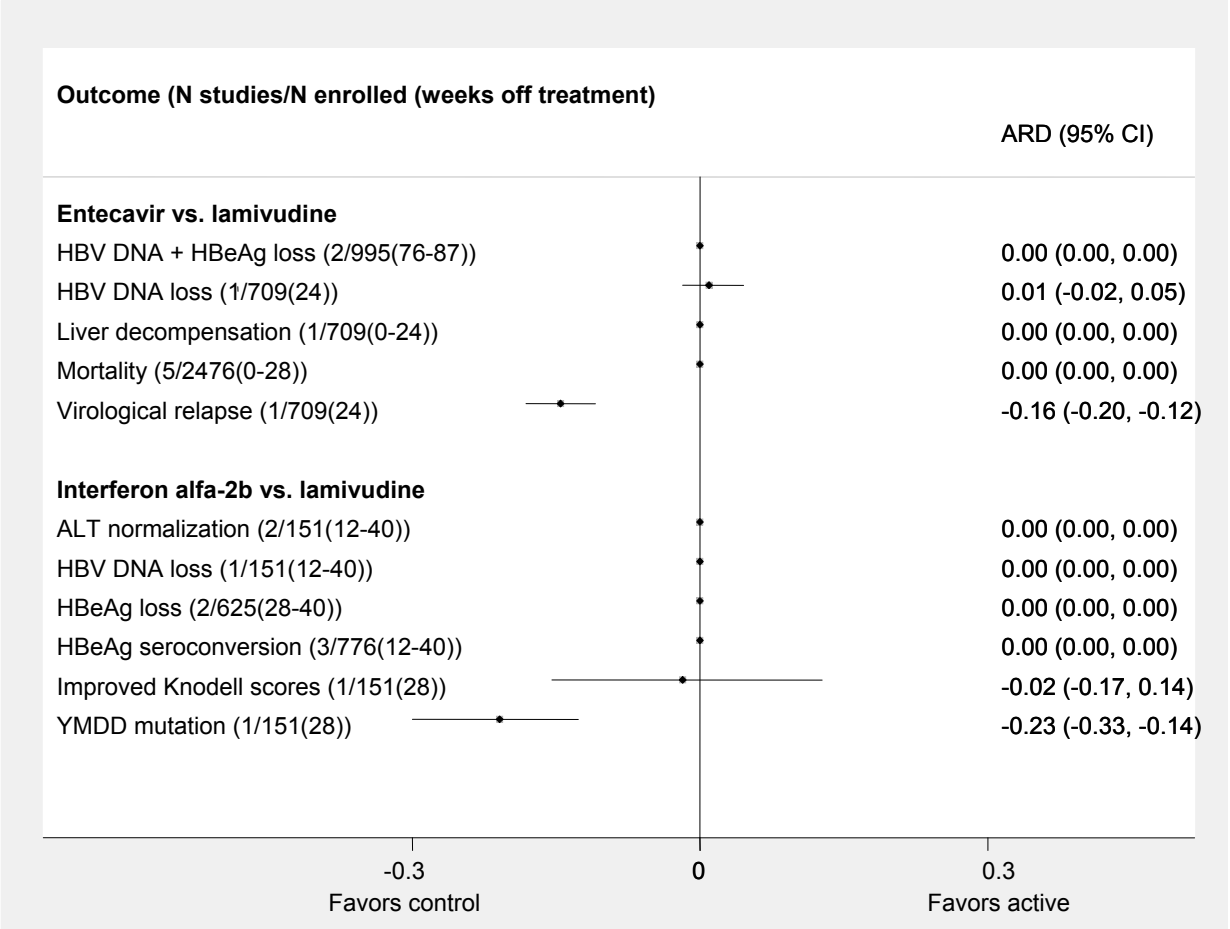


Figure 8. Off treatment comparative effectiveness of combined with interferon or reverse transcriptase inhibitors (results from individual studies and pooled analysis with random effects model)

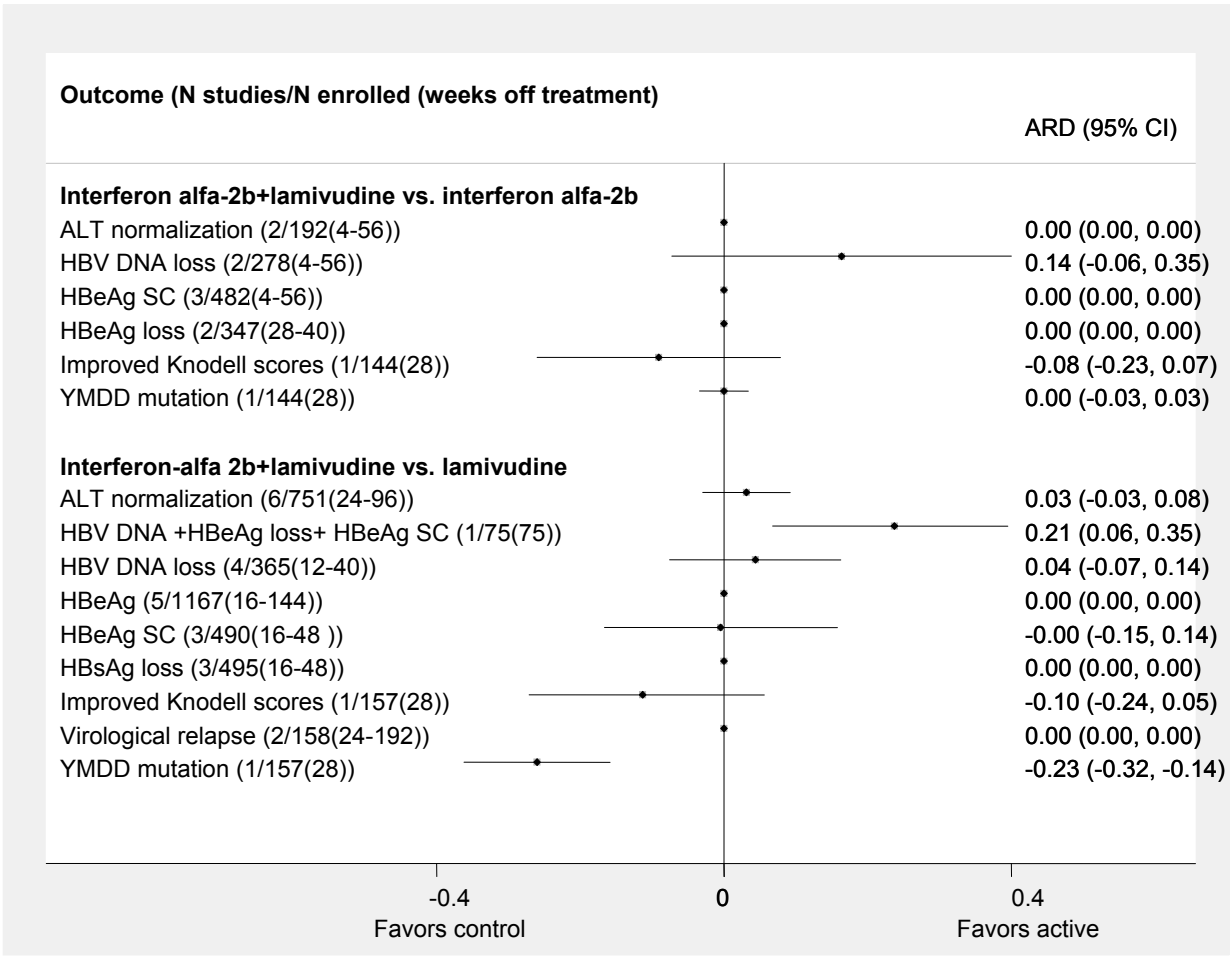


Figure 9. Off treatment comparative effectiveness of monotherapy with pegylated interferon alfa-2a compared to lamivudine (results from individual studies and pooled analysis)

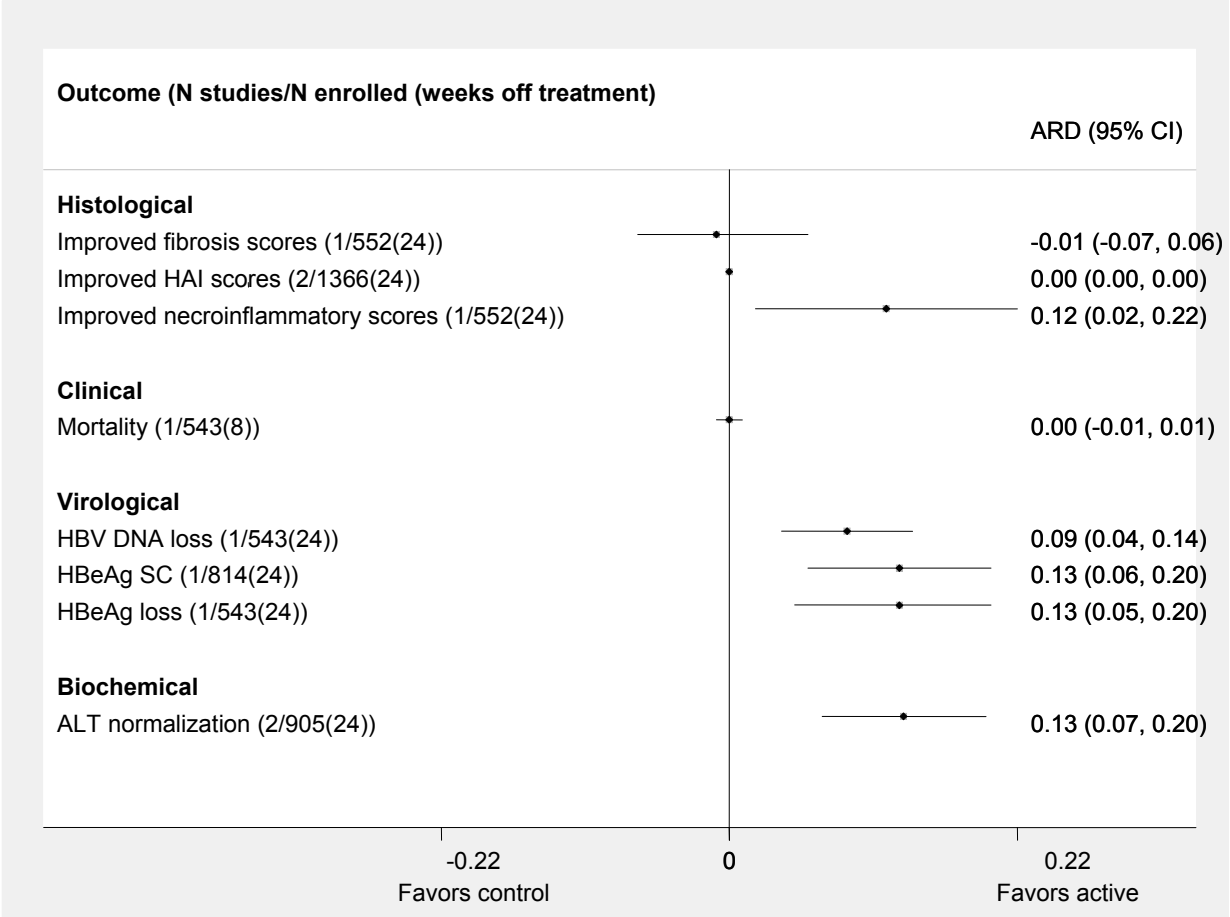


Figure 10. Off treatment comparative effectiveness of combined therapy with pegylated interferon alfa-2a and lamivudine (results from individual studies and pooled analysis)

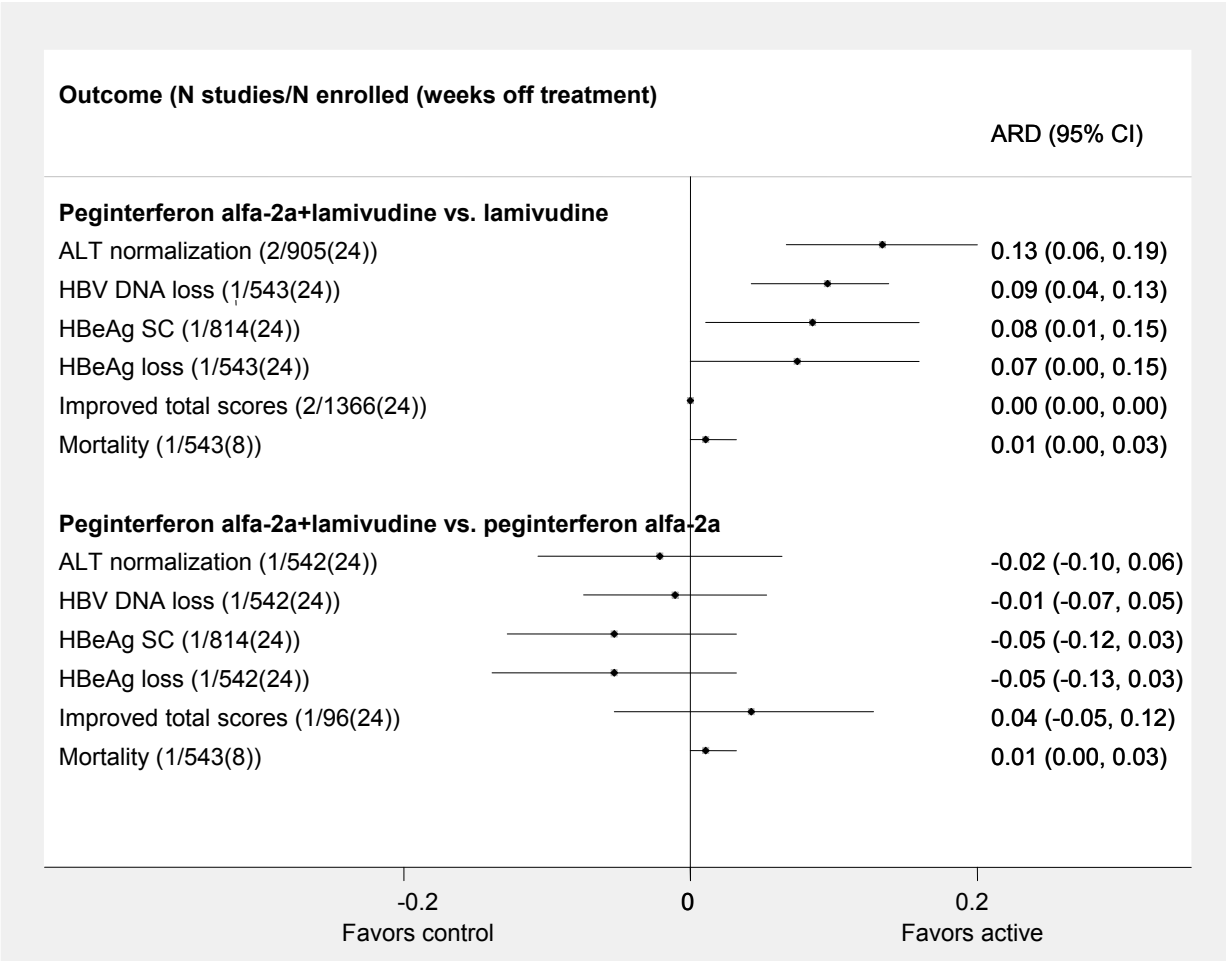


Table 6. Subjects withdrawing from treatment and experiencing adverse events from randomized controlled trials

A. Adefovir monotherapy

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
vs. placebo[95,110]						
Subjects not completing study / treatment	1	26 / 345 (7.5) (10 and 30 mg)	13 / 170 (7.6)	0 [-5 to 5]	0.99 [0.52 to 1.87]	48 weeks
Any adverse event	1	94 / 123 (76.4)	45 / 61 (73.7)	3 [-11 to 16]	1.04 [0.87 to1.24]	
Severe adverse event (grade III or IV)	2	24 / 294 (8.2)	19 / 228 (8.3)	0 [-6 to 6]	0.95 [0.45 to 2.01]	
AE leading to discontinuation of study drug	2	4 / 294 (1.4)	1 / 228 (<1)	1 [-1 to 3]	2.34 [0.37 to 14.75]	
vs. lamivudine, subjects with lamivudine resistance[119]						
Subjects not completing study / treatment	1	1 / 20 (5)	1 / 19 (5.3)	0 [-14 to 14]	0.95 [0.06 to 14.13]	48 weeks
Any adverse event	1	18 / 19 (94.7)	19 / 19 (100)	-5 [-19 to 8]	0.95 [0.82 to 1.09]	
Serious adverse event	1	3 / 19 (15.8)	1 / 19 (5.3)	11 [-9 to 30]	3.0 [0.34 to 26.3]	
AE leading to discontinuation of study drug	1	0 / 19	0 / 19	0	-	
vs. telbivudine[120]						
Subjects not completing study / treatment	1	2 / 45 (4.4)	2 / 45 (4.4)	0 [-9 to 9]	1.00 [0.13 to 7.43]	52 weeks
Any adverse event	1	27 / 44 (61.4)	34 / 45 (75.6)	-14 [-33 to 5]	0.81 [0.61 to 1.08]	
AE leading to discontinuation of study drug	1	0 / 44	0 / 45	0	-	

B. Lamivudine monotherapy

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
vs. placebo[136 ,139,145]						
Subjects not completing study / treatment	2	33 / 374 (8.8)	16 / 120 (13.3)	-1 [-7 to 4]	0.87 [0.51 to 1.49]	52-104 weeks
Any adverse event	1	224 / 285 (78.6)	56 / 73 (76.7)	2 [-9 to 13]	1.02 [0.89 to 1.18]	52 weeks
Serious adverse event	2	18 / 374 (4.8)	6 / 120 (5)	2 [-1 to 4]	1.24 [0.53 to 2.93]	52-104 weeks
vs. placebo, subjects refractory interferon therapy[67]						
Subjects not completing study / treatment	1	9 / 119 (7.6)	10 / 56 (17.9)	-10 [-21 to 1]	0.42 [0.18 to 0.98]	68 weeks
AE leading to discontinuation of study drug	1	1 / 119 (<1)	4 / 56 (7.1)	-6 [-13 to 1]	0.12 [0.01 to 1.03]	

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
vs. placebo, subjects with advanced liver disease[132]						
Any adverse event	1	335 / 436 (76.8)	178 / 215 (82.8)	-6 [-12 to 0]	0.93 [0.86 to 1.01]	32 months (median)
Serious adverse event	1	54 / 436 (12.4)	38 / 215 (17.7)	-5 [-11 to 1]	0.70 [0.48 to 1.03]	
vs. placebo, HBV antigen-negative/ HBV DNA-positive (precore mutant) patients[142]						
Any adverse event	1	40 / 65 (61.5)	28 / 60 (46.7)	15 [-2 to 32]	1.32 [0.95 to 1.84]	26 weeks
vs. pegylated interferon-α-2a monotherapy[95,96]						
Subjects not completing treatment / study	2	71 / 456 (15.6)	45 / 453 (9.9)	6 [1 to 10]	1.57 [1.10 to 2.22]	72 weeks
Any adverse event	2	238 / 453 (52.5)	395 / 448 (88.2)	-36 [-43 to -29]	0.59 [0.51 to 0.69]	
Serious adverse event	2	10 / 453 (2.2)	21 / 448 (4.7)	-2 [-5 to 0]	0.47 [0.22 to 0.99]	
AE leading to discontinuation of study drug	2	2 / 453 (<1)	21 / 448 (4.7)	-5 [-10 to 1]	0.13 [0.20 to 0.90]	
Dose modification due to AE	2	0 / 453	33 / 448 (7.4)	-7 [-10 to -5]	0.03 [0.00 to 0.22]	
vs. combined pegylated Interferon-α-2a and Lamivudine[95,96]						
Subjects not completing treatment / study	2	71 / 456* (15.6)	49 / 457* (10.7)	5 [1 to 9]	1.45 [1.03 to 2.03]	72 weeks
Any adverse event	2	238 / 453 (52.5)	395 / 450 (87.8)	-35 [-41 to -29]	0.60 [0.52 to 0.68]	
Serious adverse event	2	10 / 453 (2.2)	28 / 450 (6.2)	-4 [-7 to -1]	0.36 [0.18 to 0.73]	
AE leading to discontinuation of study drug	2	2 / 453 (<1)	19 / 450 (4.2)	-4 [-6 to -2]	0.13 [0.03 to 0.47]	
Dose modification due to AE	2	0 / 453	48 / 450 (10.7)	-10 [-15 to -6]	0.02 [0.00 to 0.15]	

C. Telbivudine monotherapy

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
vs. adefovir (see above)						
vs. lamivudine, attributed to study drug (SEBIVO INSERT – 007 GLOBE)[143]						
Subjects not completing treatment / study	1	18 / 680 (2.6)	32 / 687 (4.7)	-2 [-4 to 0]	0.57 [0.32 to 1.00]	52 weeks
Any adverse event		NR	NR			
Serious adverse event	1	18 / 680 (2.6)	33 / 687 (4.8)	-2 [-4 to 0]	0.55 [0.31 to 0.97]	
AE leading to discontinuation of study drug	1	2 / 680 (<1)	5 / 687 (<1)	0 [-1 to 0]	0.40 [0.08 to 2.08]	

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
AE leading to discontinuation, possibly related to study drug	1	1 / 680 *myopathy*	1 / 687 *urticaria*	0 [0 to 0]	1.01 [0.06 to 16.12	

D. Entecavir monotherapy (acyclic guanosine derivative)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
0.5 mg dose vs. lamivudine, nucleoside-naïve subjects[121,122]						
Subjects not completing study / treatment	2	37 / 688 (5.4)	58 / 675 (8.6)	-3 [-8 to 2]	0.64 [0.33 to 1.26]	E 56-75 weeks
Any adverse event	2	552 / 679 (80.3)	545 / 668 (81.1)	0 [-6 to 6]	1.00 [0.92 to 1.08]	L 56-65 weeks
Serious adverse event	2	48 / 679 (7.1)	54 / 668 (8.1)	-1 [-4 to 2]	0.88 [0.60 to 1.27]	
AE leading to discontinuation of study drug	2	7 / 679 (1.0)	18 / 668 (2.7)	-2 [-3 to 0]	0.33 [0.06 to 1.86]	
0.5 mg dose vs. lamivudine, nucleoside-naïve subjects. Patient information sheet (Bristol Myers Squibb)						
Any Grade 2-4 adverse event	1	102 / 679 (15)	120 / 668 (18)	-3 [-7 to 1]	0.84 [0.66 to 1.06]	Through 2 years
1 mg dose vs. lamivudine in lamivudine-refractory subjects. Patient information sheet (Bristol Myers Squibb)						
Any Grade 2-4 adverse event	2	40 / 183 (21.9)	44 / 190 (23.2)	-1 [-10 to 7]	0.94 [0.87 to 1.14]	Through 2 years
vs. lamivudine in lamivudine-refractory subjects[124,125]						
Subjects not completing study / treatment (48 weeks)	2	39 / 283 (13.9)	38 / 191 (19.9)	-12 [-30 to 6]	0.54 [0.36 to 0.81]	48 weeks
AE leading to discontinuation of study drug	2	11 / 277 (4.0)	14 / 190 (7.4)	-5 [-9 to 1]	0.43 [0.12 to 1.54]	
Any adverse event	2	225 / 277 (81.2)	155 / 190 (81.6)	0 [-12 to 11]	0.99 [0.87 to 1.14]	
Serious adverse event	2	22 / 277 (7.9)	14 / 190 (7.4)	1 [-4 to 6]	1.18 [0.62 to 2.27]	

E. Pegylated interferon-α-2a monotherapy (See lamivudine)

F. Combination pegylated interferon-α-2a and lamivudine therapy

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
vs. lamivudine (see above)[95,96]						
vs. pegylated interferon-α-2a monotherapy[95,96]						
Subjects not completing treatment / study	2	49 / 457 (10.7)	45 / 453 (9.9)	1 [-4 to 5]	1.08 [0.71 to 1.66]	72 weeks
Any adverse event	2	395 / 450 (87.8)	395 / 448 (88.2)	0 [-58 to 4]	1.00 [0.95 to 1.05]	
Serious adverse event	2	28 / 450 (6.2)	21 / 448 (4.7)	2 [-1 to 4]	1.33 [0.77 to 2.30]	
AE leading to	2	19 / 450	21 / 448	-1	0.90	

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
discontinuation of study drug		(4.2)	(4.7)	[-6 to 4]	[0.33 to 2.48]	

G. Combination pegylated interferon-α-2b and lamivudine therapy (interferon)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
vs. pegylated interferon-α-2b monotherapy[99]						
Subjects not completing treatment / study	1	38 / 152 (25)	37 / 155 (23.9)	1 [-8 to 11]	1.05 [0.71 to 1.55]	78 weeks
Serious adverse event	1	32 total, 17 probably related to therapy				
AE leading to discontinuation of study drug	1	12 / 152 (7.9)	11 / 155 (7.1)	1 [-5 to 7]	1.11 [0.51 to 2.44]	

I. Pegylated interferon-α-2b vs. interferon-α-2b[109]

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Subjects not completing treatment / study	1	7 / 115 (6.1)	20 / 115 (17.4)	-11 [-19 to -3]	0.35 [0.15 to 0.80]	72 weeks
AE leading to discontinuation of study drug	1	0 / 115	4 / 115 (3.5)	-3 [-7 to 0]	0.11 [0.01 to 2.04]	
Any adverse event	75% of patients in each treatment group experienced various clinical forms of drug-related adverse effects.					

K. Interferon-α-2b monotherapy (Interferon)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Prolonged (32 weeks) vs. standard (16 weeks) duration[61]						
Dose reduction due to AE	11.5% (7/61) in the prolonged group. Not reported in standard group.					
AE leading to discontinuation of study drug	4.9% (3/61) in the prolonged group. Not reported in standard group.					
Phase A – all subjects prior to randomization	Dose modification due to AE: 16/162 (10%)					
[91] IFN (n=21) vs. no treatment (n=21). Study duration was 104 weeks. 5/21 (23.8%) IFN subjects withdrew from study. Dose in reduction in two subjects.						
vs. no treatment						
[90] 6 months (n=19) vs. 12 months (n=19). "Treatment was well tolerated by all subjects who finished the study, and no dose modification was needed."						
[83] IFN (n=20) vs. no treatment (n=20). Study duration was 68 weeks. 4 IFN and 5 NC subjects did not complete study.						
[82] IFN (n=30) vs. no treatment (n=28). Study duration was 10 months. One subject with a pre-existing depressive state converted to overt depression and was taken off treatment.						
[81] IFN (n=25) vs. no treatment (n=25). Study duration was 52 weeks. IFN therapy well tolerated, no serious AE observed.						

Consensus Conference Question 3
Which Persons With Hepatitis B Should be Treated?

EPC Question 3a. Are there differences in efficacy/effectiveness of treatments for treatment naïve versus drug-resistant patients, HBeAg-positive versus HBeAg-negative patients, or for other subpopulations (as defined previously)?

We reviewed 15 studies that examined differences in treatment effects among patient subpopulations (as noted above) at the end of drug administration[61,64,75,93,105,107,124,130,132,133,135,140,141,143,145] and at followup off active drugs (n=23)[61-65,72,73,75,84,85,90,93,96,97,99,100,102,104,106,108,109,114,126] (Appendix E Table 9).

Clinical outcomes. Information is very limited because none of the studies reported mortality, liver related mortality, or hepatocellular carcinoma. Reported subgroup analyses appear to be exploratory in nature, varied in their definitions of outcomes and predictors and lack confirmatory findings. The French Multicenter Group[85] conducted subgroup analysis of incident cirrhosis after 24 weeks of interferon alfa-2 with steroid administration among patients with baseline ALT more than three times the upper limit of normal and did not find significant protective effects of combined therapy compared to interferon monotherapy (RR 0.40, 95 percent CI 0.04; 4.19). One small Korean trial[141] analyzed odds ratio of hepatic decompensation defined as an increase in Child-Turcotte-Pugh score of two or more points in patients with lamivudine-resistant mutants and found that gender, baseline HBeAg-positive status, and elevated ALT or viral load were not associated with progressive hepatic functional deterioration. However, patients with baseline platelet count less than versus greater than 65,000/μl experienced hepatic decompensation less often (RR 0.98, 95 percent CI 0.97; 0.99). Investigators for the Cirrhosis Asian Lamivudine Multicentre Study Group conducted subgroup analysis of overall disease progression, defined by hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease in males and females treated with lamivudine or placebo and found significant protective effects of lamivudine in both genders (RR in males 0.53, 95 percent CI 0.33; 0.84 and in females 0.12, 95 percent CI 0.03; 0.58).[132]

In conclusion, little evidence is available regarding effectiveness of antiviral agents on clinical outcomes, especially to determine which groups should be treated or whether clinical outcomes vary according to key patient/disease characteristics. Clinical outcomes in Asian patients treated with lamivudine compared to placebo did not vary according to gender.

The vast majority of the studies described nonclinical outcomes among patient subgroups with different baseline liver enzymes, virological, or histological status. Even in these situations, studies did not provide power calculations and did not analyze baseline similarities in such subgroups. Analyses were exploratory in nature, lacked justification for subpopulation thresholds utilized, often were inconsistent in findings or thresholds employed, combined several different outcomes into a global effectiveness measure, and may have been selectively reported. Therefore, an accurate assessment and clear/concise summary is difficult (insufficient evidence).

Age (two studies, two antiviral agents, lamivudine and peginterferon, used as monotherapy). Limited evidence from two studies suggested that increased patient age was associated with lower sustained response to pegylated interferon alfa-2a or lamivudine as defined by HBV DNA clearance and ALT normalization. Younger patients had higher rates of HBV DNA clearance and ALT normalization (adjusted RR 1.26, 95 percent CI 1.00; 1.50) per 10 year decrease in age after 48 weeks of treatment and 24 weeks of treatment-free followup with peginterferon alfa-2a or lamivudine.[93] Sustained response to pegylated interferon alfa-2a was lower (adjusted RR 0.39, 95 percent CI 0.16; 0.92) among patients above 25 years compared to those below.[109]

In conclusion, low levels of evidence suggested that decreased patient age was associated with enhanced treatment efficacy as measured by HBV DNA clearance and ALT normalization. No evidence was available for clinical outcomes.

Body weight (one study, Peginterferon Alfa-2a HBeAg-Negative Chronic Hepatitis B Study Group, two antiviral agents used as monotherapy). Patient body weight was not associated with sustained HBV DNA loss and ALT normalization after 48 weeks of treatment and 24 weeks of treatment-free followup with pegylated interferon alfa or lamivudine (adjusted RR 1.03, 95 percent CI 0.81; 1.3 per 10 kg increase in body weight).[93]

In conclusion, low levels of evidence suggested that baseline body weight is not associated with treatment efficacy as measured by HBV DNA loss and ALT normalization. No evidence was available for clinical outcomes.

Duration of hepatitis (one study- Lamivudine Italian Study Group Investigators, two antiviral agents used as combination therapy). Sustained virologic response at 48 weeks off therapy (suppression of serum levels of HBeAg and HBV DNA) to interferon alfa-2b combined with lamivudine was greater in those with an estimated duration of hepatitis of 10 years or less after adjustment for patient gender and age (adjusted OR 2.55, 95 percent CI 1.26; 19).[63]

In conclusion, low levels of evidence suggested that patients with longer duration of hepatitis responded to lamivudine therapy 2.5 times less frequent compared to those with shorter duration of the disease. No evidence was available for clinical outcomes or other therapies.

Gender (five studies, three antiviral agents, peginterferon, interferon, and lamivudine, used as monotherapy). Patient gender demonstrated inconsistent associations in five studies that evaluated this factor.[72,93,109,132,141] One study reported that adjusted odds ratios of sustained combined response (ALT normalization and HBV DNA level <20,000 copies/ml) 24 weeks off peginterferon alfa-2a or lamivudine therapy was greater among women compared to men (OR 1.93, 95 percent CI 1.1; 3.4).[93] The association was not significant at year 1 off treatment (OR males versus females 0.68, 95 percent CI 0.34; 1.37).[93] Multivariate adjusted odds ratio of sustained 24 week off therapy combined response (HBeAg-negative, HBV DNA <5 log 10 copies/mL, and normal ALT level) to peginterferon alfa-2b or interferon alfa-2b was not significant (OR 0.59, 95 percent CI 0.22; 01.6) in males compared to females.[109]

In conclusion, low levels of evidence suggested that disease progression or treatment induced sustained ALT normalization and HBV DNA clearance did not vary by gender.

Baseline histology (four studies, three antiviral agents, peginterferon, interferon, and lamivudine, used as mono or combination therapy). Lamivudine administration compared to placebo reduced overall disease progression, defined as an increase of at least two points in the Child-Pugh score in patients with baseline Child-Pugh score 5-6 or baseline Ishak fibrosis

score = 6 but not in those with baseline Child-Pugh score >7 and Ishak fibrosis score <4 or 5[132] (Appendix E Table 10). Lamivudine compared to placebo increased HBeAg clearance among patients with baseline HAI scores >5 but failed in those with pretreatment HAI Score 0-4.[64] HBeAg loss was 117 percent higher per unit increase in baseline HAI score (adjusted RR 1.17, 95 percent CI 1.10; 1.24).[64] Lamivudine improved histology compared to placebo among patients with moderate or severe hepatitis (RR 2.30, 95 percent CI 1.39; 3.81) but failed in those with mild hepatitis.[145]

Interferon alfa-2b increased maintained HBeAg loss off treatment compared to placebo among patients with pretreatment HAI score 5-9 (RR 5.76, 95 percent CI 1.48; 22.42) but failed in patients with pretreatment HAI score 0-4 or >10.[64] The same trial reported that interferon alfa-2b combined with lamivudine compared to placebo increased sustained HBeAg clearance in the same subpopulation with pretreatment HAI score 5-9 (RR 5.32, 95 percent CI 1.51; 18.72) with no effects in those with pretreatment HAI score 0-4 (RR 3.39, 95 percent CI 0.89; 12.87) or >10 (RR 1.79, 95 percent CI 0.89; 3.59).[64] Off treatment virologic response to interferon alfa-2b combined with lamivudine increased in those with a baseline HAI Knodell inflammation score of seven or more, independent of gender and age (adjusted RR 2.91, 95 percent CI 1.04; 8.22).[63] Baseline fibrosis scores were not associated with better sustained response to this treatment.[63] Presence of steatosis did not modify the effect of peginterferon alfa-2a combined with lamivudine on sustained response defined as HBV DNA disappearance and ALT normalization in both HBeAg-positive and negative patients;[97] however, the adjusted rates of sustained response were greater per increase in baseline Knodell HAI (adjusted OR 14.97, 95 percent CI 2.43; 92.28).[97]

In conclusion, there was a low level of evidence that treatment induced followup histology, HBeAg loss or DNA disappearance and ALT normalization varies by baseline histology severity. There was no evidence for clinical outcomes.

Baseline viral load (eight studies, three antiviral agents, peginterferon, interferon, and lamivudine, as mono or combination therapy) (Appendix E Tables 9 and 10). Lamivudine was more effective in patients with higher baseline HBV DNA levels. HBV DNA loss increased among patients with baseline HBV DNA >1.6pg/ml (RR 6.41, 95 percent CI 3.92; 10.47),[140] and disease progression (defined as increase of at least two points in the Child-Pugh score) was lower in patients with baseline HBV DNA >100 meq/ml;[132] however, dose response was not significant (HBeAg loss did not differ per 10-unit increase baseline HBV-DNA level).[64]

At followup off the treatment, interferon alfa-2b, 5MU/day compared to no treatment increased HBV DNA and HBeAg loss among patients with baseline HBV DNA 2-99 pg/ml (RR 5.24, 95 percent CI 1.22; 22.50) but failed among those with baseline HBV DNA 100-200 pg/ml or >200 pg/ml[84] without a significant HBV DNA unit dose response association (RR 1.87, 95 percent CI 0.59; 5.87 per one unit increase in HBV DNA).[61] Interferon alfa 2b, 10 MU three times per week versus no antiviral treatment increased sustained rates of HBeAg loss among patients with baseline HBV DNA <10pg/ml (RR 3.18, 95 percent CI 1.25; 8.05) but failed in those with higher viral load HBV DNA >10pg/ml.[61] Interferon alfa-2b with steroid pretreatment increased sustained off treatment rates of HBV and HBeAg loss among patients with baseline HBV DNA 2-99 pg/ml (RR 5.38, 95 percent CI 1.26; 22.84) but failed in those with elevated baseline viral load (HBV DNA >100 pg/ml).[84] While monotherapy with interferon alfa-2b was

more effective in patients with lower compared to elevated baseline HBV DNA, combined administration of interferon alfa-2b with lamivudine resulted in greater sustained HBV DNA loss and HBeAg seroconversion in patients with elevated baseline HBV DNA $>10^7$ copies/mL.[75] Peginterferon alfa-2a resulted in greater sustained response compared to lamivudine in patients with baseline HBV DNA range of 25-75 percentile[93,96] with random differences among those below 25 percent or above the 75th percentile. Sustained combined response was increased by one log 10 unit (copies/ml) decrease in baseline HBV DNA (adjusted OR 1.28, 95 percent CI 1.10; 1.40).[93] Baseline mean viral load (copy/mL) was not associated with sustained response to the combined therapy with peginterferon alfa-2a plus lamivudine versus lamivudine alone.[97]

In conclusion, there was a low level of evidence that treatment induced HBeAg loss, DNA normalization, or histology varies with baseline viral load. There was no evidence for clinical outcomes.

Baseline HBeAg status (Appendix E Tables 9 and 10).

Evidence from trials that combined patients with HBeAg-negative and positive baseline status. Lamivudine at the end of 130 week administration decreased disease progression defined by hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease compared to placebo among patients HBeAg-positive at baseline (RR 0.30, 95 percent CI 0.16; 0.55).[132] There were no significant effects among HBeAg-negative patients (RR 0.72, 95 percent CI 0.36; 1.43).[132] Entecavir in a dose of 1mg/day compared to lamivudine resulted in higher rates of undetectable HBV DNA and normal ALT level among patients with HBeAg-negative baseline status (RR 18.38, 95 percent CI 1.18; 285.96) with random differences in HBeAg-positive patients.[124] Telbivudine compared to lamivudine reduced the rates of detectable HBV DNA (RR 0.67, 95 percent CI 0.54; 0.82) and improved necroinflammatory scores, with no worsening in the Knodell fibrosis score (RR 1.15, 95 percent CI 1.03; 1.27) among patients with HBeAg-positive baseline status with random differences in HBeAg-negative patients.[143] Telbivudine compared to lamivudine for 52 weeks in Chinese patients with compensated hepatitis B resulted in better outcomes in HBeAg-positive patients with no difference in small subsample of HBeAg-negative patients. [57]

Evidence from trials that included exclusively patients with HBeAg-negative status (11 studies; four antiviral agents used as mono or combination therapy). We reviewed the drug effects reported in the RCTs that enrolled all HBeAg-negative patients,[10,71,74,76,79,81,91,93,95,110,111] including the Peginterferon Alfa-2a HBeAg-Negative Chronic Hepatitis B Study Group[93,95] and the Adefovir Dipivoxil 438 Study Group[10,110,111] (Table 7). Adefovir improved biochemical, virological, and histological outcomes in HBeAg-negative patients at the end of drug administration and at followup off the treatment without development of genetic mutations.[10,110] Interferon alfa-2b combined with lamivudine was not more effective compared to lamivudine alone to improve combined virologcial with biochemical[71]or virological[71,74,76] outcomes in HBeAg-negative patients but lowered the rates of relapse defined as reappearance of detectable serum HBV DNA by polymerase chain reaction (PCR) after an initial virologic response[74] and genetic viral mutations.[76] Interferon alfa-2b compared to no antiviral treatments increased sustained HBV DNA clearance and ALT normalization in a large RCT[81] with random differences

in a small study;[91] however, it failed to increase HBsAg loss and did not improve histological scores.[91] Peginterferon alfa-2a compared to lamivudine improved sustained biochemical and virological outcomes and necroinflammatory scores but failed to improve fibrosis scores.[95] Peginterferon alfa-2a combined with lamivudine compared to lamivudine improved sustained biochemical and virological outcomes with no differences on liver histology.[95]

In conclusion, low level of evidence suggested that lamivudine monotherapy decreased disease progression among patients HBeAg-positive at baseline but not in HBeAg-negative patients. Telbivudine increased viral clearance and improved histology compared to lamivudine in HBeAg-positive but not in HBeAg-negative patients. Entecavir was more effective compared to lamivudine in HBeAg-negative patients to increase viral clearance and ALT normalization. Patients without HBeAg at baseline experienced improvement in biochemical, virological, and histological outcomes after adefovir therapy and pegylated interferon alfa-2a monotherapy or combination with lamivudine. There was no evidence for clinical outcomes.

Baseline liver function (ten studies, three medications, peginterferon, interferon, and lamivudine were used as mono or combination therapy) (Appendix E Tables 9 and 10). The effects of lamivudine on disease progression defined as hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease or liver decompensation at the end of the treatment did not differ among patients with different baseline ALT levels (Appendix E Figure 20).[93,107,132,141] Comparative effectiveness of peginterferon alfa-2a versus lamivudine on combined response defined as ALT normalization and an HBV DNA level of <20 000 copies/ml at the end of the treatment was greater per increase by 1 log 10 unit (IU/1) in baseline ALT levels (Table 8).[93] Lamivudine increased HBeAg clearance and seroconversion among patients with elevated baseline ALT with no effects in those with ALT <2 ULN (Appendix E. Figure 21).[64]

At 24 weeks of followup off the administration of interferon alfa-2b with corticosteroid pretreatment, compared to interferon alfa-2b alone, HBV DNA loss was more frequent among patients with elevated baseline ALT (RR 1.22, 95 percent CI 1.05; 1.42)[65] (Appendix E Tables 9 and 10). Adjusted odds of sustained virologic response to interferon alfa-2b combined with lamivudine compared to lamivudine were higher in patients with baseline ALT >150UL (RR 3.12, 95 percent CI 1.43; 6.82).[63] Sustained HBeAg loss or seroconversion after interferon alfa-2b combined with lamivudine compared to lamivudine alone was higher among patients with elevated ALT with nonsignificant differences among those with baseline ALT <1 ULN or 1-2 ULN.[64] Sustained response to peginterferon alfa-2a combined with lamivudine compared to lamivudine alone was greater per increase in one unit (U/L) in baseline ALT (RR 10.32, 95 percent CI 9.71; 10.97).[97] Sustained HBeAg seroconversion after peginterferon alfa-2a combined with lamivudine compared to lamivudine alone was greater among patients with baseline ALT >5 ULN (RR 1.93, 95 percent CI 1.01; 3.69) with random differences among those with baseline ALT <2 or 2-5 ULN.[96] However, several studies reported no association between dose response increase in baseline ALT and sustained response to peginterferon alfa-2a compared to lamivudine[96] or peginterferon alfa-2b combined with lamivudine versus lamivudine.[108]

In conclusion, the low level of evidence indicated that treatment induced effects on disease progression and liver decompensation do not vary by baseline ALT levels. The low level of evidence indicated that treatment induced HBeAg clearance and seroconversion, HBeAg loss, or virologic loss vary by baseline liver function with inconsistent across the studies evidence of better response among patients with elevated baseline ALT.

Genotype of HBV DNA (eight studies, two antiviral agents, peginterferon and lamivudine used as mono or combination therapy) (Appendix E Tables 9 and 10). The effects of antiviral drugs on intermediary outcomes among patients with different HBV DNA genotype have been evaluated at the end of treatments[93] and at followup off the therapies (seven studies).[65,93,96,99,100,108,109] (Appendix E Tables 9 and 10). Adjusted odds ratios of ALT normalization and reduction of HBV DNA level <20,000 copies/ml after 48 weeks of peginterferon alfa-2a administration compared to lamivudine were significantly greater among patients with genotype B versus D (OR 2.31, 95 percent CI 1.30; 4.20) and genotype C versus D (OR 2.90, 95 percent CI 1.70; 5.00). Patients with genotype A had lower adjusted odds of response defined as ALT normalization and an HBV DNA level of <20,000 copies/ml compared to patients with genotype C (OR 0.33, 95 percent CI 0.10; 0.90).[93] No differences in treatment effects were found between patients with genotype A versus B, A versus D, or B versus C.[93]

Off treatment response to the same treatments also differed with greater adjusted odds of success among patients with genotype B versus D (OR 3.69, 95 percent CI 1.54; 8.79) and with genotype C versus D (OR 5.46, 95 percent CI 2.46; 12.10).[93] Patients with genotype B HBV DNA experienced sustained clearance of serum HBV DNA after interferon alfa-2b combined with steroid pretreatment compared to interferon alfa-2b alone more often than those with genotype C (adjusted OR 1.28, 95 percent CI 1.06; 1.42).[65] One RCT reported no significant differences in sustained HBeAg seroconversion after peginterferon alfa-2a combined with lamivudine compared to peginterferon alfa-2a or lamivudine alone among all genotypes of HBV DNA.[96]

In conclusion, the low level of evidence indicated that treatment induced ALT normalization and HBV DNA clearance or HBeAg seroconversion vary by HBV DNA genotype with better response among patients with genotype B and C. There was no evidence for clinical outcomes.

Previous treatment status (seven studies, four antiviral agents, peginterferon, interferon, adefovir, and lamivudine used as mono or combination therapy) (Appendix E Tables 9 and 10). Off-treatment rates of HBeAg seroconversion after administration of peginterferon alfa-2a plus lamivudine compared to lamivudine were higher among patients with no previous exposure to lamivudine (RR 1.52, 95 percent CI 1.08; 2.12)[96] with no significant differences among previously treated patients. Off-treatment HBeAg seroconversion was better after monotherapy with peginterferon alfa-2a compared to lamivudine in naïve to lamivudine patients (RR 1.72, 95 percent CI 1.24; 2.38).[96] Random differences were observed in patients previously treated with lamivudine.[96]

Five RCTs enrolled lamivudine resistant patients,[118,119,124,125,141] and one enrolled interferon resistant patients.[92] Adefovir combined with lamivudine for 48 weeks did not result in better outcomes, including rates of HBV DNA reduction to less than <2,000 copies/ml and ALT normalization compared to adefovir alone in lamivudine resistant patients.[118] Adefovir combined with lamivudine compared to lamivudine alone resulted in greater rates of ALT normalization (ARD 0.45, 95 percent CI 0.21; 0.69) and HBV DNA clearance (ARD 0.35, 95 percent CI 0.13; 0.57) in patients with lamivudine-resistant CHB with random differences in HBeAg clearance or seroconversion;[119] however, the same trial reported that combined treatment did not improve outcomes compared to adefovir alone.[119] Adefovir monotherapy improved ALT normalization compared to lamivudine alone (ARD after lamivudine versus adefovir -0.42, 9 percent CI -0.67; -0.18) with random differences in HBeAg clearance and seroconversion.[119] The BEHoLD Study Group enrolled 182 lamivudine-refractory patients to

start entecavir administration or continued on lamivudine for 48 weeks.[124] Mortality after 48 weeks of therapy and at 28 weeks of followup did not differ among treatment groups.[124] The largest dose of entecavir (1mg/day) increased HBV DNA loss in combination with normalization of ALT level at 48 weeks of the treatment (ARD 0.67, 95 percent CI 0.41; 0.92).[124] Viral clearance (HBV DNA <400 copies/mL) or normalization of ALT levels was greater after all doses of entecavir compared to lamivudine.[124] Entecavir increased the rates of HBV DNA and HBeAg clearance and normalization of ALT level in lamivudine-refractory, HBeAg-positive CHB patients compared to lamivudine, the effects were significant after 1mg/day (ARD 0.67, 95 percent CI 0.41; 0.92) or 0.5mg/day (ARD 0.40, 95 percent CI 0.14; 0.66).[125] The BEHoLD Study Group enrolled HBeAg-positive patients with persistent viremia or documented YMDD mutations after previous lamivudine therapy that were randomized to switch to entecavir 1 mg daily or continue lamivudine for a minimum of 52 weeks.[125] Entecavir increased rates of HBV DNA clearance and ALT normalization (ARD 0.50, 95 percent CI 0.42; 0.59), HBV DNA loss (<300 copies/mL by PCR) (ARD 0.18, 95 percent CI 0.11; 0.25), and HBeAg clearance (ARD 0.06, 95 percent CI 0.01; 0.12).[125] Improvement in necroinflammatory Knodell score (ARD 0.26, 95 percent CI 0.16; 0.37) and Ishak fibrosis scores (ARD 0.17, 95 percent CI 0.07; 0.26) was greater after entecavir therapy.[125] Discontinuation of lamivudine in 74 patients with lamivudine-resistant mutants resulted in the same rates of hepatic decompensation, ALT normalization, or HBeAg seroconversion compared to continuous administration of lamivudine.[141] A combination of interferon alfa-2b with lamivudine in 20 patients who failed previous interferon therapy did not improve HBV DNA or HBeAg clearance and ALT normalization.[92]

In conclusion, the low to moderate level of evidence indicated that treatment induced HBeAg seroconversion, ALT normalization, HBV DNA clearance, and improved histology are greater in patients naïve to antiviral medications. Entecavir improved virological and biochemical outcomes in lamivudine resistant patients without differences in mortality.

YMDD mutation (two studies, one antiviral agent used as monotherapy) (Appendix E Tables 9 and 10). One study examined the effect of 48 week lamivudine treatment versus placebo on liver histology in Chinese patients with and without YMDD mutations.[130] The authors reported improvement in necroinflammatory but not in fibrosis scores in patients with and without mutations; however, lamivudine improved the outcome of "worsened histology" only among patients without YMDD mutation (ARD 0.15, 95 percent CI 0.04; 0.54) (there was no protective effect in patients with YMDD mutations).[130] A study of discontinuing lamivudine in lamivudine resistant patients reported no association between YMDD mutations and hepatic decompensation, defined as change in the Child-Turcotte-Pugh score of two or more points after adjustments for ALT, baseline viral load, sex, YMDD variant, platelet, bilirubin, and albumin.[141]

In conclusion, low level of evidence indicated that treatment induced changes in liver histology are associated with baseline YMDD mutation. There was no evidence that this mutation was associated with differences in clinical outcomes.

Outcomes across studies with different patient populations. We analyzed the differences in off treatment outcomes across the studies that included different proportions of patients with HBeAg-positive status, baseline cirrhosis, and previous antiviral treatments. Clinical outcomes were not reported. Interferon alfa-2b combined with lamivudine compared to interferon alfa-2b alone increased HBV DNA clearance in studies that enrolled treatment naïve patients with random differences in the studies of previously treated patients (Appendix E. Figure

22).[62,68,69,72,74,75,84,87] However, the effects of interferon alfa-2b compared to no treatment or after combined interferon alfa-2b+lamivudine compared to lamivudine alone on HBV DNA loss did not show a clear pattern according to patient populations across the studies. Sustained HBeAg clearance after compared treatments was the same across the studies (Appendix E. Figure 23).[62-64,67,80,83,87,88,91,98,99,136] Sustained HBeAg seroconversion was greater after interferon alfa-2b combined with lamivudine versus lamivudine monotherapy in one study;[63] however, another study[67] that assessed interferon nonresponders and a European trial of previously untreated patients reported opposite association with better effects from lamivudine monotherapy therapy.[67] Sustained ALT normalization after compared treatments was the same across the studies (Appendix E. Figure 24).[10,62,63,72,74-76,84,87,95,96,113]

Summary. There is no high quality evidence that clinical outcomes of all-cause or disease specific mortality, hepatocellular carcinoma or hepatic decompensation are improved with currently approved and investigated therapeutic strategies (i.e., drug, dose, duration, patient population). Changes in biochemical, virologic, and histologic measures at the end of treatment or off treatment are frequently used to assess therapeutic effectiveness. However, these measures have not been demonstrated to be accurate surrogates for determining long-term clinical outcomes due to treatments. All treatments are associated with harms and immediate pharmaceutical costs, though most drugs are well tolerated and adverse effects are relatively mild. Therefore, it is difficult to determine what patients would derive clinical benefit. There is low evidence that treatment improves HBsAg clearance and measures of hepatitis resolution. This is beneficial because loss of HBsAg likely eliminates viral transmission to noninfected individuals and defines resolved hepatitis B. Individuals who are inactive carriers also have persistence of HBsAg positivity and a very favorable long-term prognosis. Therefore, for these individuals treatment is unlikely to provide a small benefit beyond risk of transmission.

EPC Question 3b. Is there evidence that specific subpopulations do not require treatment for hepatitis B (i.e., that the surrogate and/or clinical outcomes are equivalent or superior when not exposed to treatment?)

Specific subpopulations would not require treatment if their clinical outcomes (and possibly validly defined surrogate measures) were equivalent or superior to similar populations not receiving treatment. Situations could result from: (a) extremely favorable long-term natural history/prognosis of various forms of hepatitis B (e.g., chronic carrier status); (b) patient characteristics (e.g., advanced age, comorbidities, poor compliance) that result in short life expectancy that markedly lowers the individual's risk of hepatitis B related complications largely independent of hepatitis B characteristics or reduces treatment effectiveness; (c) ineffective therapy or disease characteristics that result in resistance to otherwise effective therapies (e.g., mutations); or (d) harms of therapy that outweigh benefits. Findings reported for EPC question 1 outline the natural history of CHB reporting on the long-term risks of hepatocellular carcinoma, cirrhosis, and death according to patient, hepatitis and comorbidity factors.

Here we review the evidence of no treatment benefit on biological, biochemical, or histological outcomes from antiviral drugs compared to placebo or symptomatic therapy without antiviral medications. Clinicians, investigators, and patients can use this information to decide in which specific patient subpopulations treatment regimens have shown lack of effectiveness.

Interferon alfa-2b compared to no treatment did not increase the sustained rates of resolved hepatitis including HBV DNA, HBeAg, and HBsAg clearance and ALT normalization in patients with HBeAg-positive hepatitis.[82,89] Interferon alfa-2b did not improve histology in HBeAg-negative[91] or HBeAg-positive patients.[83] Two RCTs, including the American Hepatitis Interventional Therapy Group[84] and a German study[69] of HBeAg-positive patients showed no significant sustained HBV DNA clearance after prednisone withdrawal followed by administration of interferon alfa-2b compared to no treatment. Interferon alfa-2b with prednisone priming failed to increase sustained HBV DNA, HBeAg, and HBsAg clearance in Chinese patients. [73] Interferon alfa-2b combined with lamivudine compared to placebo failed to increase HBeAg clearance or sustained HBeAg seroconversion in patients who were participating in four lamivudine-controlled Phase III trials[64] and in nonresponders to the previous interferon therapy (International Lamivudine Investigator Group.)[67] The International Lamivudine Investigator Group also reported that interferon nonresponders did not experience sustained HBsAg clearance and improvement in histological scores after combined therapy with interferon alfa-2b and lamivudine.[67]

Lamivudine compared to placebo failed to maintain sustained HBeAg seroconversion in interferon non responders[67] and in treatment naïve patients with CHB.[136] Patients with HBeAg-positive[67,136] and HBeAg-negative[139] hepatitis B did not experience sustained HBsAg loss after lamivudine administration compared to placebo. Patients with HBeAg-negative CHB also did not have better rates of sustained HBV DNA clearance and ALT normalization after two years of lamivudine administration.[139]

In conclusion, the low level of evidence suggested that individuals who failed previous interferon alfa-2b therapy did not benefit after combined interferon and lamivudine treatment. Patients with HBeAg did not experience sustained HBeAg seroconversion after interferon alfa-2b combined with lamivudine.

High risk of serious adverse events or noncompliance. We next assessed whether certain patient or hepatitis characteristics were associated with unacceptably high risk of serious adverse events or noncompliance. Little data were available to assess this issue.

Adefovir. Administration of adefovir compared to placebo[10,110,112,113,115,116] was well tolerated in HBeAg-positive[112,113] and HBeAg-negative patients.[10,110] Discontinuation of therapy due to adverse events did not differ between administration of adefovir and placebo in HBeAg-positive patients.[112,113] The Adefovir Dipivoxil 438 Study Group found no differences in the rates of any or serious adverse events compared to placebo in HBeAg-negative[110] and HBeAg-positive patients.[112] Previously treated patients and those with baseline cirrhosis were not at greater risk after adefovir therapy compared to placebo. Lamivudine-resistant HBeAg-positive patients experienced less insomnia and rash (ARD -0.21, 95 percent CI -0.40; -0.02) and increase in ALT (ARD -0.32, 95 percent CI -0.56; -0.08) after adding adefovir to lamivudine therapy compared to lamivudine or adefovir alone[119] with random differences in other examined adverse effects. Patients with YMDD mutant tolerated well addition of adefovir to ongoing lamivudine therapy.[117]

In conclusion, adefovir alone was well tolerated in patients with CHB. Lamivudine resistant patients experienced less frequent adverse events after combined therapy of adefovir and lamivudine.

Entecavir. The rates of any or serious adverse effects did not differ after administration of entecavir compared to lamivudine.[121-126] Discontinuation rates due to adverse events were less

after administration of entecavir (ARD -0.02, 95 percent CI -0.04; -0.01) in HBeAg-positive naïve to antiviral drugs patients[122] and in lamivudine-resistant, HBeAg-positive patients (ARD -0.05, 95 percent CI -0.10; -0.01).[125]

In conclusion, entecavir was better tolerated compared to lamivudine in examined patient populations, though serious adverse effects were similar.

Interferon alfa-2b. The European Concerted Action on Viral Hepatitis (EUROHEP)[61] reported increased rates of dose reduction due to depression, fatigue, hair loss, and headache after interferon alfa-2b compared to placebo (11 versus 0 percent) in HBeAg-positive patients with CHB. Patients with HBeAg-negative baseline status discontinued interferon administration due to adverse effects more often compared to placebo (24 versus 0 percent).[91] Reduction in dose of interferon alfa-2b due to adverse effects was reported in HBeAg-positive American patients (34 versus 0 percent after placebo).[87] Other adverse effects were comparable after administration of interferon compared to placebo.[61,69,82,84,87,89,91]

Combined therapy with interferon alfa-2b and lamivudine. The International Lamivudine Investigator Group included HBeAg-positive patients with CHB who had failed previous interferon therapy[67] and reported that combined therapy with interferon alfa-2b and lamivudine compared to placebo increased the rates of malaise/fatigue (95 versus32 percent), fever (95 versus 0 percent), headache (76 versus 23 percent), nausea/vomiting (59 versus 20 percent), hair loss/alopecia (48 versus 4 percent), muscle pain (46 versus 9 percent), viral respiratory infections (35 versus 0 percent), feeding problems (30 versus 4 percent), depression (27 versus 4 percent), decreased white blood cells (WBCs) (25 versus 0 percent), rheumatism (25 versus 4 percent), diarrhea (21 versus 0 percent), and musculoskeletal pain (16 versus 4 percent).[67]

In conclusion, HBeAg-positive patients tolerant to interferon alfa-2b experienced frequent adverse events after adding of lamivudine to continued interferon alfa-2b.

Monotherapy with interferon alfa-2b compared to lamivudine in treatment naïve, HBeAg-positive, predominantly Caucasian patients increased the rates of malaise and fatigue (100 versus 42 percent), arthralgia (33 versus 5 percent), anorexia (47 versus 5 percent), dizziness (27 versus 10 percent), nausea and vomiting (49 versus 23 percent), fever/chills (61 versus 7 percent), hair loss and alopecia (30 versus 10 percent), histological relapse (increase in Knodell score by at least two points) (25 versus 9 percent), headache (67 versus 32 percent), and muscle pain (57 versus 13 percent).[62] Adverse effects did not cause discontinuation of interferon alfa-2b more often than lamivudine.[62]

Reduction in dose because of severe side effects,[80,88] virological relapse,[84,85] or unchanged HBV DNA load[69] after interferon alfa-2b following prednisone withdrawal were the same compared to interferon alfa-2b alone.

Interferon alfa-2b combined with lamivudine compared to interferon alfa-2b alone[62,68] increased the rates of dry mouth (ARD 0.57, 95 percent CI 0.33; 0.81) in a Turkish RCT of HBeAg-positive previously untreated patients[68] and the rates of headache (ARD 0.26, 95 percent CI 0.14; 0.39) in predominantly Caucasian patients naïve to antiviral drugs.[62] Combined treatments reduced the rates of malaise and fatigue (87 versus 100 percent), arthralgia (12 versus 33 percent), dizziness (12 versus 27 percent), and hepatitis flares (0 versus 11 percent);[62] however, the rates of adverse effects were higher after combined therapy when compared to lamivudine alone.[62,63,67,71,72,74-77,79] Patients experienced influenza like symptoms more frequently (pooled ARD 0.47, 95 percent CI 0.36; 0.58),[63,75] viral respiratory infection (pooled ARD 0.23, 95 percent CI 0.03; 0.43),[62,67] muscle pain (pooled ARD 0.31, 95 percent CI 0.21; 0.41),[62,67]

malaise and fatigue (ARD 0.45, 95 percent CI 0.32; 0.58),[62] anorexia (ARD 0.35, 95 percent CI 0.23; 0.47),[62] nausea and vomiting (ARD 0.21, 95 percent CI 0.07; 0.35),[62] fever/chills (ARD 0.53, 95 percent CI 0.41; 0.66),[62] alopecia (ARD 0.30, 95 percent CI 0.173; 0.43),[62] fever (ARD 0.88, 95 percent CI 0.81; 0.95),[67] and decreased WBCs (ARD 0.25, 95 percent CI 0.14; 0.35).[67] Discontinuation of combined therapy due to adverse effects did not differ compared to lamivudine alone across different patient populations.[62,67,72,74,75,77,79] Chinese patients with HBeAg-negative CHB experienced serious adverse events, including pyrexia, fatigue, myalgia, and headache more often after combined therapy compared to lamivudine alone (ARD 0.09, 95 percent CI 0.02; 0.17).[76]

In conclusion, adverse events requiring dose reduction or discontinuation of medication are relatively common in patients with CHB treated with interferon alfa-2b alone or in combination with other antiviral therapies.

Lamivudine compared to placebo[67,130-133,136,139,140,142,145] did not require discontinuation of therapy due to adverse effects in HBeAg-positive patients (International Lamivudine Investigator Group),[67] serious adverse events in Asian patients with advanced cirrhosis or fibrosis (Cirrhosis Asian Lamivudine Multicentre Study Group),[132] or any adverse events in HBeAg-positive[132,145] or HBeAg-negative patients (Lamivudine Precore Mutant Study Group).[142] Lamivudine prevented worsening of liver necroinflammatory scores in Asian[130,145] and American HBeAg-positive patients[136] but was not effective in HBeAg-negative Asian patients[139] or in patients who did not respond to previous interferon alfa-2b therapy.[67] Lamivudine compared to telbivudine resulted in comparable rates of any adverse events in HBeAg-positive patients (Telbivudine Phase II Investigator Group).[127] In all examined adverse effects, only the rates of dyspepsia (21 versus 0 percent) were higher after lamivudine administration compared to telbivudine.[127] Combined therapy with telbivudine and lamivudine compared to telbivudine increased the rates of depression (5 versus 0 percent) in HBeAg-positive patients, participants in the Telbivudine Phase II Investigator Group.[127] One large RCT of 1,370 patients with CHB, participants in the Globe Study Group,[143] experienced a reduction in HBV DNA reappearance and the rates of treatment-emergent resistance mutations after telbivudine compared to lamivudine therapy.

In conclusion, HBeAg-negative Asian patients and patients tolerant to interferon alfa-2b therapy did not benefit from lamivudine therapy. Telbivudine had comparable safety compared to lamivudine with lower probability of relapse and resistance.

*Peginterferon alfa-2a.*The HBeAg-Negative Chronic Hepatitis B Study Group[95] and the Peginterferon alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group[96] reported increased rates of more than one adverse effect in both patient populations (89 versus 56 percent in HBeAg-positive patients and 86 versus 48 percent in HBeAg-negative patients) and more than one serious adverse effect (7 versus 3 percent in HBeAg-negative patients and 6 versus 2 percent in HBeAg-positive patients) as well as discontinuation of therapy for safety reasons (4 versus 1 percent in HBeAg-positive patients and 4 versus 0 percent in HBeAg-negative patients) after combined peginterferon alfa-2a with lamivudine compared to lamivudine alone.

Adverse event rates varied among patients with different HBeAg baseline status without statistical significance among them (p value for meta regression >0.05). Combined therapy increased the rates of alopecia (11 versus 1 percent in HBeAg-negative and 29 versus 2 percent in HBeAg-positive), arthralgia (15 versus 3 percent in HBeAg-negative and 9 versus 3 percent in HBeAg-positive), dose modification due to adverse events (8 versus 0 percent in HBeAg-positive and 13 versus 0 percent in HBeAg-negative) or laboratory abnormalities (35 versus 0

percent in HBeAg-negative and 38 versus 0 percent in HBeAg-positive).[95,96] Fatigue was experienced by 41 percent of HBeAg-negative and 37 percent of HBeAg-positive patients after combined therapy (versus 14 percent and 18 percent after lamivudine alone in HBeAg-negative and positive respectively). [95,96] Myalgia was more common after combined therapy in HBeAg-negative (27 versus 6 percent) and positive (28 versus 3 percent) patients compared to lamivudine alone. More than half the patients experienced pyrexia after combined therapy (54 versus 4 percent in HBeAg-negative and 55 versus 4 percent in HBeAg-positive).[95,96]

However, several adverse effects were specific for patients with different HBeAg baseline status. Only HBeAg-negative patients experienced dose modification due to neutropenia after combined therapy with lamivudine and peginterferon alfa-2a (24 versus 0 percent after lamivudine alone) or thrombocytopenia (12 versus 0 percent after lamivudine alone).[95] Combined therapy could not prevent worsening of fibrosis scores from 0 (none) to 18 (severe) in HBeAg-negative patients only (8 versus 3 percent after lamivudine alone).[95] In contrast, HBeAg-positive patients had depression (6 versus 1 percent), diarrhea (10 versus 3 percent), dizziness (12 versus 4 percent), nausea (10 versus 2 percent), pruritus (10 versus 2 percent), rash (8 versus 4 percent), or rigors (10 versus 0 percent) more common after combined therapy compared to lamivudine alone.[96] Alopecia (29 versus 20 percent) and YMDD mutations (3 versus 0 percent) were more common in HBeAg-positive patients after combined therapy compared to peginterferon alfa-2a alone.[96]

In conclusion, the moderate level of evidence indicates that a large proportion of patients treated with peginterferon alfa-2a+lamivudine experienced adverse events; the rates varied among patients with different HBeAg baseline status without statistical significance among them.

Monotherapy with peginterferon alfa-2a compared to monotherapy with lamivudine increased the rates of any adverse effects (86 versus 48 percent in HBeAg-negative[95] and 89 versus 56 percent in HBeAg-positive[96] patients) and dose modification due to adverse effects (7 versus 0 percent in HBeAg-negative[95] and 7 versus 0 percent in HBeAg-positive[96] patients). Pyrexia was more prevalent after peginterferon alfa-2a compared to lamivudine in HBeAg-negative (58 versus 4 percent) and HBeAg-positive (49 versus 4 percent) patients;[95,96] however, only patients who were HBeAg-positive at baseline experienced ≥1 serious adverse event (4 versus 2 percent),[96] while only HBeAg-negative patients needed dose modification due to neutropenia (17 versus 0 percent) or thrombocytopenia (19 versus 0 percent).[95] As expected, the rates of YMDD mutations were lower after interferon compared to lamivudine (0 versus 25 percent) in patients with HBeAg-positive CHB.[96]

In conclusion, peginterferon alfa-2a resulted in very high rates of adverse events and increased the need to modify treatment dose due to adverse events independent of baseline HBeAg status.

Absolute rates of outcomes by baseline HBeAg status. We summarized the absolute probability of examined outcomes and frequent adverse events (>10 percent) at the end and at followup off the active drugs in trials that included predominantly HBeAg-positive (>98 percent) or HBeAg-negative (>98 percent) patients (Appendix E Table 11). Since none of the treatment regimes demonstrated consistent positive effects on clinical outcomes or all intermediate outcomes, treatment decisions must be made based on a balance between absolute rates of positive intermediate outcomes and harm effects. Some treatments have never been compared to placebo or to each other in head-to-head RCTs. Indirect comparisons were not possible to

examine due to differences in comparators in eligible RCTs. However, consumers, clinicians, and policymakers can analyze the balance between treatment effectiveness and harms for clinical and economical decisions.

Adefovir. At the end of adefovir administration, 1 percent of HBeAg-negative patients experienced HBsAg seroconversion, 63 percent had HBV DNA clearance, 36 percent had improved histology, and 66 percent had normal ALT (Appendix E Table 11). The rates of mutation were 4 percent. Sustained HBV DNA loss and improved histology were found in 66 and 71 percent HBeAg-negative patients, respectively. Any adverse events were reported in 70 percent of HBeAg-negative patients treated with adefovir. Abdominal pain, flu-like syndrome, pharyngitis, and asthenia were among the most common adverse events. Virological outcomes in HBeAg-positive patients were assessed at the end of the treatments only (Appendix E Table 11). HBV DNA clearance was demonstrated in 25 percent, HBeAg loss in 17 percent, and HBeAg seroconversion in 12 percent of the patients. Nine percent had virological relapse measured by HBV DNA. Sustained ALT normalization was less common in HBeAg-positive patients (39 percent) compared to HBeAg-negative patients (54 percent). Almost all (95 percent) HBeAg-positive patients experienced some adverse events after adefovir. Asthenia was more common (29 percent) in HBeAg-positive patients compared to HBeAg-negative (10 percent). More than 10 percent of HBeAg-positive patients experienced elevated ALT and urine glucose levels.

In conclusion, more than half of HBeAg-negative patients had sustained HBV DNA clearance, ALT normalization, and histological improvement. HBsAg loss occurred in <10 percent. Overall adverse events were frequent; asthenia and flu like syndrome were observed in approximately 15 percents of HBeAg-negative patients. Sustained outcomes in HBeAg-positive patients have not been examined, yet at the end of the treatment half of the patients had improved histology, <25 percent loss HBV DNA, and HBeAg. Adverse events were very common; asthenia and flu like syndrome were reported more frequent than among HBeAg-negative patients.

Entecavir (Appendix E Table 11). At the end of the therapy HBsAg loss was observed in 4 percent and HBsAg seroconversion in 2 percent of HBeAg-positive patients, sustained HBsAg response in HBeAg-negative patients have not been investigated yet. At the end of the treatments, 15 percent of HBeAg-positive patients experienced HBeAg clearance and 17 percent seroconversion; sustained response was not available from the published trials. HBV DNA clearance at the end of the treatment was more common in HBeAg-negative patients; sustained response was reported in HBeAg-positive patients only and was <10 percent. HBeAg-negative patients had normal ALT and improved histology more often compared to HBeAg-positive patients, More than half the patients reported adverse events, the rates were higher among HBeAg-positive patients; however, elevation of ALT was observed in 10 percent of HBeAg-positive patients.

In conclusion, sustained response to entecavir therapy was reported in HBeAg-positive patients and was small. More than half of HBeAg-negative patients had improved histology and 90 percent loss HBV DNA at the end of the treatment. More than half the patients reported adverse events, but only the rates of elevated ALT in HBeAg-positive patients exceeded 10 percent.

Telbivudine (Appendix E Table 11). Evidence was available only for HBeAg-positive patients at the end of the therapy. HBeAg loss or seroconversion demonstrated 25 percent, ALT normalization 82 percent, and HBV DNA clearance 55 percent; 5 percent had virological relapse

with reappeared HBV DNA. Total adverse events were common; however, only the rates of influenza exceeded 10 percent.

In conclusion, there is low to moderate level of evidence that telbivudine has been examined exclusively in HBeAg-positive patients. Sustained response to telbivudine in HBeAg-negative patients is not known. Half of the treated HBeAg-positive patients lost HBV DNA and a quarter had HBeAg clearance. Total adverse events were common (70 percent); however, only the rates of influenza exceeded 10 percent.

Interferon alfa-2b (Appendix E Table 11). Sustained HBsAg loss was uncommon in both HBeAg-positive and negative patients. Sustained HBeAg loss was 43 percent and sustained HBeAg seroconversion was 32 percent among those with HBeAg-positive at baseline. Sustained HBV DNA clearance was 27 percent Sustained ALT normalization and histological improvements have not been examined in HBeAg-negative patients; 27 percent of HBeAg-positive patients had improved histology at followup off the treatment. Virological relapse in HBeAg-positive and mutation in HBeAg-positive and negative patients were uncommon. More than 10 percent of HBeAg-negative patients needed dose reduction or discontinued therapy due to adverse events; however, almost all HBeAg-positive patients had fever or malaise and fatigue and more than 10 percent reported depressions, anorexia, nausea and vomiting, and other adverse events.

In conclusion, sustained HBV DNA clearance in known only in HBeAg-positive patients. One-third of HBeAg-positive patients experienced HBeAg seroconversion and improved histology. Adverse events were common in HBeAg-positive patients and 24 percent of HBeAg-negative patients discontinued therapy because of adverse events.

Peginterferon alfa-2a (Appendix E Table 11). Virological outcomes were examined in HBeAg-positive patients. Fourteen percent had sustained HBV DNA clearance, 32 percent sustained HBeAg seroconversion, and 37 percent sustained HBeAg loss. Sustained ALT normalization was more common among HBeAg-negative (58 percent) than HBeAg-positive (36 percent) patients. HBeAg-positive patients experienced sustained histological improvement (38 percent) compared to HBeAg-negative patients (29 percent). More than 80 percent of all patients experienced adverse events; pyrexia was the most common adverse event (58 percent). Dose modification was required by 37 percent HBeAg-positive and 46 percent HBeAg-negative patients.

In conclusion, one-third of the patients experienced sustained histological improvement after peginterferon alfa-2a therapy, a third of HBeAg-positive patients had sustained HBeAg clearance, and <15 percent of HBeAg-positive had loss of HBV DNA. Viral clearance in HBeAg-negative patients has not been reported. Most patients had adverse events. Around 40 percent required dose modification.

Table 7. Effects of antiviral drugs on HBeAg-negative patients (relative risk from individual RCTs)

Treatments	Clinical or Combined Outcomes	Biochemical	Virological (HBV DNA, HBsAg)	Histological	Mutation
Adefovir (dose, time)		NS[10]	HBsAg seroconversion-NS[10] HBV DNA loss- NS[10]	Improved histology-NS[10]	NS[10]
Adefovir vs. placebo		**2.45 (1.61; 3.73)** **1.79 (1.07; 3.00)***[10,110]	HBsAg seroconversion[10] 1.52 (0.06; 36.46) loss HBV DNA[110] **63.50** (**4.00; 1009.28)** loss HBV DNA [10]* **8.83** (**2.94; 26.52**)	Failure[110] **0.11 (0.04; 0.27)** Improved[10,110] Significant improvement in necroinflammatory or fibrosis scores with NS changes in total scores	NS[10,110]
Interferon alfa 2b+lamivudine vs. lamivudine	NS[71]	Flare-NS[71,74] Normalization of ALT: 1.29 (0.89; 1.86)[74] 1.30 (0.46; 3.71)[74] 1.08(0.82;1.41)[76] **1.45 (1.02; 2.05)**[76]*	HBV DNA loss-NS[71,74,76] Relapse **0.30 (0.09;0.93)**[74] HBsAg loss-NS[71,74,76]		**0.03 (0.00; 0.55)** **0.18 (0.04; 0.73)**[76]
Interferon alfa 2b vs. no treatment	Loss of HBV DNA and normalization of ALT[81]* **5.50 (1.36; 22.32)** Loss of HBV DNA and normalization of ALT[91]* 13(0.78; 217.03) Relapse – NS[81]* 2.00(0.40; 9.95)	Flare **0.27** **(0.11;** 0.67)[91]	HBsAg loss – NS [91]	Improved histology-NS [91] Resistance-NS[91]	
Peginterferon alfa-2a+lamivudine vs. lamivudine	Normalization of ALT and loss of HBV DNA[95]* **2.64 (1.36; 5.11)**	Normalization ALT[95] **0.66 (0.55; 0.79)** Normalization ALT*[95] **1.34 (1.09; 1.64)**	HBV DNA loss[95] **1.17 (1.06; 1.30)** HBV DNA loss*[95] **2.92 (1.57; 5.44)**	Failure NS[95] Improved histology-NS[95]	
Peginterferon alfa-2a+placebo vs. lamivudine	Normalization of ALT and HBV DNA loss*[95] **2.36 (1.20; 4.64)**	Normalization ALT[95] **0.51 (0.41; 0.63)** Normalization ALT*[95] **1.31 (1.07; 1.61)**	HBV DNA Loss[95] **0.84 (0.73; 0.97)** **2.83 (1.52; 5.29)***	Failure NS[95] Improved necroinflammatory scores[95]* **1.39 (1.06; 1.82)** Improved HAI-NS*[95] Improved fibrosis-NS[95]	

* off treatment; NS = not significant

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
Baseline ALT						
HBV DNA loss	Interferon alfa 2b+corticosteroid vs. interferon alfa 2b	24/24	1/115	Wai, 2002[65]	**1.22 (1.05; 1.42)**	HBV DNA loss was more frequent among patients with elevated baseline ALT
HBV DNA and HBeAg loss	Interferon alfa 2b+corticosteroid vs. no treatment	24/24	1/43	Perrillo, 1990[84]	**7.82 (1.02; 59.88)**	Loss of HBV DNA and HBeAg was greater among patients with baseline ALT <100U/L with random differences among those with baseline ALT100-200 and >200U/L
Odds ratio of HBeAg and HBV DNA loss independent of gender and age	Interferon alfa 2b+lamivudine vs. lamivudine	24/48	1/150	Barbaro, 2001[63]	**3.12 (1.43; 6.82)**	Adjusted odds of virologic response were higher in patients with baseline ALT >150UL
HBeAg loss	Interferon alfa 2b+lamivudine vs. placebo	24/28	1/331	Perrillo, 2002[64]	**2.90 (1.35; 6.27)**	HBeAg loss was higher among patients with ALT >2 but <5ULN with random differences among those with <1ULN or 1-2ULN
HBeAg seroconversion	Interferon alfa 2b+lamivudine vs. placebo	24/28	1/331	Perrillo, 2002[64]	**2.70 (1.10; 6.58)**	HBeAg seroconversion was greater among patients with >2-<5 ULN
					3.27 (1.03; 10.39)	HBeAg seroconversion was greater among patients with ALT >5 ULN with random differences among those with baseline ALT<1ULN or 1-2ULN
Adjusted for treatment status odds ratio of HBeAg seroconversion, HBV DNA loss and ALT normalization in HBeAg (+) patients. In HBeAg (-) patients: loss of HBV DNA+ALT normalization	Peginterferon alfa-2a+lamivudine vs. lamivudine	9/24	1/140	Cindoruk, 2007[97]	**10.32 (9.71; 10.97)**	Sustained response was greater per increase in 1unit (U/L) in baseline ALT

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations (continued)

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/542	Lau, 2005[96]	**1.93 (1.01; 3.69)**	Response was greater among patients with baseline ALT >5ULN, random differences among those with baseline ALT <2 or 2-5ULN
HBeAg seroconversion	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/542	Lau, 2005[96]	**1.81 (1.07; 3.04)**	HBeAg seroconversion was greater in patients with baseline ALT >2 but <5ULN. Random differences among those with baseline ALT <2 or >5ULN
Adjusted odds ratios of ALT normalization and an HBV DNA loss	Peginterferon alfa-2a vs. lamivudine	48/24	1/1036	Bonino, 2007[93]	Random association per 1 U/L increase in baseline ALT	
Adjusted for treatment allocation, HBV genotype and log HBV DNA odds ratio of HBeAg loss	Peginterferon alfa-2b+lamivudine vs. lamivudine	60/24	1/100	Chan, 2006[108]	Random association per 1 U/L increase in baseline ALT	
Adjusted odds ratio of sustained HBeAg loss	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/26	1/310	Janssen, 2005[99]	Random differences among patients with elevated vs. normal baseline ALT	
Adjusted odds ratio of HBeAg and HBV DNA loss, and normal ALT level	Peginterferon alfa-2b+vs. interferon alfa 2b	24/24	1/230	Zhao, 2007[109]	1.23 (0.51; 2.92)	RR, random differences between patients with baseline ALT level >3.4 vs. <3.4 ULN
Baseline histology						
HBeAg loss	Interferon alfa 2b vs. placebo	24/28	1/264	Perrillo, 2002[64]	**5.76 (1.48; 22.42)**	Interferon alfa 2b vs. placebo increased HBeAg loss among patients with pretreatment HAI score 5-9 but failed among patients with pretreatment HAI score 0-4 or >10
HBeAg loss	Interferon alfa 2b+lamivudine vs. placebo	24/28	1/331	Perrillo, 2002[64]	**5.32 (1.51; 18.72)**	Interferon alfa 2b+lamivudine vs. placebo increased HBeAg loss in patients with pretreatment HAI Score 5-9 but failed among patients with pretreatment HAI score 0-4 or >10

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations (continued)

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
Odds ratio of HBeAg and HBV DNA loss independent on gender and age	Interferon alfa 2b+ lamivudine vs. lamivudine	24/48	1/151	Barbaro, 2001[63]	**2.91 (1.04; 8.22)**	The rate of sustained response after interferon alfa 2b+ lamivudine vs. lamivudine was increased by an increase in baseline inflammation scores
					2.58 (0.88; 7.60)	The rate of sustained response after interferon alfa 2b+ lamivudine vs. lamivudine was not increased by an increase in baseline fibrosis scores
Adjusted for treatment status odds ratio of HBeAg seroconversion, HBV DNA loss and ALT normalization in HBeAg (+) patients. In HBeAg (-) patients: loss of HBV DNA, ALT normalization	Peginterferon alfa-2a+lamivudine vs. lamivudine	9/15	1/160	Cindoruk, 2007[97]	Presence of steatosis did not modify the effect of peginterferon alfa-2a + lamivudine vs. lamivudine on sustained response	
					14.97 (2.43; 92.28)	The adjusted rates of sustained response were increased per increase in baseline Knodell HAI
Adjusted relative risk of HBeAg seroconversion and HBV DNA loss	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/78	1/310	Buster, 2007[100]	0.98 (0.17; 5.23)	Presence of advanced fibrosis-fibrosis score of 4–6 (HAI) did not change adjusted relative risk of HBV DAN loss and HBeAg seroconversion
Baseline viral load						
HBV DNA loss with persistent HBeAg	Interferon alfa 2b vs. no treatment	32/20-52	1/118	Janssen, 1999[61]	1.87 (0.59; 5.87)	No association between baseline positive HBV DNA (per 1 unit increase) and the effects of interferon alfa 2b vs. no treatment
HBV DNA and HBeAg loss	Interferon alfa 2b vs. no treatment	24/24	1/169	Perrillo, 1990[84]	**5.24 (1.22; 22.50)**	interferon alfa 2b, 5MU/day vs. no treatment increased rates of HBV DNA and HBeAg loss among patients with baseline HBV DNA 2-99pg/ml. Random differences after interferon 1MU/day and after interferon 1 or 5 MU/day among the patients with baseline HBV DNA 100-200 pg/ml or >200 pg/ml

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations (continued)

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
HBeAg loss	Interferon alfa 2b vs. no treatment	32/20	1/118	Janssen, 1999[61]	**3.18 (1.25; 8.05)**	RR, Interferon Alfa 2b, 10 MU three times per week vs. no treatments increased rates of HBeAg loss among the patients with baseline HBV DNA <10pg/ml. Random differences among the patients with baseline HBV DNA >10pg/ml
HBV DNA and HBeAg loss	Interferon alfa 2b+corticosteroid vs. no treatment	24/24	1/169	Perrillo, 1990[84]	**5.38 (1.26; 22.84)**	interferon alfa 2b+corticosteroid vs. no treatment increased rates of HBV and HBeAg loss among patients with baseline HBV DNA 2-99pg/ml
					8.80 (0.49; 158.66)	interferon alfa 2b+corticosteroid vs. no treatment did not increase the rates of HBV DNA and HBeAg loss among patients with baseline HBV DNA 100-200 pg/ml
					0.98 (0.06; 15.13)	interferon alfa 2b+corticosteroid vs. no treatment did not increase the rates of HBV DNA and HBeAg loss among patients with baseline HBV DNA >200 pg/ml
HBeAg loss	Interferon alfa 2b+corticosteroid vs. interferon alfa 2b	24/24	1/183	Wai, 2002[65]	**1.10 (1.03; 1.17)**	Interferon alfa 2b+corticosteroid vs. interferon alfa 2b increased the rates of HBeAg loss in patients with low baseline HBV-DNA level
					1.10 (1.01; 1.21)	Interferon alfa 2b+corticosteroid vs. interferon alfa 2b increased the rates of HBeAg loss in patients with low baseline HBV-DNA and elevated baseline ALT
Odds ratio of HBeAg and HBV DNA loss	Interferon alfa 2b+lamivudine vs. lamivudine	24/48	1/151	Barbaro, 2001[63]	**7.23 (2.71; 19.57)**	Odds of sustained suppression of serum levels of HBeAg and HBV DNA was significant in those with baseline viral load of 200 pg/ml or less independent of gender and age
HBeAg loss	Interferon alfa 2b+lamivudine vs. lamivudine	52/24	1/75	Sarin, 2005[75]	**3.89 (1.20; 12.69)**	Interferon alfa 2b+lamivudine vs. lamivudine resulted in increase rates of HBeAg loss in patients with baseline HBV DNA >107 copies/mL

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations (continued)

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
HBeAg loss and seroconversion	Interferon alfa 2b+lamivudine vs. lamivudine	52/24	1/75	Sarin, 2005[75]	**4.87 (1.14; 20.74)**	Interferon alfa 2b+lamivudine vs. lamivudine resulted in increase rates of HBeAg seroconversion and HBV DNA loss in patients with baseline HBV DNA >107 copies/mL
Viral breakthrough -reappearance of serum HBV-DNA	Interferon alfa 2b+lamivudine vs. lamivudine	176/192	1/83	Jang, 2004[72]	Random association with baseline HBV DNA levels (1 unit increase)	
Adjusted for treatment status odds ratio of HBeAg seroconversion, HBV DNA loss and ALT normalization in HBeAg (+) patients. In HBeAg (-) patients: loss of HBV DNA, ALT normalization	Peginterferon alfa-2a+lamivudine vs. lamivudine	9/6	1/140	Cindoruk, 2007[97]	1.05 (0.13; 8.14)	Baseline mean viral load (copy/mL)was not associated with sustained response to the therapy
Sustained combined response: ALT normalization and an HBV DNA loss	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/76	Bonino, 2007[93]	**2.24 (1.31; 3.83)**	Peginterferon alfa-2a+lamivudine vs. lamivudine increased sustained response among patients with baseline HBV DNA <6.12 log10 copies/ml
					1.78 (1.11; 2.84)	Peginterferon alfa-2a+lamivudine vs. lamivudine increased sustained response among patients with baseline HBV DNA >6.12-8.42 log 10 copies/ml
					1.37 (0.67; 2.80)	Peginterferon alfa-2a+lamivudine vs. lamivudine did not increase sustained response among patients with baseline HBV DNA >8.42 log 10 copies/ml
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/543	Lau, 2005[96]	0.84 (0.47; 1.48)	Peginterferon alfa-2a+lamivudine vs. lamivudine did not increase HBeAg seroconversion among patients with baseline HBV DNA levels ≤9.07 (log copies/ml)
					1.91 (1.16; 3.15)	Peginterferon alfa-2a+lamivudine vs.

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations (continued)

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
						lamivudine increased HBeAg seroconversion among patients baseline HBV DNA levels >9.07–10.26 (log copies/ml)
					2.01 (0.82; 4.90)	Peginterferon alfa-2a+lamivudine vs. lamivudine did not increase HBeAg seroconversion among patients with baseline HBV DNA levels >10.26 (log copies/ml)
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a	48/24	1/542	Lau, 2005[96]	0.54 (0.32; 0.91)	The rates of HBeAg seroconversion were lower after peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a among the patients with baseline HBV DNA levels ≤9.07 (log copies/ml)
					1.03 (0.68; 1.54)	Random differences among patients with baseline HBV DNA levels >9.07–10.26 (log copies/ml)
					1.27 (0.59; 2.75)	Random differences among patients with baseline HBV DNA levels>10.26 (log copies/ml)
Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/96	Bonino, 2007[93]	1.27 (0.71; 2.30)	Random differences among patients with baseline HBV DNA <6.12 log10 copies/ml
					3.87 (2.55; 5.88)	Peginterferon alfa-2a+ placebo vs. lamivudine increased the rates of sustained response among patients with baseline HBV DNA >6.12-8.42 log 10 copies/ml
					1.80 (0.91; 3.57)	Random differences among patients with baseline HBV DNA >8.42 log 10 copies/ml
HBeAg seroconversion	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/543	Lau, 2005[96]	1.55 (0.95; 2.51)	Random differences among patients with baseline HBV DNA levels ≤9.07 (log copies/ml)
					1.86 (1.13; 3.08)	Peginterferon alfa-2a+placebo vs. lamivudine increased rates of HBeAg seroconversion among patients with baseline HBV DNA levels >9.07–10.26 (log copies/ml)

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations (continued)

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
					1.58 (0.62; 4.01)	Random differences among patients with baseline HBV DNA levels >10.26 (log copies/ml)
Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a vs. lamivudine	48/24	1/1036	Bonino, 2007[93]	1.06 (0.93; 1.21)	Baseline HBV DNA (Log10) was not associated with sustained response to therapy
Adjusted for treatment allocation, hepatitis B virus (HBV) genotype, baseline ALT odds ratio of persistent HBeAg loss	Peginterferon alfa-2b+lamivudine vs. lamivudine	60/0	1/100	Chan, 2006[108]	0.70 (0.38; 1.30)	Baseline HBV DNA (log10) was not associated with sustained response to therapy
Adjusted for treatment allocation, HBV DNA genotype, IL-1b-511 polymorphism, baseline ALT odds ratio of persistent HBeAg loss and had less than 2 occasions with HBV DNA <100,000 copies/mL	Peginterferon alfa-2b+lamivudine vs. lamivudine	60/0	1/100	Chan, 2006[108]	0.65 (0.35; 1.20)	Baseline HBV DNA (log10) was not associated with sustained response to therapy
Adjusted odds ratio of sustained HBeAg loss	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/0	1/307	Janssen, 2005[99]	**1.60 (1.30; 1.80)**	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b increased the rates of HBeAg loss among patients with low baseline viral load

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations (continued)

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
Multivariate adjusted odds ratio of sustained combined response: HBeAg-negative, HBV DNA <5 log10 copies/mL, and normal ALT level	Peginterferon alfa-2b vs. interferon alfa 2b	24/0	1/230	Zhao, 2007[109]	0.53 (0.22; 1.28)	Random difference among patients with baseline HBV DNA >8.1 vs. <8.1 log 10 copies/mL
Genotype, outcomes at followup off treatment						
Adjusted for age, gender, baseline ALT, HBV DNA, and histology, precore G1896A mutation, core promoter A1762T, G1764A, and treatment with interferon with and without prednisone pretreatment odds ratios of sustained HBV DNA loss	Interferon alfa 2b+corticosteroid vs. interferon alfa 2b	24/0	1/115	Wai, 2002[65]	**1.28 (1.06; 1.42)**	Patients with HBV genotype B vs. C had better sustained response to the therapy
			1/68	Wai, 2002[65]	**1.47 (1.18; 1.82)**	Patients with HBV genotype B vs. C and elevated baseline ALT had better sustained response to the therapy
Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/126	Bonino, 2007[93]	**2.09 (1.29; 3.40) - C** **3.33 (1.53; 7.27) - D**	Peginterferon alfa-2a+lamivudine vs. lamivudine increased the rates of sustained response among patients with genotype C or genotype D
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/543	Lau, 2005[96]	1.34 (0.30; 5.92)	Random difference among patients with HBV genotype A
					1.42 (0.78; 2.58)	Random difference among patients with HBV genotype B
					1.49 (0.96; 2.31)	Random difference among patients with HBV genotype C
					0.67 (0.11; 3.97)	Random difference among patients with HBV genotype D

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations (continued)

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a	48/24	1/542	Lau, 2005[96]	0.33 (0.11; 1.02)	Random difference among patients with HBV genotype A
					1.04 (0.60; 1.80)	Random difference among patients with HBV genotype B
					0.86 (0.59; 1.25)	Random difference among patients with HBV genotype C
					1.00 (0.14; 7.05)	Random difference among patients with HBV genotype D
Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/19	Bonino, 2007[93]	2.18 (0.27; 17.32)	Random differences among patients with genotype A
					1.14 (0.70; 1.85)	Random differences among patients with genotype B
					2.22 (1.36; 3.63)	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of sustained response among patients with genotype C
					1.47 (0.59; 3.69)	Random differences among patients with genotype D
HBeAg seroconversion	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/543	Lau, 2005[96]	**4.01 (1.15; 14.07)**	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of e Ag seroconversion among patients with HBV genotype A
					1.36 (0.74; 2.48)	Random differences among patients with HBV genotype B
					1.73 (1.13; 2.65)	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of e Ag seroconversion among patients with HBV genotype C
					0.67 (0.11; 3.97)	Random differences among patients with HBV genotype D
Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a vs. lamivudine	48/24	1/1036	Bonino, 2007[93]	2.58 (0.73; 9.20)	Random difference between genotypes (A vs. D)
					3.69 (1.54; 8.79)	Rates of sustained response were higher among patients with genotype B vs. D
					5.46 (2.46; 12.10)	Rates of sustained response were higher among patients with genotype C vs. D

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations (continued)

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
Adjusted for treatment allocation, HBV genotype, baseline ALT, and log HBV DNA odds ratio of persistent HBeAg loss at any time up to week 76 of post-treatment	Peginterferon alfa-2b+lamivudine vs. lamivudine	60/24	1/100	Chan, 2006[108]	**10.37 (1.11; 96.96)**	Rates of response were higher among patients with interleukin (IL)-1b-511 baseline genotype C/T vs. C/C
					Random differences in patients with genotype C vs. B	
					Random differences in patients with Haplotype -511/-31 of interleukin (IL)-1b C-T vs. T-C	
					Random differences in patients with interleukin (IL)-1b-511 baseline genotype T/T vs. C/C	
					Random differences in patients with interleukin (IL)-1b-31 baseline genotype C/T vs. T/T or C/C vs. T/T	
					Random differences in patients with IL-1 receptor antagonist genotype IL-1RN 1/2 vs. 1/1	
					Random differences in patients with interleukin (IL)-1b-511 baseline genotype C/T and T/T vs. C/C	
					Random differences in patients with interleukin (IL)-1b-31 baseline genotype C/T and C/C vs. T/T	
Adjusted relative risk of HBeAg seroconversion and HBV DNA <10,000 copies/ml.	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/26	1/307	Buster, 2007[100]	**11.30 (1.38; 92.57)**	Adjusted rates of sustained response were higher among patients with genotype A vs. C
					4.28 (1.39; 13.21)	Adjusted rates of sustained response were higher among patients with genotype A vs. D
					12.13 (1.24; 118.30)	Adjusted rates of sustained response were higher among patients with genotype B vs. C
					4.59 (1.14; 18.43)	Adjusted rates of sustained response were higher among patients with genotype B vs. D
Adjusted odds ratio of sustained HBeAg loss	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/26	1/307	Janssen, 2005[99]	**2.40 (1.30; 4.60)**	Adjusted rates of sustained response were higher among patients with HBV genotype A vs. D
					3.60 (1.40; 8.90)	Adjusted rates of sustained response were higher among patients with HBV genotype A vs. C
					2.20 (0.70; 7.00)	Random difference among patients with HBV genotype B vs. C

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations (continued)

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
Multivariate adjusted odds ratio of sustained HBeAg loss, HBV DNA <5 log 10 copies/mL, and normal ALT level	Peginterferon alfa-2b vs. interferon alfa 2b	24/24	0/250	Zhao, 2007[109]	**0.19 (0.08; 0.46)**	RR, response was lower among patients with genotype C vs. B
Previous treatment, outcomes at followup off treatment						
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/543	Lau, 2005[96]	**1.52 (1.08; 2.12)**	Rates of HBeAg seroconversion were higher among patients with no previous exposure to lamivudine
					Random differences among those with previous LAM or Interferon therapy	
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a	48/24	1/542	Lau, 2005[96]	Random differences among all patients with and without previous treatment	
HBeAg seroconversion	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/543	Lau, 2005[96]	**1.58 (1.11; 2.23)**	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of HBeAg seroconversion among patients with no previous anti-HBV therapy
					1.43 (0.55; 3.71)	Random differences among patients with previous treatment: LAM
					1.72 (1.24; 2.38)	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of HBeAg seroconversion among patients with no previous exposure to lamivudine
					3.26 (1.08; 9.88)	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of HBeAg seroconversion among patients with previous treatment: IFN
					1.55 (1.12; 2.14)	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of HBeAg seroconversion among patients with no previous exposure to conventional interferon

Table 8. Effects of antiviral drugs for chronic hepatitis B on off treatment outcomes in patient subpopulations (continued)

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds Ratios (95% CI)	Level of Evidence From Individual Studies is Low for All Comparisons/Comments
HBeAg loss	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/26	2/307	Janssen, 2005[99]	**2.20 (1.10; 4.50)**	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b increased the rates of HBeAg loss among patients without previous interferon therapy
				Flink, 2006[102]	0.94 (0.63; 1.40)	Random differences among naïve to any treatments patients
			1/307	Flink, 2006[102]	Random differences among patients with previous IFN, LAM, and combined therapy	
HBV DNA loss, normalization of ALT					Random differences among patients naïve to any antiviral treatment	

Consensus Conference Question 4
What Measures are Appropriate to Monitor Therapy and Assess Outcomes?

EPC Question 4. What is the evidence that changes in surrogate endpoints in response to treatment are reliable predictors of long-term resolution or slowed progression of disease?

Surrogate outcomes of interest.

- ALT and/or AST levels
- HBV viral load
- Change in HBeAg status
- Liver biopsy findings
- Drug resistance

Clinical outcomes of interest.

- Hepatocellular carcinoma (HCC)
- Liver failure
- Cirrhosis
- Liver-related death
- All-cause mortality

Results. We reviewed all studies eligible for question 2 or question 3 to identify RCTs that assessed clinical outcomes in association with monitored changes in viral load or ALT levels. We conducted an additional literature search to identify original epidemiologic observations of more than 50 subjects that examined the association between clinical outcome and changes in biochemical or virological surrogates in patients with active CHB treated with pharmacological agents approved by the FDA with longer than 1 year of followup (Mesh terms "Biological Factors," "Disease Progression," "Hepatitis B, Chronic/prevention and control," OR "Hepatitis B, Chronic/therapy"). From 646 articles retrieved, and one found with a manual search, seven articles were eligible because they reported the association of change in a putative surrogate of interest due to treatment with a clinical outcome of interest.[182] We assessed results based on established criteria for determining the validity of surrogate measures: (1) The biological marker must be correlated with the clinical endpoint and (2) the marker must fully capture the net effect of the intervention on the clinical-efficacy endpoint. We used the definition of a surrogate endpoint proposed in a Summary of a National Institutes of Health Workshop: Considerations in the Evaluation of Surrogate Endpoints in Clinical Trials: "a laboratory measurement or physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives. A clinical investigator uses epidemiologic, therapeutic, pathophysiologic, or other scientific evidence to select a surrogate endpoint that is expected to predict clinical benefit, harm, or lack of benefit or harm. For a biomarker to serve as a surrogate for the effect of an intervention on a clinical endpoint at the population level, more is required than just the ability of the marker measured on an individual to predict that individual's clinical endpoint. The extent to which a biomarker is appropriate for use as a surrogate endpoint in

evaluating a new treatment depends on the degree to which the biomarker can reliably predict the clinical benefit of that therapy, as compared to a standard therapy. Such use generally requires extrapolation from data generated for different treatments than the one under investigation. Substituting a surrogate requires that it not only predicts the clinical outcome of interest but also fully captures all the major effects of the new treatment. Surrogate endpoints might also be used to advise patients about modifications of treatment after they have reached a surrogate endpoint but not yet reached the true clinical endpoint."

Overall summary.

- Evidence presented for questions 2 and 3 indicated that no study was designed to assess the effectiveness of treatment on clinical outcomes, a necessary prerequisite for determining the validity of surrogates. Among studies that reported clinical outcomes, treatments did not improve all-cause mortality, liver related death, hepatic carcinoma, or hepatic decompensation.
- In evidence presented for questions 2 and 3, even fewer studies assessed the association of baseline 'surrogates' with clinical outcomes.
- We did not find any RCTs that evaluated the association in the change in potential surrogate due to treatment with a clinical outcome.
- We found associations of certain biochemical, virological, and histological measures with clinical outcomes, and advise caution in calling these measures surrogates.
- Out of the seven included studies, the four that met our inclusion criteria were either long-term followup of prior RCTs, with randomization no longer preserved, or cohort studies of once-treated patients, where potential surrogate markers were assessed in relation to long-term clinical outcomes.
- We identified a critical shortage of studies evaluating of the association of surrogates (or change in surrogates) on clinical outcomes. In most studies, the followup was not adequate, both in terms of duration of followup and assessment of outcome, the endpoint events were few, and methods were not inadequate. There were several 'missed opportunities' to further assess associations where it appeared that authors could have been able to report relevant data, but this was not done. Clinical outcomes were combined into a single category, such as 'liver complications' or 'decompensation' making definitions heterogeneous from study to study and not possible to adequately assess.
- Regarding surrogates and endpoints, there was lack of uniformity in measurement, timing of measurement, definitions, and measurement of effect controlling for relevant effect modifiers, such as treatment.
- Regarding treatment, of the four included studies, two studies were in populations that received interferon versus no treatment or placebo. The effect of treatment was adjusted for in the multivariable model reporting the relevant putative surrogate measure and outcome.[174,175] One study evaluated a cohort of interferon treated patients[183] and one compared lamivudine versus combination of lamivudine and interferon.[106] None of these studies were adequately designed to assess surrogacy.
- Taken together, these data preclude us from drawing firm conclusions regarding the effect of change in surrogate markers and outcomes, and even less so regarding effect modification by treatment. Therefore, we have low confidence in determining whether any of these listed biochemical, histologic, or virologic measures are adequate surrogate markers. As noted previously, patients with of HBV HBsAg are capable of transmitting the hepatitis B virus to uninfected individuals. Therefore, clearance of HBV HBsAg

could be considered an appropriate clinical outcome from the perspective of transmissionprevention and public health, in addition to its possibly being a surrogate for later clinical outcomes in a given patient infected with hepatitis B.

Summary of findings. Of the seven included studies that addressed the question, one reported the association of ALT normalization during end of treatment with interferon versus placebo and hepatic decompensation and death among patients with treatment-naive CHB (HBeAg-positive and HBeAg-negative, with and without cirrhosis);[175] one study reported the effect of change in HBeAg status at the end of treatment on decompensation among treatment naive, HBeAg-positive CHB patients receiving lamivudine with or without peginterferon alpha 2b;[106] one study reported the association of detectable DNA during treatment on risk of progression of liver disease among treatment-naive patients with HBeAg-positive CHB treated with interferon alpha (a or b not specified) versus untreated;[174] and one study reported on the effect of worsening histology on progression of liver disease and cirrhosis and hepatocellular carcinoma, respectively, among a cohort of patients with HBeAg-positive CHB treated with interferon alpha-2a or 2b.[183]

In the other three studies, either the surrogate or endpoint reported did not strictly meet the criteria set forth by the question. For example, one study evaluated worsening necroinflammatory activity on rate of fibrosis progression but did not assess the impact of treatment on necroinflammatory activity or fibrosis (furthermore, fibrosis and cirrhosis are arguably potential surrogate and not clinical outcomes).[171] Two other studies reported outcome by baseline factors, such as lower fibrosis score at baseline[170] as a predictor of long-term overall and event-free survival, and staging score at baseline[173]as a predictor of liver-related complications. These studies are discussed briefly in this section as well, to give the reader perspective on published evidence that implies that these measures are accurate surrogates of clinical outcomes (Appendix E Table 12).

Individual surrogates and effect on outcomes.

ALT normalization and outcomes. One study reported the association between ALT normalization due to treatment and decompensation and death.[175] This study was a long-term followup of 302 patients (71 percent were male, average age was 34±15 years) with CHB that presented to the Liver Clinic in Palermo, Italy, between January 1982 and December 1991. Patients were eligible if they were HBsAg-positive with ALT at least two times ULN in the past 6 months and active hepatitis with or without cirrhosis on liver biopsy. At baseline, 28.5 percent were HBeAg-positive. Of the 302 patients that met the eligibility criteria, 109 received treatment with interferon alpha (presumed to be 2b; dose and duration not reported) and the remaining were untreated. It is unclear how the decision was made to treat or not treat, but the authors reported that the treated and untreated patients were 'fully comparable for all baseline and clinical features, except ALT levels.' The mean length of followup was 94±37.6 months. Followup was defined as number of months from liver biopsy to clinical events, death or last contact. Prior to the first followup visit, 9.6 percent of the patients were lost to followup, yet included in the analysis. The primary outcome was survival. Authors also reported adjusted relative risk for death and decompensation. Decompensation was defined as HCC, ascites, jaundice, encephalopathy, and portal hypertensive bleeding (low level of evidence).

Results.

Decompensation. Multivariate analysis showed that older age, cirrhosis at baseline, and abnormal ALT during followup were independent predictors of decompensation, controlling for treatment with interferon. Compared to those without ALT normalization, patients that had

normal ALT levels during treatment had a 76 percent relative risk reduction of decompensation [RR 0.24 (0.1; 0.6)] (low level of evidence).

Death. Multivariate analysis showed that older age, cirrhosis at baseline, and abnormal ALT during followup were independent predictors of death, controlling for treatment with interferon. Compared to those without ALT normalization, patients that had normal ALT levels during treatment had a relative risk reduction of 76 percent in their risk of decompensation [RR 0.24 (0.08; 0.7)] (Table 9 and Appendix E Table 13).

In conclusion, the low level of evidence of these findings suggests that ALT normalization due to treatment with interferon alpha may be a possible surrogate to assess the composite endpoint of decompensation and death in patients treated with interferon alpha.

Changes in HBV DNA level during/end of treatment and outcomes. There were two studies that reported the effect of changes in HBV DNA during or at end of treatment and outcome.[174,183] The patient populations were distinctly different, as discussed below.

The first study[183] was a longitudinal cohort study from Hong Kong on 133 HBeAg-positive CHB patients treated with interferon alpha-2a (55 percent) or 2b (45 percent) for 24 weeks between 1989 and 1997 (dose not reported) and followed up for at least 5 years after treatment, and had undergone two serial liver biopsies, the first within 6 months prior to treatment, and the second at 24-48 weeks after treatment. HBV DNA was quantified by RT-PCR with a linear range of 10^3-10^8 copies/ml. Of the 133 patients, 89 (67 percent) fulfilled the study criteria. Of these, 77 percent were male, median age was 30 years (range 18-53 years), and median followup was 119.4 months (range 60-238 months). The primary endpoint was 'liver complications' defined as HBV-related decompensated liver cirrhosis or HCC. Decompensated cirrhosis was defined as at least one of the following: ascites, spontaneous bacterial peritonitis, encephalopathy, and bleeding esophageal varices. Diagnosis of HCC was made histologically or on imaging studies plus alpha fetoprotein (AFP) of >400ng/ml.

Liver complications. The authors reported an association of HBV DNA $\geq 10^4$ copies/ml at 24 weeks after treatment with liver complications, among the 89 included patients. Of the 68 patients with HBV DNA $\geq 10^4$ copies/ml at 24 weeks after treatment, 10 (1.7 percent) developed liver complications, compared to 1 (4.8 percent) out of the 21 patients with HBV DNA $< 10^4$ copies/ml. We calculated the unadjusted OR for this association to be 3.08 (95 percent CI 0.44; 22.7, p=0.3).

The second study[174]is a long-term followup of a cohort of 164 consecutive patients with antiHBeAg-positive CHB that presented to liver clinics in Torina, Italy, between 1986 and 1993. Of these, 103 patients underwent treatment with interferon alpha-2a (46 patients participated in two clinical trials and the remaining 57 patients received interferon alpha-2a, 9MU three times weekly for 4-12 months. Twenty-one patients received more than one course of treatment with interferon alpha-2a. These patients were compared to 54 untreated patients that had either served as controls in a prior RCT (n=12) or refused treatment/were not candidates for treatment (n=42). Patients were followed for a median of 6 years (range 21 months to 12 years).

Serum HBV DNA was measured using a hybridization assay (sensitivity 10pg/ml). Negative samples underwent PCR amplification. The primary outcome of interest was the cumulative probability of event-free survival. The authors also reported multivariate analysis of factors influencing disease progression. Disease progression was defined as progression of fibrosis to stage 4, occurrence of decompensation (ascites or variceal bleeding), or development of HCC. HBV DNA was dichotomized as pattern 1 (yes/no) defined as always or frequently >10 pg/ml before and during treatment.

Out of the 164 patients, 128 were considered for analysis of factors influencing outcomes, after excluding 36 patients who did not undergo a second liver biopsy or had decompensated liver cirrhosis at baseline. Of these, 57 (42 percent) had cirrhosis at end of treatment.

Disease progression. Controlling for age, prior history of HBeAg positivity, and treatment with interferon, pattern 1 of HBV DNA (always or frequently >10pg/ml) was associated with increased odds of progression (OR 1.58, 1.12; 2.25) (Table 9 and Appendix E Table 13).

In conclusion, the low levels of evidence among HBeAg-positive CHB patients treated with interferon alpha-2a or 2b for 24 weeks, with HBV DNA levels $\geq 10^4$ copies/ml at end of treatment, may be a candidate to assess surrogacy for a composite endpoint of liver complications. Low levels of evidence among inpatients with CHB who are antiHBeAg-positive, with HBV DNA levels always or frequently higher than 10 pg/ml during treatment with interferon alpha 2a for 16 to 52 weeks, may serve as a potential surrogate for a composite endpoint of disease progression.

Worsening histology and outcomes. One study reported that changes in histology at end of interferon treatment may be associated with liver complications.[183] A longitudinal cohort study from Hong Kong included 133 HBeAg-positive CHB patients treated with interferon alpha-2a (55 percent) or 2b (45 percent) for 24 weeks between 1989 and 1997 and followed up for at least 5 years after end of treatment with those who had undergone two serial liver biopsies, the first within 6 months prior to treatment and the second at 24-48 weeks after treatment. All liver biopsies were scored by a single pathologist blinded to treatment and outcomes, according to the modified HAI score (0-18) and Ishak fibrosis score. An increase in modified HAI score of two points was considered significant. Of the 133 patients, 89 (67 percent) fulfilled study criteria. Of these, 77 percent were male, median age was 30 years (range 18-53 years) (median followup was 119.4 months; range 60-238 months). The primary endpoint was 'liver complications' defined as HBV-related decompensated liver cirrhosis or HCC. Decompensated cirrhosis was defined as at least one of the following: ascites, spontaneous bacterial peritonitis, encephalopathy, and bleeding esophageal varices. Diagnosis of HCC was made histologically or on imaging studies plus AFP of >400ng/ml.

Eight of the 19 patients with a two point increase in HAI score developed liver complications versus three of the 70 patients without a two point increase in HAI score at end of treatment(42 percent versus 4 percent). The authors reported adjusted relative risk of liver complications. It is unclear what the analysis is adjusted for, but after adjustment 'of other risk factors,' the relative risk of liver complications in patients with a two point increase in HAI score was 5.56 (95 percent CI 1.12-27.6) (Table 9 and Appendix E Table 13).

In conclusion, low levels of evidence suggested that among patients with CHB and HBeAg-positive, a two point increase in HAI score at the end of treatment with interferon alpha-2a or 2b for 24 weeks may serve as a potential surrogate for liver complications.

Loss of HBeAg at end of treatment and outcomes. One study[106] reported that seroconversion in HBeAg status due to treatment with lamivudine alone or lamivudine plus peginterferon is associated with lower risk of hepatic decompensation. Ninety-six patients had previously completed an RCT comparing lamivudine plus peginterferon alpha-2b versus lamivudine monotherapy at a single center in Hong Kong. All patients were treatment-naive CHB, HBeAg-positive, with HBV DNA of at least 500,000 copies/ml and serum ALT 1.3-5 times ULN. They received either lamivudine 100 mg orally once daily for 52 weeks (n=48) or lamivudine 100 mg orally once daily for 52 weeks plus peginterferon alpha-2b at a dose of 1.5 mcg/kg/week for 32 weeks (n=48). After completion of treatment, all patients were followed for at least 52 weeks.

HBeAg was measured at the end of treatment (52 weeks in both groups) by enzyme-linked immunoSorbent assay (ELISA). Primary measures of interest were probability of sustained virological response, factors associated with sustained virological response among those treated with combination therapy, and HBeAg seroconversion among nonresponders. Decompensation was defined as elevated serum bilirubin >50 IU/L accompanied with biochemical relapse (defined as ALT elevation greater than two times ULN).

Of the 96 patients, 95 were included in the final analyses. One patient who had HBeAg seroconversion prior to commencement of therapy was excluded. The mean ages reported for combination arm and lamivudine treatment were 32±10 and 35±10 years respectively; and 60 percent and 72 percent of the combination arm and lamivudine treated arm, respectively, were male. The post-treatment followup was 117±34 weeks for the combination arm and 124±29 weeks for the lamivudine arm.

Decompensation. Thirty (63 percent) patients in the combination arm (out of 48) had HBeAg seroconversion; of these, one developed decompensated disease, while 18 (37 percent) remained HBeAg-positive at end of treatment, of which one patient developed decompensated disease. We calculated unadjusted odds ratio of decompensation associated with seroconversion of HBeAg among those receiving combination treatment to be 0.6 (95 percent CI 0.03; 9.01) (p-value 0.7).

Thirteen (28 percent) patients in the lamivudine arm (of 47) had HBeAg seroconversion, one patient developed decompensated disease, and 34 remained HBeAg-positive at end of treatment, out of which three patients developed decompensated disease. We calculated unadjusted odds ratio of decompensation associated with seroconversion of HBeAg among those receiving lamivudine treatment to be 0.87 (95 percent CI 0.09; 7.64, p-value 0.9) (Table 9 and Appendix E Table 13).

In conclusion, the low level of evidence among patients with CHB who are HBeAg-positive, seroconversion at 52 weeks of combination therapy with peginterferon interferon alpha-2a + lamivudine is an incomplete surrogate for the composite endpoint of decompensation. The low level of evidence among patients with CHB who are HBeAg-positive, seroconversion at 52 weeks of treatment with lamivudine HBeAg seroconversion may be an incomplete surrogate for composite end point of decompensation.

Summary of evidence.

- There is no evidence to accurately determine whether biochemical, virological, or histological measures can serve as reliable surrogates to assess the effect of CHB treatments on clinical outcomes.
- There is limited information on the association of potential surrogates of ALT normalization, detectable HBV DNA, worsening histology, and change in HBeAg on composite endpoint of decompensation, cirrhosis and HCC, and all-cause mortality among patients with CHB treated with peginterferon-2a plus lamivudine, interferon alpha-2a or 2b or lamivudine.
- ALT normalization may be a candidate to assess as a surrogate for the composite endpoint of decompensation and death in patients treated with interferon alpha (low confidence).
- Among HBeAg-positive CHB patients treated with interferon alpha-2a or 2b for 24 weeks, HBV DNA levels >104 copies/ml at end of treatment may be a candidate to evaluate as an incomplete surrogate for liver complications (low confidence).

- Among antiHBeAg-positive CHB patients treated with interferon alpha-2a for 16 to 52 weeks, HBV DNA levels always or frequently higher than 10 pg/ml may be a potential surrogate for disease progression (low confidence).
- Among HBeAg-positive CHB patients treated with interferon alpha-2a or 2b for 24 weeks, a two point increase in the HAI score at end of treatment may be a potential surrogate for the composite endpoint of liver complications (low confidence).
- Among HBeAg-positive CHB patients treated with a combination of peginterferon interferon alpha-2a plus lamivudine, HBeAg seroconversion may be a candidate for an incomplete surrogate for decompensation (low confidence).
- Among HBeAg-positive CHB patients treated with lamivudine, HBeAg seroconversion may be an incomplete surrogate for decompensation (low confidence).
- There are no data assessing HBsAg seroconversion among treated patients on clinical outcomes.
- There are no data that assess the effect of drug resistance among treated patients on clinical outcomes.
- We did not find any published studies evaluating change in surrogates after treatment with adefovir or telbivudine and effect on clinical outcomes.

Summary of studies evaluating baseline variables as predictors of clinical outcomes and nonclinical endpoints. Three studies that did not meet the definitions of strictor definitions of associations or outcomes are listed in question 4. We describe these to show associations of baseline or other intermediate markers with outcomes.

Effect of baseline variables on clinical outcomes. Two studies evaluated baseline variables as predictors of long-term outcomes.

Baseline fibrosis score as predictor of liver-related complications.[173] A cohort study of 101 patients with HBeAg-positive CHB suggested that baseline fibrosis score was a predictor of liver related complications in patients treated with interferon. Patients had to have elevated ALT and staging score of 3 or greater, or ATL >200 IU/L if staging score was <3, in the 12 months prior to treatment. Patients received treatment with interferon alpha-2b at a dose of 6 MU intramuscularly three times weekly for 24 months between 1990 and 1997 and were followed for the next 4.5 years. The average age of the group was 46±0 years, 87 percent were male and the average followup was 68 months (range 5-136 months). The primary endpoint was biochemical and virological response. A secondary outcome was liver-related complication-free survival. Authors used the Cox proportional hazards model to estimate the effect of predictor variables of nonresponse to treatment and baseline fibrosis on liver-related complications. Nonresponders were defined as patients showing elevated ALT and/or detectable HBV DNA during treatment. Liver biopsies at baseline were scored using the Ishak scoring for fibrosis (scored 1-6). Liver-related complications included any of the following: histological progression to cirrhosis, ascites, jaundice, hepatic encephalopathy, gastrointestinal bleeding, or HCC.

Results showed that of the 101 patients, 30 (30 percent) had a sustained response to treatment while 71 (70 percent) were nonresponders. In multivariate analysis, controlling for age and treatment failure, staging score at baseline was a predictor of liver related complications (HR 1.71, 95 percent CI 1.17; 2.0).

Baseline fibrosis score and cirrhosis as predictors of overall and event-free survival.[170] A retrospective cohort study compared 201 patients with HBeAg-negative CHB that received lamivudine therapy between 1997 and 2001 at four liver centers in Greece. Additional eligibility criteria were elevated ALT, detectable HBV DNA, and histological findings of chronic

hepatitis.The dose was 100-150 mg orally once daily for the duration of followup (3.8±1.4 years). These patients were compared to two historical controls, one group of 209 patients that had received treatment with interferon alpha (type of interferon, dose and duration not reported) and followed for 6±2.7 years. The second historical control was a group of 195 patients that remained untreated, with followup of 6.1±3.9 years. Patients were followed until a major event, such as development of HCC or liver decompensation, orthotopic liver transplantation, or death. Controlling for age and type of therapy, lower fibrosis scores and absence of cirrhosis at baseline were independent predictors of survival and event-free survival. Estimates are reported with a significant p-value, but the actual estimates are not reported (Table 9 and Appendix E Table 14).

In conclusion, baseline fibrosis score may be a predictor of composite outcome of liver-related complications for patients undergoing treatment with interferon alpha-2b. Baseline fibrosis and absence of cirrhosis may be predictors of survival and event-free survival in patients with HBeAg-negative CHB treated with lamivudine, interferon alpha, or untreated. These findings do not demonstrate that fibrosis or absence of cirrhosis are validated surrogates to evaluate effect of treatments on clinical outcomes.

Effect of baseline and end of treatment variables on nonclinical outcomes. One study evaluated the effect of baseline and end of treatment variables on nonclinical outcome of rate of fibrosis progression.

Effect of histological fibrosis at baseline and worsening necroinflammatory activity during treatment on rate of fibrosis progression.[171] This was a retrospective study of patients with HBeAg-negative CHB presenting to liver clinics in Greece between 1993 and 2002. Criteria for treatment included patients with at least two serial liver biopsies, increased ALT, detectable HBV DNA, and histology compatible with chronic hepatitis. One hundred twenty patients were treated with interferon alpha (2a or 2b not specified) at a dose of 3-5MU three times weekly for 6-12 months. The treated patients were compared with 27 untreated patients, who either refused treatment or did not meet eligibility criteria for treatment. The average age for interferon alpha treated and untreated patients was 45±11 and 49±15 years respectively. Eighty-one percent of treated patients were male, while 89 percent of untreated patients were male. All patients underwent liver biopsy prior to treatment and at the end of treatment. Liver biopsies were scored by a single pathologist according to Ishak classification for grade (0-18) and stage (0-6). Patients with a decrease in necroinflammatory activity at followup liver biopsy ≥2 points compared to baseline liver biopsy were considered 'improved.' Fibrosis stage of ≥4 was considered severe or advanced. The outcome measure was 'annual rate of fibrosis' defined as change in fibrosis score between followup and baseline liver biopsy divided by number of years between the two biopsies. Controlling for age and interferon treatment, worsening of necroinflammatory activity (increase of ≥ 2 points on the Ishak grading score) (OR 1.05, 95 percent CI 1.03; 1.08) and milder fibrosis at baseline (OR 1.05, 95 percent CI 1.0; 1.11) were predictors of worse annual rate of fibrosis progression (Table 9 and Appendix E Table 14).

Table 9. Characteristics of included studies

Country/ID	Population/ Design	Treatment	Subjects Included	Dose/ Treatment and Followup Duration	Surrogates	Outcomes	Results	Quality	Comments
Italy[175]	CHB / cohort	Interferon alpha versus untreated	302	Dose NR / 24 weeks / 94 months	ALT normalization during/end of treatment	1. Decompensation (HCC, acites, jaundice, encephalopathy or portal hypertensive bleeding) 2. Death	Decompensation RR 0.24 (0.1;0.6) Death RR 0.24 (0.0; 0.7)	Moderate	Not primary outcome, secondary analysis
Hong Kong[183]	HBeAg+ CHB / cohort	All treated with Interferon alpha 2a or 2b	133, reported: 89	Dose NR / 24 weeks/ 5 years	1. HBV DNA at end of treatment ($\geq 10^4$ copies/ml) 2. 2 point increase in HAI score on liver biopsy	Liver complications (decompensation or HCC)	Unadjusted OR 3.08 (0.44;22.7) Adjusted RR 5.56 (1.12; 27.6)	Moderate	All treated, subgroups reported
Italy[174]	HBeAg+ CHB / cohort	Interferon alpha 2a versus untreated	164	9 MU TIW / 4-12 months / 6 years	HBV DNA pattern1 (always or frequently >10pg/ml)	Disease progression: fibrosis stage 4, occurrence of decompensation or HCC	Adjusted OR 1.58 (1.12; 2.25)	Moderate	Selection for treatment and treatment course and duration variable
Hong Kong[106]	HBeAg+ CHB / cohort	Lamivudine plus peginterferon alpha 2b versus lamivudine	95	100-150 po QD for LAM, 1.5mcg/kg/wk for peg-IFN / 52 weeks for LAM, 32 weeks for peg-INF / 52 weeks	Loss of HBeAg end of treatment	Decompensation (elevated serum bilirubin> 50IU/L+ ALT>2 times ULN	For LAM+ peginterferon-IFN: unadjusted OR: 0.6 (0.03;9.01) For LAM: unadjusted OR 0.87 (0.09; 7.6)	Low	Incomplete followup and reporting, few events
Italy[173]	HBeAg+ CHB / cohort	All treated with interferon alpha 2b	101	6 MU TIW / 24 months/68 months	Staging score at baseline	Liver related complications (histological progression, ascites, jaundice, encephalopathy, gastrointestinal bleeding or HCC)	HR 1.71 (1.17;2.0)	Low	Baseline predictor rather than surrogate

Table 9. Characteristics of included studies (continued)

Country/ID	Population/ Design	Treatment	Subjects Included	Dose/ Treatment and Followup Duration	Surrogates	Outcomes	Results	Quality	Comments
Greece[170]	HBeAg-CHB / retrospective cohort	Lamivudine versus interferon alpha versus untreated	201	LAM 100-150 mg/day for 3.8 years, Interferon NR / 3-6 years	Fibrosis score at baseline, cirrhosis at baseline	Survival and event-free survival (event defined as HCC, decompensation or liver transplantation)	NR	Low	Historical controls, effect measure not reported
Greece[171]	HBeAg-CHB / cohort	Interferon alpha versus untreated	147	3-5 MU TIW for 6-12 months	1. Worsening of necroinflammatory activity (>2 point increase in Ishak grading score) 2. Milder fibrosis at baseline	Annual rate of progression of fibrosis	1. OR 1.05 (1.03;1.08) 2. OR 1.05 (1.00-1.11)	Low	Historical controls, definitions not clear

Chapter 4. Discussion

This report synthesizes the evidence of the natural history of CHB and the effectiveness and harms of antiviral drugs on clinical, virological, histological, and biochemical outcomes. The primary goal in the management of adults with CHB is to initiate effective and safe therapies to improve health outcomes. CHB is a common and potentially serious health condition with a very long and complex clinical course. Predicting its natural history and accurately evaluating the effectiveness of treatments is very difficult, in part due to the long-term and heterogeneous nature of the disease. The data available are insufficient to provide patients, clinicians, researchers, and policymakers with high-quality information with which to make accurate prognostic and treatment decisions. Evidence from 38 observational studies suggested that increased age and duration of infection, male gender, coinfection with HIV, HCV or HDV, increased HBV DNA viral load, and cirrhosis were associated with increased risk of death and cancer, though the absolute risk is generally small. The magnitude and the confidence in the risk estimates of these variables varied. Cirrhosis was the factor associated with the highest degree of risk and greatest certainty in effect estimate.

Examined treatments failed to improve clinical outcomes versus placebo or relative to other interventions (low level of evidence from underpowered RCTs). Low to moderate level of evidence from 93 publications of RCTs suggested that improvements off treatment (<3 months to >6months) in biochemical, virological and histological outcomes occurred after mid-duration treatment: interferon alfa-2b maintained HBV DNA and HBeAg clearance and seroconversion and ALT normalization; adefovir maintained ALT normalization and HBV DNA clearance without evidence of genotypic resistance; lamivudine maintained HBV DNA and HBeAg clearance and ALT normalization; interferon alfa-2b+lamivudine versus lamivudine maintained HBV DNA and HBeAg clearance and seroconversion and reduced HBV DNA mutations; pegylated interferon alfa-2a versus lamivudine maintained HBV DNA and HBeAg clearance and seroconversion and ALT normalization and improved necroinflammatory scores; pegylated interferon alfa-2a+lamivudine versus lamivudine maintained HBV DNA and HBeAg clearance and seroconversion and ALT normalization but was not better when compared to pegylated interferon alfa-2a alone. High level of evidence and confidence indicated that adverse events were common but generally mild (especially with nucleos[t]ide analogs) and did not result in increased discontinuation of treatments. Interferons were associated with increased adverse effects especially flu like syndromes and need for dose modifications due to laboratory abnormalities. Nucleoside analogs have been shown to result in an increase in viral resistance and mutations. The impact that these have on clinical outcomes is not known. Low level of evidence suggested that increased age, longer duration of hepatitis, gender, baseline viral load and genotype, antigen, and histological status may change the effect of treatments on maintained intermediate outcomes. Because no studies reported an improvement in clinical outcomes due to treatments, there is inadequate information to determine if any of the proposed surrogate measures are reliable for assessing treatment effectiveness in reducing mortality, cirrhosis, or liver cancer.

Sustained outcomes 6 months off treatment were available for only 24 percent of the tested hypotheses. Three-quarters, 2,257 of 3,188 analyzed hypotheses, reported the outcomes at the end of the treatment. The limited evidence of sustained responses or end of treatment response does not provide sufficient evidence to recommend life-long or very long (years-decades)

treatment for CHB. Very limited and low quality evidence was available for patient subpopulations. Few authors reported appropriate interaction models or multivariate adjustment. We were unable to assess treatment consistency in outcomes due to the large variability in patient characteristics, examined treatments, and different definitions of the outcomes. For example, authors examined different outcomes including six positive (HBV DNA loss or reduction, HBsAg, or HBeAg loss or seroconversion) and two negative (relapse and mutation) virological outcomes, ALT normalization, and improvement in necroinflammatory and fibrosis histological scores and their combinations without clear definitions of clinical importance of expected changes for individual patients and the public's health. Investigators assessed outcomes using methods with different sensitivity, cutoffs, and scales. The majority of examined treatments demonstrated marginal or random effects on the sustained HBsAg seroconversion combined with other criteria of resolve hepatitis B. Consistent pooled risk reductions from multiple studies were observed for the following agents: interferon alfa-2b (HBeAg loss and HBV DNA loss); adefovir (ALT normalization and HBV DNA loss), and lamivudine (HBeAg seroconversion, HBV DNA loss, improved necroinflammatory scores, and ALT normalization).

Deciding which patients should not receive treatment is difficult and necessarily made between patient and health care provider. While the literature did not find evidence that any therapies improved clinical outcomes, it was inadequate to exclude potential benefits. RCTs were generally small and of short duration. Few clinical events occurred. Evidence indicated that the magnitude of effect of drug treatments on a combined virological outcome sometimes used to define disease resolution (HBV DNA and HBeAg clearance and HBeAg seroconversion) was relatively large (absolute risk differences greater than 20 percent), suggesting potential long-term benefits in clinical outcomes due to hepatitis B. Another measure of hepatitis resolution was less favorable. Loss of HBsAg and seroconversion due to treatment was very infrequent and not consistently observed.

There was little evidence to indicate that a trial of antiviral treatments was harmful or not indicated. Exceptions could include individuals with a very low long-term risk of death due to hepatitis B, cirrhosis, or HCC or substantially greater risk of immediate harms. None of the included treatment RCTs included hepatitis B carriers without active hepatitis. Future research should examine treatment effects in this population, though their long-term risk of symptomatic disease progression is low.

Limited evidence suggested small treatment benefits in HBeAg-negative patients, while probability of harms was the same, independent of baseline HBeAg status. Patients with active CHB experienced sustained benefits on selected intermediate outcomes after interferon alfa-2b, adefovir, lamivudine, or pegylated interferon alfa-2a. However, absolute rates were low, and indirect comparisons of absolute rates not valid unless tested in well-designed direct comparison RCTs.

Data from RCTs demonstrated that nucleotide analogues adefovir and lamivudine were well tolerated with safety profiles comparable to placebo. Adverse events were usually mild, including fatigue, headache, abdominal pain, nausea, and diarrhea. Approximately 8 percent of both adefovir and placebo subjects did not complete treatment for any reason or reported a serious adverse event in two RCTs reporting. Approximately 5 percent in both groups reported a serious adverse event. Pegylated interferon therapy, alone or combined with lamivudine, was not as well tolerated as lamivudine monotherapy. Subjects treated with combined or monotherapy were more likely to withdraw from a study or have dose modification due to an adverse events compared to lamivudine. An initial flu-like illness is commonly associated with peginterferon

alpha-2a treatment, noted by pyrexia, fatigue, myalgia, and headache. Other adverse events include hair loss, anorexia, and, less commonly, depression. Pegylated interferon and conventional interferon therapy had comparable safety profiles. Similar incidences of Grade 3 or 4 laboratory abnormalities were observed for adefovir and placebo with the exception of significant increases in ALT and AST levels. A black box warning from the prescribing information states subjects with or at risk of impaired renal function may develop nephrotoxicity with chronic administration of adefovir. Overall, dose modification was required for 46 and 47 percent of mono and combined therapy recipients, respectively. No subject assigned lamivudine required dose modification. Approximately 37 percent of peginterferon mono and combined therapy subjects required dose medication due to a lab abnormality. Neutropenia and thrombocytopenia were cited as the most common causes.

We found sparse data on whether the biochemical, virological, and histological markers used by clinicians, researchers, and drug approval agencies are true surrogates to accurately assess effect of treatment on clinical outcomes. There were no well designed, well executed studies of sufficient size or duration where patients were randomized to treatment and had complete followup. The potential surrogates studied were often dichotomized or collapsed into categorical metrics of variable definitions. The rationale for these analytic decisions was not clear. For example, 'change in fibrosis' may be defined as a two point or four point change in fibrosis. There was also variability in definition of outcome. Authors pooled multiple clinical endpoints of varying severity into a combined outcome, such as 'liver complications,' which made estimating effect on individual endpoints and comparing them across studies difficult. Additionally, for some potential surrogates, such as HBsAg seroconversion and formation of viral mutations, we did not find studies evaluating effect of change on clinical outcomes.

Limitations of the Review

We restricted our review to publications in the English language but conducted additional searches in Medline® for RCTs of eligible antiviral drugs. We identified ten publications in the Chinese language, including one study of adefovir, [184] two studies of entecavir,[185,186] two studies of interferon alfa-2b or pegylated interferon alfa-2b,[187,188] and five publications of lamivudine[189-193] We reviewed the abstracts and concluded that language bias, if present, could not change overall conclusions about efficacy of the tested antiviral drugs in adults with CHB. Tenovir has recently been approved by the FDA for treatment of CHB. However, we were unable to find any published data regarding efficacy and safety in these patients.

We did not review the effects of antiviral drugs that have not been approved by the FDA for CHB. Several new medications have been tested in the published and ongoing clinical trials, including emtricitabine, clevudine, pradefovir, valtorcitabine, thymosin alpha1, and anti viral vaccine.[11] The drugs did not show significant prevention of liver cancer or decompensation. The studies of emtricitabine reported improvement in laboratory measures of normalized ALT and loss of HBV DNA,[194] HBeAg seroconversion and improved histology,[195] and antiviral mutations.[196] One study addressed the question of which biological markers specific for the disease can predict better response to emtricitabine. The authors concluded that HBV core-specific clusters of differentiation (CD) CD4+T-cells were associated with viral clearance with no changes in HBV-specific CD8+T-cells.[196] Clevudine sustained viral clearance and ALT normalization 6 months off the treatments in HBeAg-positive[197,198] but not in HBeAg-negative

patients.[199] Two drugs, pradefovir and valtorcitabine, are being tested in phase I and II clinical trials. Tenofavir showed promising results in patients coinfected with HBV and HIV.[200,201]

Ongoing clinical trials do not aim to examine clinical outcomes but rather evaluate safety and effectiveness of antiviral drugs in specific patient populations. Effects of entecavir are being tested in Blacks/African Americans and Hispanics with HBV infection (Clinical Trials Database-number NCT00371150) (Appendix E* Tables 15 and 16). Sustained HBV DNA loss is expected after combined therapy with entecavir and tenofovir versus adefovir in adults with lamivudine-resistant HBV infection (NCT00605384). Patients experiencing virologic breakthrough after lamivudine therapy are being recruited to the RCTs of telbivudine, adefovir, or their combinations (NCT00376259). Adefovir plus entecavir or adefovir plus lamivudine compared to entecavir alone is being examined on several criteria of resolved hepatitis B in lamivudine-resistant adults with HBV infection (NCT00410202). Peginterferon alfa-2a is being tested in phase IV clinical trial to resolve hepatitis B in HBeAg-positive patients that would experience sustained loss of HBeAg and HBV DNA, HBsAg loss and seroconversion, and ALT normalization 6 months off the treatment (NCT00435825). Ongoing trails will not show the long-term effects of antiviral drugs on all cause and liver related mortality, liver cancer, and decompensation.

Ongoing (Appendix E Table 15) and completed (Appendix E Table 16) RCTs in patients with CHB did not aim to examine clinical outcomes but rather intermediate viral, biochemical, histological measures, and nonspecified safety outcomes. Only one (NCT00096785) RCT was completed less than a year ago; 10 RCTs (Appendix E Table 16) were completed more than year ago without identified publications in PubMed. We could not explore the reasons for nonpublications or pending status of the submitted publications since such information is not available on either the www.clinicaltrials.gov or the FDA web site. Reporting of outcomes during trial registration was not consistent with different levels of details (Appendix E Tables 15 and 16). However, variability in definitions of HBV DNA clearance is substantial, as well as the length of sustained outcomes assessment. Some studies did not provide any information about examined outcomes. Safety outcomes were not defined; few studies intend to evaluate rates of discontinuation of drug administration due to adverse events of laboratory toxicity. One study (NCT00412750) that evaluated the effects of telbivudine and peginterferon alpha-2a mono was terminated for safety issues with no further details about severity and frequency of adverse events. The study was designed to evaluate HBV DNA loss. Safety outcomes were not specified and require larger sample size. We can only assume that the rates of adverse events were unexpected and substantial to stop the study due to safety issues.

Few ongoing RCTs plan to examine the effects of drugs in patient subpopulations; therefore, individualized treatment recommendations based on RCTs would not be possible during the next decade. Few nonrandomized phase IV clinical trials (not shown) aim to investigate the role of baseline viral load on the effects of peginterferon alfa-2a plus ribavirin (NCT00154869) in patients with hepatitis B and C or liver function after telbivudine versus adefovir administration among patients with different viral genotype (NCT00640588). Ongoing observational studies did not intend to examine clinical outcomes or intermediate laboratory measured in patient subpopulations; therefore, upcoming publications would not clarify which subgroups may

* Appendixes and evidence tables cited in this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/hepb/hepb.pdf

experience the greatest benefit from the treatments. The fact that several registered RCTs were terminated due to poor recruiting may serve as additional justification for creating a national registry of the patients with CHB.

Gaps in Evidence and Recommendations for Future Research

The greatest gap in knowledge in the management of CHB derives from the lack of large, long-term RCTs assessing the effect of antiviral agents, alone or in combination, on clinical outcomes such as all-cause mortality, liver-related mortality, hepatocellular carcinoma, and hepatic decompensation. Additional valid clinical outcomes could include quality of life and hospitalizations. Cirrhosis is frequently described as a clinical outcome, but in most cases this is determined by liver biopsy performed in the absence of clinical symptoms. While predictive of future clinical events, such as liver-related mortality and all-cause mortality, cirrhosis may be more appropriately defined as a prognostic and potential surrogate measure. There is a moderate level of evidence that therapies can improve combined biochemical and virological outcomes used to define resolved hepatitis. However, randomized trials did not reliably demonstrate sustained HBsAg clearance off therapy. Therefore, there is insufficient evidence that any of these agents can reduce long-term infectivity or that they will improve clinical outcomes. Until randomized trials demonstrate that antiviral drugs improve clinical outcomes or provide sustained reduction in hepatitis B virus transmissibility, the accurate assessment of clinical effectiveness, the validity of putatitve surrogate measures, and decisions on whom to treat remain unknown.

Studies were not designed to detect significant effects of the drugs on clinical outcomes. Only one trial reported significant protective effect on clinical outcomes. Lamivudine reduced hepatocellular carcinoma, but only after post hoc adjusted analyses that excluded five individuals who developed hepatocellular cancer within the first year of the study.[132] Because the incidence of clinical outcomes is generally low among patients with CHB, randomized trials will require large sample sizes and long duration to have power to accurately assess clinical effects. Alternatively, enrollment of patients at high-risk of disease outcomes (e.g., patients with cirrhosis) would provide an opportunity to more quickly examine the effects of antiviral drugs in this group. Until such studies are completed, a multinational registry combining individual patient data may provide sufficient estimations of drug benefits and harms in patient subgroups.

We recommend that future research focus on clinically important outcomes (mortality, HCC, hepatic decompensation) or sustained criteria of resolved hepatitis B (s and e antigen seroconversion and loss of HBV DNA). More than 75 percent of 3,188 abstracted hypotheses from 92 publications resulted in random differences in outcomes. Available studies examined selected outcomes at the end of the treatments and at different times of followup off the treatments. Therefore, any positive effects could be at least partly due to statistical chance. Additionally, selective reporting of outcomes to emphasize positive is a real possibility.

Studies were not designed to test treatment differences on clinical outcomes and resolved hepatitis in patient subpopulations. Additionally, these studies involved relatively short-term treatment and followup evaluation off treatment. Many were designed to test treatment efficacy related to selected intermediate biochemical or virological measures rather than clinical outcomes. This is of particular concern due to the long natural history of the disease, including long subclinical phase prior to initiation of any treatment and the long followup required prior to

development of any clinical events. The reported studies may not reflect current practice that is initiating longer courses (including indefinite length) of treatment. Further research is needed to determine whether current treatment strategies will improve long-term clinical outcomes. Studies should be sufficiently large to assess outcomes in patients with multiple clinical and disease characteristics currently used by clinicians and guideline groups to make treatment decisions (e.g., according to eAg and HBV DNA status).

There have been several very large prospective studies on patients with chronic HBV infection. These studies have shown that various patient characteristics and clinical markers are predictive of important chronic HBV-related outcomes such as cirrhosis, HCC, and death. What remains to be addressed is the extent to which these predictors of disease progression represent clinically useful therapeutic targets or disease surrogates. Observational studies that report longitudinal measurements of these predictors and collect outcome data could better identify whether change in predictor status leads to change in outcomes, instead of the currently more common approach of whether a one-time measurement predicts outcomes. While there was strong evidence that cirrhosis was associated with significantly poorer clinical outcomes, there was very little evidence available that provided information on the predictive ability of other indicators of liver histology. Large studies with baseline histology measurements would help to fill this gap. The vast majority of research on the natural history of chronic hepatitis, even within the United States, is comprised primarily of people with perinatally acquired HBV infections. Therefore the evidence base for patients with HBV infection acquired later in life is much weaker and basically involves extrapolation other populations. Since recent clinical guidelines classify patients into diagnostic groups based on HBeAg status, serum HBV DNA, ALT/AST levels and biopsy results, it is important that future observational studies at a minimum measure these factors and analyze data controlling or stratifying for these variables. Future studies would benefit from creating cohorts of people within existing diagnostic groups: inactive carrier, chronic hepatitis HBeAg-positive, chronic hepatitis HBeAg-negative, and chronic hepatitis with cirrhosis, and presenting key findings separately for these groups.

Additional research needs include:

- Develop valid surrogates and demonstrate the effect of a treatment agent on the surrogate as well as the clinical endpoints.
- Clarify candidate surrogate markers. The change in surrogate due to treatment should predict and explain the change in the outcome.
- Differentiate a surrogate from an outcome. Cirrhosis is frequently described as a clinical outcome. However, many studies included patients with baseline cirrhosis to predict difference in future clinical events, such as liver-related mortality and all-cause mortality. The role of viral mutations and drug resistance during treatment with reverse transcriptase inhibitors as surrogate or endpoint measures had not been defined yet.
- Develop and standardize definitions of surrogate markers. Adopting a uniform scoring system for liver biopsies and deciding on a single definition of what constitutes clinically meaningful change in score, such as ‘fibrosis progression’ (is it a one, two, or four point change in fibrosis or necroinflammatory activity or both). This requires an international effort, particularly since different continents seem to use different scoring systems. Definitions of ALT elevation should be standardized (any abnormal ALT, two times or four times the upper limit of normal). For HBV DNA, we found the greatest heterogeneity in assay used limit of detection and definition of what constituted ‘high’

versus ‘low’ viral load. In the absence of uniform definitions, clinical significance is often lost, as data are grouped and categorized to achieve a statistical significance.

- Develop, standardize, and disseminate the laboratory assay and methods used to quantify surrogate markers of interest. In the case of HBV DNA, we need to have a uniform requirement of real-time PCR with a standard cutoff for upper and lower detection limit.
- Develop standard timing of measurement of intermediary measures to demonstrate a change. For example, should we measure ALT and HBV DNA at baseline and every 6 months on treatment and after treatment for at least 5 years? What magnitude of change between which of these values constitutes a ‘change’ that can be predictive of outcome?
- In the absence of hard clinical endpoints, additional valid clinical outcomes could be considered as endpoints, such as quality of life, cost effectiveness, and hospitalizations. These may be additional benefits favoring treatment, but it needs to be made clear to the patient and treating physician for clinical decisionmaking.

Conclusion

Adults with CHB are at increased risk for poorer health outcomes, though the absolute risk generally is small and requires many years to manifest. Available drugs have not been demonstrated to improve clinical outcomes or resolve hepatitis B. Presence of cirrhosis is the greatest risk factor leading to poor clinical outcomes. Interferons, reverse transcriptase inhibitors, and their combinations provided mid-duration sustained off treatment improvements in selected intermediate outcomes. Baseline patient and disease characteristics may change the natural history of the disease and response in intermediate outcomes. Most drugs are relatively well tolerated with few adverse effects that are generally mild. Reliable surrogate measures to assess treatment effectiveness do not exist. Long-term RCTs are needed to assess long-term effects of antiviral agents on clinical outcomes and among patient subpopulations.

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(Note that there is a separate set of references at the end of the evidence tables in Appendix E and reference numbers differ from those in the text of the report.)

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197. Lee HS, Chung YH, Lee K, et al. A 12-week clevudine therapy showed potent and durable antiviral activity in HBeAg-positive chronic hepatitis B. Hepatology 2006 May; 43(5):982-8.
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201. Dore GJ, Cooper DA, Pozniak AL, et al. Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and -experienced patients coinfected with HIV-1 and hepatitis B virus. J Infect Dis 2004 Apr 1; 189(7):1185-92.

List of Acronyms and Abbreviations

AFP	Alpha fetoprotein
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransferase
ARD	Absolute risk difference
AST	Aspartate aminotransferase
BCP	Basal core promoter
BEHoLD	Benefits of Entecavir for Hepatitis B Liver Disease
BMI	Body mass index
CD	Cluster of differentiation
CHB	Chronic hepatitis B
CI	Confidence interval
CK	Creatine kinase
DNA	Deoxyribonucleic Acid
ELISA	Enzyme-Linked ImmunoSorbent Assay
EPC	Evidence-based practice center
FDA	Food and Drug Administration
HAI	Histological activity index
HBeAg	Hepatitis B “e” antigen
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis delta virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
MACS	Multicenter AIDS cohort study
MU	Million units
NIH	National Institutes of Health
PC	Precore
PCR	Polymerase chain reaction
OR	Odds ratio
RCT	Randomized controlled trial
RR	Relative risk
RT-PCR	Reverse transcriptase - polymerase chain reaction
SD	Standard deviation
TEP	Technical expert panel
ULN	Upper limit of normal
WBC	White blood cells

Appendix A. Exact Search Strings

Key Question 1 – literature search string

Database: Ovid MEDLINE(R)

	Medical Subject Heading Terms	Number of Retrieved References
1	Exp Hepatitis B, chronic/ or exp Hepatitis B/ or exp Hepatitis B virus/	39,405
2	Exp hepatocellular carcinoma	40,097
3	Exp liver failure	12,710
4	Liver cirrhosis.mp. or exp liver cirrhosis	59,664
5	Liver cirrhosis.mp. or exp liver cirrhosis/	393,300
6	Exp Death/ or death.mp	366,266
7	Exp Survival/ or survival.mp. or exp survival rate	480,039
8	or/2-7	1,076,543
9	Natural history/ or cohort studies/ or prospective studies/ or longitudinal studies/ or cohort.mp. or prospective.mp. or longitudinal.mp.	491,684
10	1 and 8 and 9	621
11	Limit 10 to (humans and English language)	558

Key Questions 2-4 – literature search strings

Medical Subject Heading Terms	Number of Retrieved References
"Hepatitis B, Chronic"[Mesh] NOT review NOT Case Reports Limits: Humans, Journal Article, English, All Adult: 19+ years	1,525
"Hepatitis B, Chronic"[Mesh] Limits: Publication Date from 1990/01/01 to 2007/12/31, Humans, Journal Article, English, All Adult: 19+ years	1,778
"Hepatitis B, Chronic"[Mesh]	4,329
"Hepatitis B, Chronic"[Mesh] Limits: Humans, Randomized Controlled Trial, English, All Adult: 19+ years	182
"Hepatitis B" Limits: Humans, Randomized Controlled Trial, English, All Adult: 19+ years	712
("Hepatitis B, Chronic/prevention and control"[Mesh] OR "Hepatitis B, Chronic/therapy"[Mesh]) AND "Epidemiologic studies" [Mesh] Limits: Humans, English, All Adult: 19+ years	286
("Hepatitis B, Chronic/prevention and control"[Mesh] OR "Hepatitis B, Chronic/therapy"[Mesh]) Limits: Humans, English, All Adult: 19+ years	855

Medical Subject Heading Terms	Number of Retrieved References
"Hepatitis B, Chronic"[Mesh] Limits: Humans, English, All Adult: 19+ years AND ("Interferons/drug effects"[Mesh] OR "Interferons/metabolism"[Mesh] OR "Interferons/pharmacokinetics"[Mesh] OR "Interferons/pharmacology"[Mesh] OR "Interferons/poisoning"[Mesh] OR "Interferons/therapeutic use"[Mesh]) Limits: Humans, Controlled Clinical Trial, English, All Adult: 19+ years	14
("Interferons/drug effects"[Mesh] OR "Interferons/metabolism"[Mesh] OR "Interferons/pharmacokinetics"[Mesh] OR "Interferons/pharmacology"[Mesh] OR "Interferons/poisoning"[Mesh] OR "Interferons/therapeutic use"[Mesh]) Limits: Humans, Controlled Clinical Trial, English, All Adult: 19+ years	398
"Hepatitis B, Chronic"[Mesh] Limits: Humans, Controlled Clinical Trial, English, All Adult: 19+ years	35
"Hepatitis B, Chronic"[Mesh] Limits: Humans, Clinical Trial, Phase IV, English, All Adult: 19+ years	0
"Hepatitis B, Chronic"[Mesh] Limits: Humans, Clinical Trial, Phase III, English, All Adult: 19+ years	16
"Hepatitis B, Chronic"[Mesh] Limits: Humans, Clinical Trial, Phase I, Clinical Trial, Phase II, English, All Adult: 19+ years	23
"Hepatitis B, Chronic"[Mesh] Limits: Humans, Clinical Trial, Phase I, English, All Adult: 19+ years	10
"Adefovir "[Substance Name] AND "hepatitis B" Limits: Entrez Date from 1990/01/01 to 2007/12/31, Humans, Randomized Controlled Trial, English, All Adult: 19+ years	1
"Adefovir "[Substance Name] Limits: Entrez Date from 1990/01/01 to 2007/12/31, Humans, Randomized Controlled Trial, English, All Adult: 19+ years	6
"Entecavir "[Substance Name] AND "hepatitis B" Limits: Entrez Date from 1990/01/01 to 2007/12/31, Humans, Randomized Controlled Trial, English, All Adult: 19+ years	5
"Entecavir "[Substance Name] Limits: Entrez Date from 1990/01/01 to 2007/12/31, Humans, Randomized Controlled Trial, English, All Adult: 19+ years	6
"Telbivudine "[Substance Name] AND "hepatitis B" Limits: Entrez Date from 1990/01/01 to 2007/12/31, Humans, Randomized Controlled Trial, English, All Adult: 19+ years	4
"Telbivudine "[Substance Name] Limits: Entrez Date from 1990/01/01 to 2007/12/31, Humans, Randomized Controlled Trial, English, All Adult: 19+ years	4
"Interferons"[Mesh] AND "hepatitis B" Limits: Entrez Date from 1990/01/01 to 2007/12/31, Humans, Randomized Controlled Trial, English, All Adult: 19+ years	169

Medical Subject Heading Terms	Number of Retrieved References
"Hepatitis B, Chronic"[Mesh] AND "Effect Modifiers (Epidemiology)"[Mesh] Limits: Humans, English, All Adult: 19+ years	1
“Hepatitis B, Chronic” AND "Treatment Outcome"[Mesh] AND "Effect Modifiers (Epidemiology)"[Mesh] Limits: Humans, English, All Adult: 19+ years	1
"Hepatitis B, Chronic"[Mesh] AND "Treatment Outcome"[Mesh] AND "Effect Modifiers (Epidemiology)"[Mesh] Limits: Humans, English, All Adult: 19+ years	1
"Epidemiologic studies"[Mesh] AND "Biological Factors"[Mesh] AND ("Hepatitis B, Chronic/prevention and control"[Mesh] OR "Hepatitis B, Chronic/therapy"[Mesh]) Limits: Humans, English, All Adult: 19+ years	202
"Biological Factors"[Mesh] AND ("Hepatitis B, Chronic/prevention and control"[Mesh] OR "Hepatitis B, Chronic/therapy"[Mesh]) Limits: Humans, English, All Adult: 19+ years	576
"Disease Progression"[Mesh] AND ("Hepatitis B, Chronic/prevention and control"[Mesh] OR "Hepatitis B, Chronic/therapy"[Mesh]) Limits: Humans, English, All Adult: 19+ years	17
Update January 7, 2008	
"Hepatitis B, Chronic"[Mesh] Limits**:** Publication Date from 2007/11/01 to 2008/3/31, Humans, Randomized Controlled Trial, English, All Adult: 19+ years	3

Appendix B: List of Excluded Studies

Key Question 1

1. Aach RD, Aach RD. What a difference an antigen makes. Gastroenterology 1982 Jul;83(1 Pt 1):146-9. *Editorial*
2. Abdo AA, Al-Jarallah BM, Sanai FM, Hersi AS, Al-Swat K, Azzam NA, et al. Hepatitis B genotypes: relation to clinical outcome in patients with chronic hepatitis B in Saudi Arabia. World J Gastroenterol 2006 Nov 21;12(43):7019-24. *Not relevant outcomes*
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4. Ahmed ME, al-Knaway B, al-Wabel AH, Malik GM, Foli AK, Ahmed ME, et al. Acute upper gastrointestinal bleeding in southern Saudi Arabia. J R Coll Physicians Lond 1997 Jan-Feb;31(1):62-4. *Not eligible exposure*
5. Alexopoulos CG, Vaslamatzis M, Hatzidimitriou G, Alexopoulos CG, Vaslamatzis M, Hatzidimitriou G. Prevalence of hepatitis B virus marker positivity and evolution of hepatitis B virus profile, during chemotherapy, in patients with solid tumours. Br J Cancer 1999 Sep;81(1):69-74. *Not relevant outcomes*
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7. Andus T, Gross V, Holstege A, Ott M, Weber M, David M, et al. High concentrations of soluble tumor necrosis factor receptors in ascites. Hepatology 1992 Sep;16(3):749-55. *Not eligible exposure*
8. Anonymous. Prevention of liver cancer. World Health Organ Tech Rep Ser 1983;691:1-30. *Review*
9. Anonymous. Effect of interferon-alpha on progression of cirrhosis to hepatocellular carcinoma: a retrospective cohort study. International Interferon-alpha Hepatocellular Carcinoma Study Group. Lancet 1998 May 23;351(9115):1535-9. *Less than 1000 patients and not US study*

Key Question 1

10. Anonymous. Treatment of chronic hepatitis B: interferon alfa first. Prescrire Int 2001 Feb;10(51):17-21. *Review*
11. Anonymous. Summaries for patients. Acute liver failure in the United States. Annals of Internal Medicine 2002 Dec 17;137(12):I24. *Review*
12. Anselmo DM, Ghobrial RM, Jung LC, Weaver M, Cao C, Saab S, et al. New era of liver transplantation for hepatitis B: a 17-year single-center experience. Ann Surg 2002 May;235(5):611-9; discussion 9-20. *Not eligible target population*
13. Arase Y, Ikeda K, Murashima N, Chayama K, Tsubota A, Koida I, et al. Time course of histological changes in patients with a sustained biochemical and virological response to corticosteroid withdrawal therapy for chronic hepatitis B. American Journal of Gastroenterology 1999 Nov;94(11):3304-9. *Not relevant outcomes*
14. Arase Y, Ikeda K, Suzuki F, Suzuki Y, Kobayashi M, Akuta N, et al. Comparison of interferon and lamivudine treatment in Japanese patients with HBeAg positive chronic hepatitis B. Journal of Medical Virology 2007 Sep;79(9):1286-92. *Not relevant outcomes*
15. Arnot R, Arnot R. The evolving efforts to control hepatitis B virus. Pediatr Infect Dis J 1998 Jul;17(7 Suppl):S26-9. *Review*
16. Asmuth DM, Busch MP, Laycock ME, Mohr BA, Kalish LA, van der Horst CM, et al. Hepatitis B and C viral load changes following initiation of highly active antiretroviral therapy (HAART) in patients with advanced HIV infection. Antiviral Res 2004 Aug;63(2):123-31. *Not relevant outcomes*
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18. Baltayiannis G, Katsanos K, Karayiannis P, Tsianos EV, Baltayiannis G, Katsanos K, et al. Interferon-alpha therapy in HBeAg-negative chronic hepatitis B: a long-term prospective study from north-western Greece. Alimentary Pharmacology & Therapeutics 2006 Aug 1;24(3):525-33. *Less than 1000 patients and not US study*

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26. Benvegnu L, Alberti A, Benvegnu L, Alberti A. Patterns of hepatocellular carcinoma development in hepatitis B virus and hepatitis C virus related cirrhosis. Antiviral Res 2001 Nov;52(2):199-207. *Less than 1000 patients and not US study*
27. Benvegnu L, Fattovich G, Noventa F, Tremolada F, Chemello L, Cecchetto A, et al. Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis. A prospective study. Cancer 1994 Nov 1;74(9):2442-8. *Less than 1000 patients and not US study*
28. Benvegnu L, Gios M, Boccato S, Alberti A, Benvegnu L, Gios M, et al. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. Gut 2004 May;53(5):744-9. *Less than 1000 patients and not US study*
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44. Bukhtiari N, Hussain T, Iqbal M, Malik AM, Qureshi AH, Hussain A, et al. Hepatitis B and C single and co-infection in chronic liver disease and their effect on the disease pattern. JPMA J Pak Med Assoc 2003 Apr;53(4):136-40. *Not relevant outcomes*
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48. Cadranel JF, Di Martino V, Dorent R, Bernard B, Hoang C, Myara A, et al. Effects of ursodeoxycholic acid (ursodiol) treatment on chronic viral hepatitis in heart transplant patients: results of a prospective, double-blind, placebo-randomized study. Transplantation 2003 Apr 15;75(7):977-82. *Not relevant outcomes*
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62. Chen CH, Wang JT, Lee CZ, Sheu JC, Wang TH, Chen DS, et al. Quantitative detection of hepatitis B virus DNA in human sera by branched-DNA signal amplification. J Virol Methods 1995 May;53(1):131-7. *Not relevant outcomes*
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Appendix C: Technical Expert Panel Members and Affiliation

TEP Member	Affiliation
Miriam Alter, Ph.D.	University of Texas Medical Branch at Galveston
Gary Davis, M.D.	Baylor University Medical Center
Daryl Lau, M.D.	Harvard University
Michael Sorrell, M.D.	NIH Consensus Development Conference Chairperson
Myron J. Tong, Ph.D., M.D.	Huntington Medical Research Institute

Appendix D. Analytic Framework

Appendix D contains details on analytical framework of the report: algorithm to define eligibility of the studies, definitions, hypotheses, and statistical models

Management of Chronic Hepatitis B:
Article Screening Form

Author (first): _____

Journal: _____

Year of publication: _____

Article Call Number (MEDLINE ID): _____

Data Abstractor: _____

VERIFICATION / SELECTION OF STUDY ELIGIBILITY

Subjects randomly assigned	Yes	No	Unclear
Subjects age ≥18 years	Yes	No	Unclear
Addresses treatments for *chronic* HVB	Yes	No	Unclear
Surrogate outcomes of interest (ALT/AST levels; HBV viral load, etc.)	Yes	No	Unclear
Clinical outcomes of interest (Cirrhosis, liver failure, death, etc.)	Yes	No	Unclear
Or			
Is a systematic review/meta-analysis based on above	Yes	No	Unclear

CHECK ONE

____ **YES / Unclear, pull article for further review**

_____ **NO, exclude article:**

Reason(s) _____

Conceptual definitions

Hepatitis B - Inflammation of the liver in humans caused by a member of the orthohepadnavirus genus, hepatitis B virus. It is primarily transmitted by parenteral exposure, such as transfusion of contaminated blood or blood products, but can also be transmitted via sexual or intimate personal contact.[1]

Chronic hepatitis B - Inflammation of the liver in humans caused by a member of the orthohepadnavirus genus, hepatitis B virus lasting six months or more.[1]

Definitions of the American Association for the Study of Liver Diseases[2]

Chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus. Chronic hepatitis B can be subdivided into HBeAg positive and HBeAg negative chronic hepatitis B.

Inactive HBsAg carrier state: Persistent HBV infection of the liver without significant, ongoing necroinflammatory disease

Resolved hepatitis B: Previous HBV infection without further virologic, biochemical or histological evidence of active virus infection or disease

Acute exacerbation or flare of hepatitis B: Intermittent elevations of aminotransferase activity to more than 10 times the upper limit of normal and more than twice the baseline value

Reactivation of hepatitis B: Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B

HBeAg clearance: Loss of HBeAg in a person who was previously HBeAg positive

HBeAg seroconversion: Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative. For analytical purpose we may define HBeAg clearance as HBeAg seroconversion considering the same immunological response to achieve the outcome

HBeAg reversion: Reappearance of HBeAg in a person who was previously HBeAg negative, anti-HBe positive

Diagnostic criteria (one of several diagnostic criteria that may be utilized)

Chronic hepatitis B

1. HBsAg + >6 months
2. Serum HBV DNA >20,000 IU/ml (10^5 degree copies/ml), lower values 2,000-20,000 IU/ml (10^4 degree-10^5 degree copies/ml) are often seen in HBeAg-negative chronic hepatitis B. For analytical purpose we will abstract the viral load as reported and further categorize it according to cut off of >20,000 IU/ml
3. Persistent or intermittent elevation in ALT/AST levels
4. Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation For analytical purpose we define moderate as 2 or higher according to grade (1-5) (Knodell, Metavir, Ishak, HAI)

Inactive HBsAg carrier state

1. HBsAg+ >6 months

2. HBeAg-, anti-Hbe+
3. Serum HBV DNA <2,000 IU/ml
4. Persistently normal ALT/AST levels
5. Liver biopsy confirms absence of significant hepatitis

Resolved hepatitis B

1. Previous known history of acute or chronic hepatitis B or the presence of anti-HBe ± anti-HBs
2. HBsAg-
3. Undetectable serum HBV DNA
4. Normal ALT levels

Table 1. Operational definitions of treatment options for hepatitis B[1,3]

Agent	Definition
Interferon Alfa-2b	A recombinant alfa interferon consisting of 165 amino acid residues with arginine in position 23 and histidine in position 34. It is used extensively as an antiviral and antineoplastic agent
Pegylated interferon alfa-2a	interferon alfa-2A chemically modified by the covalent attachment of a polyethylene glycol
Lamivudine	A reverse transcriptase inhibitor and ZALCITABINE analog in which a sulfur atom replaces the 3' carbon of the pentose ring. Active Ingredient: ABACAVIR SULFATE; LAMIVUDINE Dosage Form;Route: TABLET; ORAL Proprietary Name: EPZICOM Active Ingredient: ABACAVIR SULFATE; LAMIVUDINE; ZIDOVUDINE Dosage Form; Route: TABLET; ORAL Proprietary Name: TRIZIVIR Active Ingredient: LAMIVUDINE Dosage Form; Route: SOLUTION; ORAL Proprietary Name: EPIVIR Active Ingredient: LAMIVUDINE Dosage Form; Route: SOLUTION; ORAL Proprietary Name: EPIVIR-HBV Active Ingredient: LAMIVUDINE; ZIDOVUDINE Dosage Form; Route: TABLET; ORAL Proprietary Name: COMBIVIR
Adefovir dipivoxil	A reverse transcriptase inhibitor. Active Ingredient: ADEFOVIR DIPIVOXIL Dosage Form; Route: TABLET; ORAL Proprietary Name: HEPSERA
Entecavir	Guanine/analogs and derivatives Active Ingredient: ENTECAVIR Dosage Form; Route: TABLET; ORAL Proprietary Name: BARACLUDE
Telbivudine	Nucleosides Active Ingredient: TELBIVUDINE Dosage Form; Route: TABLET; ORAL Proprietary Name: TYZEKA

Definition of Response to Antiviral Chronic Hepatitis B

Category of response

Biochemical (BR): Decrease in serum ALT to within the normal range

Virologic (VR): Decrease in serum HBV DNA to undetectable levels by PCR assays, and loss of HBeAg in patients who were initially HBeAg positive. Primary nonresponse (not applicable to interferon therapy): Decrease in serum HBV DNA by <2 log10 IU/ml after at least 24 weeks of therapy

Virologic relapse: Increase in serum HBV DNA of 1 log10 IU/ml after discontinuation of treatment in at least two determinations more than 4 weeks apart

Histologic (HR): Decrease in histology activity index by at least 2 points and no worsening of fibrosis score compared to pre-treatment liver biopsy

Complete (CR): Fulfill criteria of biochemical and virological response and loss of HBsAg

Time of assessment

On-therapy: During therapy

Maintained: Persist throughout the course of treatment

End-of-treatment: At the end of a defined course of therapy

Off-therapy: After discontinuation of therapy

Sustained (SR-6): 6 months after discontinuation of therapy

Sustained (SR-12): 12 months after discontinuation of therapy

Definition of Terms Relating to Antiviral Resistance to Nucleoside Analogue (NA) Treatment

Virologic breakthrough: Increase in serum HBV DNA by >1 log10 (10-fold) above nadir after achieving virologic response, during continued treatment

Viral rebound: Increase in serum HBV DNA to >20,000 IU/ml or above pretreatment level after achieving virologic response, during continued treatment

Biochemical breakthrough: Increase in ALT above upper limit of normal after achieving normalization, during continued treatment

Genotypic resistance: Detection of mutations that have been shown *in vitro* studies to confer resistance to the NA that is being administered

Phenotypic resistance: In vitro confirmation that the mutation detected decreases susceptibility (as demonstrated by increase in inhibitory concentrations) to the NA administered.

Definitions of the studies' design characteristics to estimate the level of evidence[4]

Level of evidence as defined by the U.S. Preventive Services Task Force

Level I: Evidence obtained from at least one properly designed randomized controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials.

Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Algorithms of meta-analysis[5]

Pooled estimate as a weighted average:

$$\theta_{IV} = \frac{\sum_i w_i \theta_i}{\sum_i w_i}$$

Weights are inverse of variance (standard error):

$$w_i = \frac{1}{SE(\theta_i)^2}$$

Standard error of pooled estimate:

$$SE(\theta_{IV}) = \frac{1}{\sqrt{\sum_i w_i}}$$

Heterogeneity (between-study variability) measured by:

$$Q = \sum_i w_i (\theta_i - \theta_{IV})^2$$

Assumptions for random effects model: true effect sizes *qi* have a normal distribution with mean *q* and variance *t2*; *t2* is the between-study variance

Between study variance:

$$\tau^2 = \frac{Q - (k-1)}{\sum_i w_i - \left(\frac{\sum_i w_i^2}{\sum_i w_i} \right)}$$

Where:
wi are the weights from the fixed effect inverse-variance method
Q is the heterogeneity test statistic from before (either from inverse-variance method or Mantel-Haenszel method)
k is the number of studies, and
t2 is set to zero if *Q*<*k*-1

Random effect pooled estimate is weighted average:

$$\theta_{DL} = \frac{\sum_i w'_i \theta_i}{\sum_i w'_i}$$

Weights used for the pooled estimate are similar to the inverse-variance, but now incorporate a component for between-study variation:

$$w'_i = \frac{1}{SE(\theta_i)^2 + \tau^2}$$

Standard error of pooled estimate:

$$SE(\theta_{DL}) = \frac{1}{\sqrt{\sum_i w'_i}}$$

Meta regression with random effects was obtained using aggregate level data.

Additive component of variance tau2 was estimated:

y[i] = a + B*x[i] + u[i] + e[i],

where u[i] is a normal error (standard deviations that may vary across units), e[i] is a normal error with variance tau2 to be estimated, assumed equal across units.
t-distribution was used calculating p-values and confidence intervals[6,7]

Number needed to treat to prevent one event of incontinence was calculated as reciprocal to absolute risk differences in rates of outcomes events in the active and control groups:[8,9]

NNT =1/(control group event rate - treatment group event rate).

The number of avoided or excess events (respectively) per 1000 population is the difference between the two event rates multiplied by 1000:

(control group event rate - treatment group event rate)*1000

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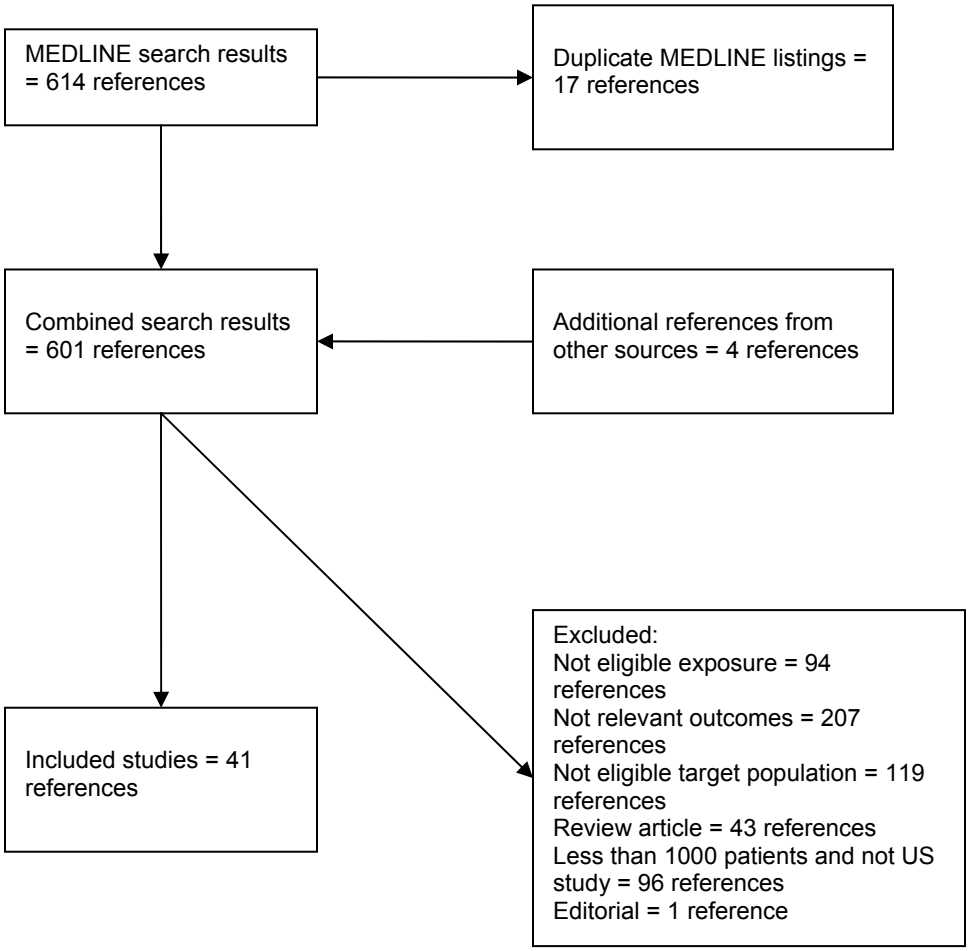
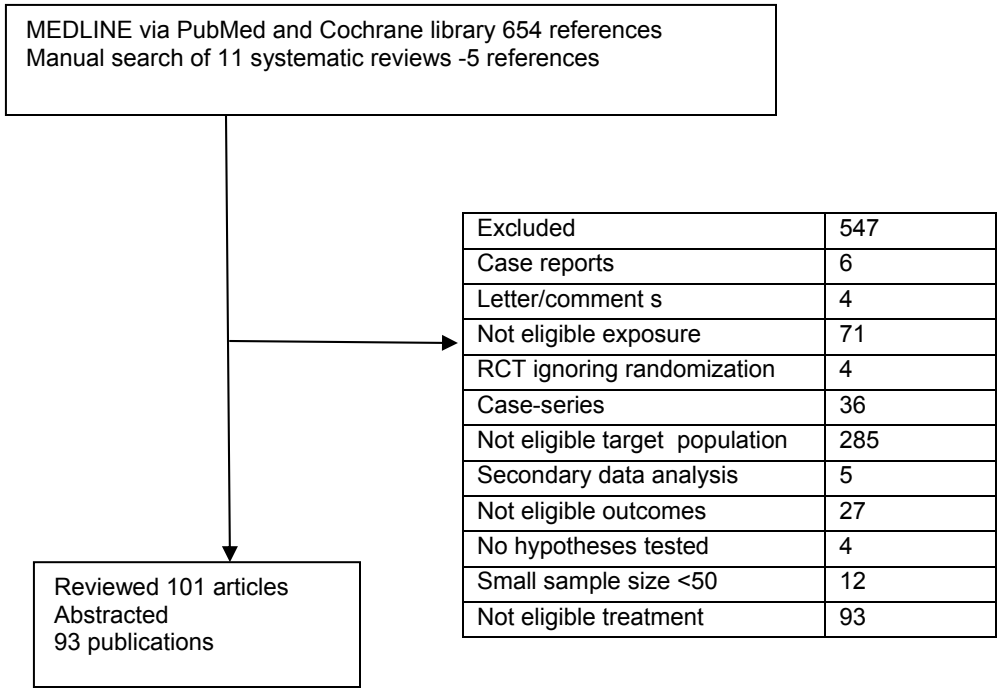
Appendix E. Figure 1. Flow Chart for Key Questions

Key Question 1



Appendix E. Figure 1. Flow Chart for Key Questions

Key Questions 2-4



Excluded	547
Case reports	6
Letter/comment s	4
Not eligible exposure	71
RCT ignoring randomization	4
Case-series	36
Not eligible target population	285
Secondary data analysis	5
Not eligible outcomes	27
No hypotheses tested	4
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Not eligible treatment	93

Appendix E. Table 1. Evidence table: Observational studies of the natural history of chronic hepatitis B in adults

Author / Country	Design Description	Subject Characteristics	Average Followup / Outcomes Description
A. American Studies			
Studies by Livingston/McMahon			
Livingston 2007[1] USA	From a cohort of Alaska Native people with chronic hepatitis B virus (HBV) infection, 47 patients with hepatocellular carcinoma (HCC) and 1129 patients without HCC were genotyped	N=1176. Alaska Native population with HBV genotype F.	21 years HCC; HBV genotypes
McMahon 2001[2]	Population based cohort study of HBV carriers observed prospectively for 12.3 years (median) as part of an active surveillance program to detect carriers with HCC	N=1536. Median age of first HBsAg-positive test 20 years (range 1 to 87). Men 59%.	12.3 years (median) HCC; liver disease mortality; end-stage liver disease
McMahon 2000[3]	Prospective 16-year, population-based cohort study to determine the impact of screening for HCC in 1,487 hepatitis-B surface antigen (HBsAg)-positive Alaska native carriers with alpha-fetoprotein (AFP) determinations every 6 months.	N=1487. Men and nonpregnant women with an elevated AFP level. Men 59%.	17 years HCC; mortality
McMahon 1990[4]	A total of 1400 hepatitis B surface antigen-positive Alaska natives were followed up prospectively over a period of 7815 carrier-years for the development of sequelae related to chronic HBV infection	N=1400	5.6 years Cirrhosis; HCC; mortality
Studies by Tong			
Tong 2007[5] USA	101 hepatitis B surface antigen-positive patients with HCC. Baseline basal core promoter (BCP) T1762/A1764 mutants, precore (PC) A1896 mutants, HBV genotypes and HBV DNA in HCC patients were compared with 67 chronic carriers prospectively.	N=168. <u>Chronic carriers (n=67)</u>: Mean age 45.4 ± 12.3 years. Men 29 (43.3%) Asian = 58 (86.6%) AST (mean) = 18.7 ± 11.4 U/L; ALT (mean) = 19.9 ± 13.8 U/L PC: Wild type 70% (n=44); A1896 mutant 30% (n=19). BCP: Wild type 79% (n=37); T1762/A1764 mutant 21% (n=10). <u>HCC patients (n=101)</u> Mean age 53.3 ± 13.5 years. Men 84 (83.2%) Asian = 91 (90.1%) AST (mean) = 128.8 ± 142.6 U/L; ALT (mean) = 92.9 ± 99.4 U/L PC: Wild type 54% (n=54); A1896 mutant 46% (n=46). BCP: Wild type 22.3% (n=21);	9.3 years HCC

Appendix E. Table 1. Evidence table: Observational studies of the natural history of chronic hepatitis B in adults

Author / Country	Design Description	Subject Characteristics	Average Followup / Outcomes Description
		T1762/A1764 mutant 77.7% (n=73)	
Tong 2006[6]	A retrospective study in 400 chronic hepatitis B patients in order to identify hepatitis B viral factors associated with complications of liver disease or development of hepatocellular carcinoma.	N=400. Mean age 48.4 years. Men 70.5% Serum HBV DNA level: Baseline (390 patients) = 2.1 log10 - 11.5 log10 copies/mL (median 6.1 ± 2.3 log10 copies/mL). Males (mean) = 6.39 ± 2.30 log10 copies/mL females (mean) = 5.52 ± 2.14 log10 copies/mL HBeAg at baseline: positive = 197 (49.9%) negative = 198 (50.1%)	7 years HCC; mortality
Tong 2006[7]	Prospective study The long-term followup of 400 patients who presented to our clinic with chronic hepatitis B is described.	N=400. Mean age 48.4 years. Men 70.5% Asian = 314 (78.5%) patients born in Asia = 70% patients born in North America = 24%	7 years HCC; mortality
Tong 2001[8]	7-year prospective surveillance study to detect hepatocellular carcinoma	N=602. Mean age 51 years. Men 59%	7 years HCC
Other studies			
Schiodt, 2003 [9] USA	A retrospective analysis of HBsAg+ patients enrolled in a US Acute Liver Failure (ALF) registry	N=26. Mean age 43 years. Men 54%, Ethnicity: white race 50%.	Survival rate
Thio 2002 [10] USA	Multicentre, prospective cohort study classified 5293 men who had sex with men, according to their HIV-1 antibody status, ascertained semiannually, and their HBsAg status, which we ascertained at baseline.	N=326. Homosexual, HIV positive men.	10.5 years Liver disease mortality
Abiad 2001[11] USA	Retrospective cohort study was conducted on 231 hepatitis B virus carriers, 65 of whom were also infected with hepatitis D virus, at thirteen Illinois state facilities for the developmentally disabled.	N=231 Men 74.9% Mean age 33 years HBV-HDV patients N= 65 Mean age 37 years Male = 48 (74%) Caucasian = 51 (79%) ALT > 60 U/L = 22 (34%) AST > 42 U/L = 37 (60%) HBeAg positive = 13 (20%) HBV only patients N=166 Mean age 31.4 Male = 125 (75%) Caucasian = 128 (77%)	10 – 12 years Overall mortality, mortality from hepatic disease, and risk of developing chronic hepatitis and cirrhosis

Appendix E. Table 1. Evidence table: Observational studies of the natural history of chronic hepatitis B in adults

Author / Country	Design Description	Subject Characteristics	Average Followup / Outcomes Description
		ALT > 60 U/L = 30 (18%) AST > 42 U/L = 52 (31%) HBeAg positive = 41 (25%)	
Nomura 1996 [12] USA	Cohort of 5924 Japanese American men was examined for HCC.	N=5924. Men 100%. Ethnicity: Asian race 100%.	25 years HCC
Norman 1993[13] USA	Large-scale serological and epidemiological followup study of the epidemic of hepatitis in the US Army in 1942.	N=69,988. White males	37 years HCC; mortality; liver disease mortality
Weissberg 1984 [14] USA	Survival data from 379 patients with chronic hepatitis B were analyzed to determine life expectancy for the patient from time of first contact	N=379. <u>Chronic persistent hepatitis (n=121)</u> Male (n) = 100 Age (yr) = 35 ± 1 Acute onset (n) = 57 Duration of HBsAg positivity (mo) = 27 ± 2 Alcoholic (n) = 10 Symptoms (n) = 59 ALT (IU) = 75 ± 4 AST (IU) = 66 ± 6 Hep-B DNA polymerase (n) = 85 <u>Chronic active hepatitis (n=128)</u> Male (n) = 112 Age (yr) = 39 ± 1 Acute onset (n) = 72 Duration of HBsAg positivity (mo) = 28 ± 2 Alcoholic (n) = 3 Symptoms (n) = 78 ALT (IU) = 95 ± 5 AST (IU) = 109 ± 9 Hep-B DNA polymerase (n) = 77 <u>Chronic active hepatitis w/cirrhosis (n=130)</u> Male (n) = 121 Age (yr) = 43 ± 1 Acute onset (n) = 67 Duration of HBsAg positivity (mo) = 31 ± 2 Alcoholic (n) = 13 Symptoms (n) = 95	2.4 years Mortality

Appendix E. Table 1. Evidence table: Observational studies of the natural history of chronic hepatitis B in adults

Author / Country	Design Description	Subject Characteristics	Average Followup / Outcomes Description
		ALT (IU) = 127 ± 6 AST (IU) = 125 ± 13 Hep-B DNA polymerase (n) = 58	
Sherman 1995[15] Canada	Prospective cohort study of chronic carriers of hepatitis B virus, to determine the prevalence and annual incidence of HCC.	N=1069. Mean age 39 years. Men 65%.	2.2 years HCC; mortality
B. European/Western nations Studies			
Amin 2006[16] Australia	The data from a cohort of 39109 HBV, 75834 HCV and 2604 HBV/HCV coinfected persons notified to the State health department, 1990-2002, were linked to the Cancer Registry and retrospectively analyzed.	N=41,713. Mean age 35 years. Men 55%	12 years HCC, other cancers
Konopnicki 2005[17] Europe, Argentina, Israel	A prospective, observational cohort study of 9802 patients with HIV-1 in 72 centers across Europe, including centers in Argentina and Israel. Coinfections with HBV and hepatitis C virus (HBC).	N=5728 (tested for HBsAg) Mean age 36. Men 78% HBsAg negative 5230 (91.3%) HBsAg positive 498 (8.7%)	7 years Mortality; liver disease mortality
Ribes 2006[18] Spain	A nested case-control study to determine the role of other risk factors in the mortality from liver disease in HBsAg-positive subjects	N=2352. Mean age 34 years. Men 70%.	21 years HCC; mortality; liver disease mortality; cirrhosis
Crook 2003[19] UK	A prospective cohort study of HBsAg-positive blood donors comparing mortality rates in the cohort with the general population.	N=3658. Median age at entry: Men 29 (17 to 64); Women 29 (17 to 65). Men 73%. Subjects born in India/Southeast Asia 8%.	22 years Mortality; liver disease mortality
B. East Asian Studies			
Chan 2008[20] China	A prospective cohort of patients infected with chronic HBV in a surveillance program for HCC was studied. Ultrasound and alpha-fetoprotein evaluation were regularly performed to detect HCC. Risk factors for HCC and the relationship between HBV DNA and HBV	N=1006. Mean age 48. Men 68%.	7.7 years HCC
Chen 2007[21] China	Male cohort of 5,581 hepatitis B surface antigen carriers in Qidong, People's Republic of China, who were recruited starting in 1989.	N=5581. Age range 30 to 65 years. Men 100%	14 years HCC; mortality
Haimen City Cohort Study			
Chen 2006 [22] China	A prospective cohort study with 11 year followup which assessed the relationship between past HBV viral load and mortality.	N=2763. Mean age 42 years. Men 61%. History of clinical hepatitis 30%. HBeAg+ at baseline 44%. Family history of HCC 12%. Current alcohol drinker (>4x/week) 38%. Current smoker 39%.	11 years HCC; mortality

Appendix E. Table 1. Evidence table: Observational studies of the natural history of chronic hepatitis B in adults

Author / Country	Design Description	Subject Characteristics	Average Followup / Outcomes Description
Chen 2005[23] China	Analyzed all-cause mortality related to HBV infection, focusing on the deaths not related to liver disease in a prospective cohort of adults living in Haimen City, China, who were followed from 1992 to 2002.	N=83,794. Age range 25 to 64 years. Men 70%. Male HBsAg+ 15% (n=8768) Female HBsAg+ 11% (n =2711)	10 years Mortality
Evans 2003[24]	8-year followup of a prospective cohort study in Haimen City, China, identifying HCC risk factors in addition to HBV infection. Two cohorts of adults between ages 25 and 64 years at study entry were followed	N=83,885. Age range 25 to 64 years. Men 70%. 1. Male (n=58454) Age (years) 25-34 19%; 35-44 36%; 45-54 29%; 55-64 17%. 2. Female (n=25340). Age (years) 25-34 24%; 35-44 39%; 45-54 25%; 55-64 12%.	10 years HCC
London 1995[25]	Nested case-control study of 183 patients (of 60,984 enrolled) who died from HCC	N=183. Age range 30 to 64 years.	2.5 years HCC; mortality
REVEAL-HBV Study			
Chen 2006[26] Taiwan	A prospective cohort study with 11 yr of followup; assessed the relationship between past HBV viral load and mortality. Surviving cohort members were evaluated for current liver disease.	N=3653. Age range 30 to 65 years. Men 62%, Age, y (%) 30-39 = 1216 (33) 40-49 = 1014 (28) 50-59 = 1058 (29) ≥60 = 365 (10) Alcohol consumption = 451 (12%) Level of ALT, U/L (%) <45 = 3435 (94) ≥45 = 218 (6) <u>Level of HBV DNA, copies/mL</u> [HBeAg negative] <300 (Undetectable) = 865 (28.0) 300-999 = 372 (12.1) 1000-9999 = 773 (25.0) 10 000-99 999 = 625 (20.2) 100 000-999 999 = 298 (9.7) 1 to 9.9 million = 96 (3.1) 10 to 99.9 million = 42 (1.4) ≥100 million = 17 (0.6) [HBeAg positive] <300 (Undetectable) = 8 (1.4)	11 years HCC; mortality

Appendix E. Table 1. Evidence table: Observational studies of the natural history of chronic hepatitis B in adults

Author / Country	Design Description	Subject Characteristics	Average Followup / Outcomes Description
		300-999 = 0 1000-9999 = 16 (2.8) 10 000-99 999 = 18 (3.2) 100 000-999 999 = 51 (9.0) 1 to 9.9 million = 58 (10.3) 10 to 99.9 million = 58 (10.3) ≥100 million = 356 (63.0) [HBeAg total] <300 (Undetectable) = 873 (23.9) 300-999 = 372 (10.2) 1000-9999 = 789 (21.6) 10 000-99 999 = 643 (17.6) 100 000-999 999 = 349 (9.6) 1 to 9.9 million = 154 (4.2) 10 to 99.9 million = 100 (2.7) ≥100 million = 373 (10.2)	
Iloeje 2006[27]	A population-based prospective cohort study of 3582 untreated HBV patients established in Taiwan from 1991 to 1992.	N=3582. Mean age 45. Men 61%. Alcohol drinkers 12%.	11 years Mortality; cirrhosis
Studies by Yu			
Yu 2005[28] Taiwan	Baseline blood samples were collected from 4841 Taiwanese men who were HBV carriers but had not been diagnosed with HCC.	N=4841. Men 100%.	14 years HCC
Yu 1999[29] Taiwan	A cohort of 4,841 male chronic carriers of HBV surface antigen aged 30 to 65 years who were free of diagnosed HCC was recruited from the Government Employee Central Clinics and the Liver Unit of Chang-Gung Memorial Hospital in Taiwan from 1988 to 1992	N=4841. Age range 30 to 65 years. Men 100%.	9 years HCC
Studies by Wang/Yang			
Wang 2003[30]	Prospective community-based cohort study. HBsAg and antibody to HVC in serum were determined	N=11,837. Age range 30 to 64 years. Men 100%. Other data provided	7.7 years HCC
Yang 2002[31]	Prospective community-based cohort study of 11,837 without evidence of HCC from seven townships in Taiwan.	N=11,837. Age range 30 to 65 years. Men 100%. Other data provided	7.8 years HCC
Other studies			
Yuen 2005[32] China	A total of 3233 Chinese chronic HBV patients were monitored for liver biochemistry, viral serology, HBV DNA levels, acute exacerbation, HBeAg seroconversion, and development of cirrhotic complications.	N=3233. Mean age 38 years (range 1 to 85). Men 66%.	3.9 years HCC; mortality

Appendix E. Table 1. Evidence table: Observational studies of the natural history of chronic hepatitis B in adults

Author / Country	Design Description	Subject Characteristics	Average Followup / Outcomes Description
Jee 2004[33] Korea	A prospective cohort study of liver cancer in Korea to assess the independent effects and interactions of smoking, alcohol consumption, and hepatitis B on risk of mortality from HCC.	N=605,844. Men 79%.	9 years Liver disease mortality
Lam 2004[34] Hong Kong		N=1863	Mortality
Tanaka 2004[35] Japan	A community-based prospective study was conducted for over 8 years by record linkage to the Osaka Cancer Registry. The subjects were 1,927 individuals who were positive for antiHCV through screening for second generation HCV antibody in voluntary blood donors. The risk factors for HCC and interaction between HCV and hepatitis B virus (HBV) infection were evaluated by including additional blood donors: 2,519 individuals positive for hepatitis B virus surface antigen (HBsAg) alone, 25 positive for both antiHCV and HBsAg	N=2544 Mean age 48 years. Men 61%.	9 years HCC
Mori 2000[36] Japan	A community-based prospective study examined the effects of viral infections and lifestyle habits on HCC risk in Japan.	N=3052. Mean age 58 years. Men 32%. Age < 54 37%; 55 - 69 43%; ≥ 70 21%. HBsAg-negative 97%. History of habitual alcohol consumption: no 65%; yes 35.0% Presence of chronic hepatitis: no 97%; yes 3%	5 years HCC
Yu 1999[37] Taiwan	Male asymptomatic HBsAg carriers were enrolled in the study to investigate prospectively for liver cirrhosis and HCC at 6-month intervals by means of ultrasonography and clinical assessment.	N=1506. Men 100%.	7.1 years HCC; cirrhosis
Tokudome 1987[38] Japan	This prospective study investigated whether female Japanese hepatitis B surface antigen positive blood donors were at high risk for HCC.	N=3769. Women 100%.	8 years HCC; mortality; liver disease mortality
Beasley 1981[39] Taiwan	Prospective population study of Chinese men (government employees) in Taiwan.	N=22,707. Age range 40-59 years 82%. Men 100%. HBsAg positive subjects 15%	3.3 years HCC; mortality; liver disease mortality

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

A. Adefovir (L-nucleotide analogue)

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Versus placebo					
Zeng, 2006[40]	Adefovir 10 mg (n=360) Placebo (n=120 x 12 weeks, then all on adefovir (open-label) x 28 weeks, then Adefovir 10 mg (n=360) Placebo (n=120 x 12 weeks	**Inclusion**: Patients ≥18 years; detectable hepatitis B surface antigen (HBsAg); detectable hepatitis B e antigen (HBeAg); serum HBV DNA ≥10 log 6 copies/mL; serum ALT level >1 times ULN(ULN), (and >2 x ULN sometime within the previous 6 months). **Exclusion**: Hepatocellular carcinoma (HCC); clinical signs of liver decompensation; serum creatinine >1.5 mg/dL; ALT >10 x ULN; hepatitis C D, or HIV*; and ADV therapy or any other anti-HBV therapy within the previous 6 months.	Mean age 32 years (range). Men 83%. Race: Asian 100%.	Polymerase chain reactions (PCR) assay (Roche Molecular Systems). Detection limit = 300 copies/mL.	Allocation concealment: adequate Double-blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: pharmaceutical
Hadziyannis, 2003[41] Adefovir 438 Study Group Multinational: Canada, Greece, Israel, France, Italy, Australia, Taiwan, Singapore	Adefovir 10 mg (n=123) Placebo (n=62, 61 included in analyses) x 48 weeks	**Inclusion**: Patients 16 to 65 years; serum HBsAg present ≥6 months; HBeAg-; DNA $\geq 10^5$ copies/mL; serum ALT level 1.5 to 15 x ULN; creatinine ≤1.5 mg/dL; adequate blood count. **Exclusion**: Decompensated cirrhosis; therapy with corticosteroids, immunosuppressive drugs or antiviral agents during last 6 months; hepatitis D, HIV.	Mean age 46 years (range 18-65). Men 83%. Race: white 66%; Asian 30%; black 3%. All subjects were HBeAg-negative. Cirrhosis 11%. Prior HBV treatment: Interferon 41%; Lamivudine 8%; Famiciclovir 8%.	Spot Molecular Hybridization (Genostics, Abbot)	Allocation concealment: unclear Double-blinded Pathologist blinded (biopsy) Intent-to-treat analyses: yes (one dose)* Study withdrawals adequately described: not reported Funding: pharmaceutical
Marcellin, 2003[42] Adefovir 437 Study Group Multinational: North	Adefovir 10 mg (n=172, 171 included in analyses)	**Inclusion**: HBeAg+; compensated liver disease; PT ≤1 second above normal; albumin ≥3g/dL, bilirubin ≤2.5 mg/dL; creatinine ≤1.5 mg/dL;	Mean age 35 years (range 16-68). Men 74%. Race: Asian 59%; white 36%; black 3%; other 2%. All subjects were HBeAg-positive.	Liquid Hybridization (Abbott). Detection limit =	Allocation concealment: unclear Double-blinded: yes

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
America, Europe, Australia, Asia	Adefovir 30 mg (n=173) Placebo (n=170, 167 included in analyses) x 48 weeks	adequate blood count. **Exclusion**: Serious comorbidities; immune therapies including steroids; within 6 months; α-fetoprotein ≥50 ng/mL; hepatic mass; prior hepatitis B therapy, hepatitis C or D or HIV.	Prior HBV treatment: Interferon 24%.	1.6 pg/mL	Pathologist blinded Intent-to-treat analyses: yes (one dose) Study withdrawals adequately described: yes Funding: pharmaceutical
Versus lamivudine					
Peters, 2004[43] Australia, Canada, France, Germany, UK, and the US.	Adefovir 10 mg (n=19) Lamivudine 100 mg (n=19) Adefovir and Lamivudine (n=20) x 48 weeks	**Inclusion**: 16-65 years; serum HBsAg present ≥6 months, positive for HBeAg+; serum ALT level 1.2 to 10 x ULN on at least 2 occasions at least 1 month apart within the preceding 6 months). **Exclusion**: Serum creatinine level ≥1.5 mg/dL; creatinine clearance ≥50 mL/min; prior use of adefovir or treatment with interferon or other immunomodulatory therapies within the 6 months preceding study screening; treatment with nephrotoxic drugs, competitors of renal excretion, and/or hepatotoxic drugs within 2 months before study screening or during the study period; prior organ transplantation; serious concurrent medical conditions, including other concurrent liver diseases; coinfection with HIV; current alcohol or substance use.	Median age 45 years (range 26 to 69). Men 79%. Race: white 60%; Asian 36%; black 2%. All patients had received treatment with lamivudine for at least 6 months that was ongoing at the time of randomization with confirmed HBV polymerase gene mutation within the YMDD motif.	PCR assay (Roche Molecular Systems).	Allocation concealment: unclear Double-blinded Intent-to-treat analyses: yes (one dose) Study withdrawals adequately described: yes Funding: not reported
Versus telbivudine					
Chan, 2007[44] 018 Study Group	Adefovir 10 mg (n=45)	**Inclusion**: Patients with treatment naïve HBV; HBeAg+.	Mean age 32 years (range 18-60). Men 76%. Race: Asian 92%; white	PCR assay (Roche Molecular	Allocation concealment:

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Multinational: Hong Kong, Australia, Canada, France, Korea, Taiwan, Singapore, Thailand, and U.S.	Telbivudine 600 mg (n=45) Adefovir 10 mg Telbivudine at week 24 (n=46) x 52 weeks	**Exclusion**: ALT <1.3 x ULN; ALT >10 x ULN; HBV DNA <6 log10 copies/mL; HBsAg negative; low absolute neutrophil count; α-fetoprotein <50 ng/mL; amylase >1.5 x ULN	4%; other 4% All subjects were HBeAg-positive and treatment naïve	Systems). Detection limit = 300 copies/mL	adequate Open-label Intent-to-treat analyses: no Study withdrawals adequately described: yes Funding: pharmaceutical
Versus combined lamivudine and adefovir					
Akyildz, 2007[45]	Adefovir 10 mg (n=25) Adefovir 10 mg and lamivudine 100 mg combination during first 3 months, and then adefovir monotherapy (n=29) x 52 weeks	**Inclusion**: HBsAg present given lamivudine therapy ≥6 months; HBV polymerase gene mutation in the YMDD motif; DNA level >5 log10 copies/mL; ALT 1.2 x ULN; compensated liver disease and no history of variceal bleeding, ascites, or hepatic encephalopathy. Serum albumin levels >3 g/dl; total bilirubin levels <2 mg/dl; Child-Pugh-Turcotte score <7. **Exclusion:** Serum creatinine level >1.4 mg/dl or creatinine clearance <50 ml/minute; HIV or hepatitis C; serum α-fetoprotein >50 ng/ml, previous AD therapy, receiving nephrotoxic or hepatotoxic drugs; coexisting other chronic liver diseases (metabolic liver diseases and alcoholic liver disease); organ transplantation; malignancy.	Median age 48 years (range). Men 63%. 65% were HBeAg-negative. All subjects were lamivudine resistant.	Real-time PCR (Applied Biosystems) Detection limit = 2000 copies/mL	Allocation concealment: unclear Open-label Intent-to-treat analyses: unclear Study withdrawals adequately described: not reported Funding: not reported
Peters 2004[43]	*See above under adefovir versus lamivudine*				

* Subjects need to receive one dose to be included in the analyses

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

B. Lamivudine monotherapy (L-nucleoside analog)

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Versus placebo					
Chan 2007[46] Anti Viral Therapy Multicenter: China	Lamivudine 100 mg (n=89) Placebo (n=47) x 104 weeks, plus 26 weeks followup	**Inclusion**: ≥18 years, HBsAg ≥6 months; HBeAg- ≥6 months prior to screening; HBV DNA detectable by non-PCR assay; significantly increased ALT levels (1.3 to 10 x ULN) and liver biopsy within 12 months showing active HBV. **Exclusion**: HCC; ALT >10 x ULN; hepatitis C or D or HIV; decompensated liver disease; treatment with antiviral or immunomodulatory drugs ≤6 months prior to study; serum creatinine level ≥1.5 ULN.	Mean age 39 years (range 17 to 63). Men 84%. All subjects were treatment-naïve and HBeAg-negative.	Real-time PCR (TaqMan)	Allocation concealment: unclear Double-blinded Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: no Funding: pharmaceutical
Schiff, 2003[47] Europe, North America	Lamivudine 100 mg x 52 weeks (n=119) Lamivudine 100 mg x 8 weeks plus Interferon-α-2b 10 MU subcutaneously x 3/week x 16 weeks (n=63) Placebo (n=56) 16 weeks followup	**Inclusion**: ≥16 years, HBsAg 6 months, HBeAg, hybridization-assay-detectable HBV DNA, ALT ≥ 1.3 x ULN; histologic chronic hepatitis, and previous treatment with ≥240 million units (MU) of IFN; IFN must have been completed ≥6 months earlier, and patients must have failed IFN for lack of efficacy, not intolerance. **Exclusion**: Prior antiviral treatment for hepatitis B; treatment with antiviral agents, immunomodulatory drugs, or corticosteroids within 6 months prior to study; history of ascites, variceal hemorrhage, or hepatic encephalopathy; coinfection with hepatitis C or D, or HIV; the presence of confounding medical illness or other types of liver disease.	Mean age 37 years (range 15 to 76). Men 81%. Race: white 82%; Asian 7%; other 11%. All subjects were HBeAg-positive and failed interferon therapy previously.	Hybridization assay	Allocation concealment: yes Double-blinded Until week 8 (IFN assigned) Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: pharmaceutical/ government/other

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Dienstag, 1999[48] United States	Lamivudine 100 mg (n=66) Placebo (n=71) x 52 weeks, plus 16 weeks followup	**Inclusion**: Patients ≥18 years; detectable HBsAg ≥6 months; serum HBeAg ≥1 month; serum ALT 1.3 to 10 x ULN ≥3 months. **Exclusion**: Prior antiviral treatment for HBV; treatment with antiviral agents or immunomodulatory drugs, history of ascites, variceal hemorrhage, or hepatic encephalopathy; hepatitis C, D, or HIV; presence of confounding medical illness or other types of liver disease.	Median age 38-40 years (range 18-73). Men 83%. Race: white 57%; Asian 20%; black 17%; other 6%. All subjects were treatment-naïve.	Liquid Hybridization (Abbott). Detection limit = 1.6 pg/mL	Allocation concealment: unclear Double-blinded Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: pharmaceutical/ Government
Tassopoulos, 1999[49] Multinational	Lamivudine 100 mg (n=60) x 52 weeks Placebo (n=64) x 24 weeks	**Inclusion**: 16 to 70 years of age; detectable hepatitis B surface antigen (HBsAg), detectable HBeAb, and undetectable HBeAg in serum ≥6 months before screening; serum HBV DNA ≥2.5 pg/mL; HBV DNA in the serum ≥3 months; and serum ALT ≥1.5 to 10 x ULN. **Exclusion**: Decompensated liver disease; hepatitis C or D, or HIV; evidence of autoimmune hepatitis; received an investigational drug within 30 days of the first dose of study drug; received any systemic antiviral therapy or immunomodulators, cytotoxic agents, or corticosteroids within 6 months of screening.	Median age 43 years (range 17-65). Men 80%. All subjects were HBeAg-negative/HBV virus DNA-positive (precore mutant).	Qualitative microparticle enzyme immunoassay (Abbott)	Allocation concealment: adequate Double-blinded Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: pharmaceutical
Lai, 1998[50] Multinational: Taiwan, Hong Kong, Singapore	Lamivudine 100 mg (n=143) Lamivudine 25 mg (n=142) Placebo (n=72) x 52 weeks	**Inclusion**: Patients 16 to 70 years; detectable HBsAg, serum HBV DNA levels of at least 5 pg per milliliter; and ALT <10 x ULN at screening and for at least the previous 3 months. **Exclusion**: Hepatitis C or D or HIV	Median age 32 years (range 15-67). Men 73%. Race: Asian 100%. All subjects were HBeAg-positive.	In situ hybridization technique	Allocation concealment: unclear Double-blinded Intent-to-treat analyses: yes

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
		infection; decompensated liver disease; evidence of autoimmune hepatitis.			Study withdrawals adequately described: no Funding: pharmaceutical
Versus placebo, subjects with advanced liver disease					
Liaw, 2004[51] Cirrhosis Asian Lamivudine Multicenter Study Group Multinational: Asian-Pacific region	Lamivudine 100 mg (n=436) Placebo (n=215) Median followup 32.4 months (range 0 to 42). Treatment was stopped for patients who received a clinically confirmed end point.	**Inclusion**: ≥16 years; positive for HBsAg ≥6 months; positive for HBeAg or negative for HBeAg with detectable HBV DNA at screening, and had had a liver biopsy showing an Ishak fibrosis score of at least 4 (where 0 indicates no fibrosis and 6 indicates cirrhosis) at screening or during the previous 2 years. **Exclusion**: HCC; serum ALT level >10 x ULN; hepatic decompensation; autoimmune hepatitis; hepatitis C or D or HIV; serious concurrent illness; pancreatic amylase or lipase levels > 2 x ULN; elevated serum creatinine level; treatment with immunomodulatory or antiviral therapy ≤6 months before screening; treatment with any investigational drug within 30 days prior to study; previous treatment with lamivudine.	Median age 43-44 years (range 17-74). Men 85%. Race: Asian 98%. All subjects were HBeAg-positive or were HBeAg-negative with detectable HBV DNA at screening, and had a liver biopsy with an Ishak fibrosis score of 4 (scale 0 to 6, 0 no fibrosis) at screening or in previous 2 years.	Branched-chain hybridization assay (Bayer) Detection limit = 0.7 mEq per m/L.	Allocation concealment: unclear Double-blinded Intent-to-treat analyses: yes Study withdrawals adequately described: no Funding: pharmaceutical
Miscellaneous Lamivudine trials					
Jang, 2006[52] South Korea	Lamivudine 100 mg daily from the start of transarterial chemo-lipiodolization (TACL)	**Inclusion**: Diagnosis of HCC based on histological evidence or elevated serum a-fetoprotein (AFP) levels (>400 ng/mL) with typical radiological findings. **Exclusion**: Previous history of antiviral therapy; baseline ALT level	Mean age 53 years. Men 84%. HCC patients undergoing using epirubicin 50 mg/m2 and cisplatin 60 mg/m2 at monthly intervals. All patients had HBV genotype C	Branched DNA assay (Bayer) Detection limit = x 10^3 to 1 x 10^8 copies/mL).	Allocation concealment: adequate Open-label Intent-to-treat analyses: no Study withdrawals

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
	(preemptive group, n=38) No lamivudine control group (n=38)	≥2.5 x ULN ; serum HBV DNA level >107 copies/mL; extrahepatic metastasis; main portal vein thrombosis; underlying cardiac or renal diseases; positive tests for antibody to hepatitis C virus or HIV; Child-Pugh classification B or C; or preexisting evidence of hepatic decompensation.			adequately described: yes Funding: Government
Ke, 2005[53] China	Lamivudine 100 mg (n=42) Routine medication with vitamin C and inosine (n=30) x 48 weeks.	**Inclusion**: >16 years of age, normal or abnormal ALT, positive HbsAg and HBeAg in serum, negative anti-HCV, anti-HDV and anti-HEV in serum, positive HBV DNA in serum and PBMCs. **Exclusion**: Other possible causes of chronic liver damages, such as drugs, alcohol and autoimmune diseases.	Mean age 32 years (18-60). Men 69%.	Not reported	Allocation concealment: unclear Open-label Intent-to-treat analyses: yes Study withdrawals adequately described: none reported Funding: not reported
Kim, 2006[54] South Korea	Patients were assigned either to ongoing lamivudine (n=37) or had lamivudine-therapy-discontinued group (n=37). There was no interruption in lamivudine-therapy before randomization. Median followup was 20 months	**Inclusion:** HBsAg positive ≥6 months; ≥18 years of age; received lamivudine treatment ≥6 at the time of randomization, who had serum HBV DNA $>10^5$ copies/ml and a HBV polymerase gene mutation within the YMDD motif, and who had relatively well-preserved liver function without a history of variceal bleeding, ascites, or encephalopathy. **Exclusion**: Coexisting serious medical or psychiatric illness; recent treatment with systemic corticosteroids; hepatic mass; seropositivity for HIV or hepatitis C or D; previously received treatment with adefovir or other antiviral agents with activity against HBV.	Mean age 45 years. Men 87%. All patients were ethnic Koreans. All subjects were lamivudine-resistant.	Serum HBV DNA $>10^5$ copies/ml (Roche) Detection limit = 200 copies/ml or Digene hybrid capture assay (Digene)	Allocation concealment: adequate Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: Institution

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Nevens, 1997[55]	Lamivudine 25 mg (n=16) Lamivudine 100 mg (n=16) Lamivudine 300 mg (n=19) x 24 weeks plus 24 weeks followup	**Inclusion:** Serum HBV DNA positive, ALT <300 IU/L; serum positive HBsAg and HBeAg for 6 months preceding study **Exclusion**: Decompensated liver disease; abnormal renal function; hemoglobin concentration ,10 g/dL, white cell count <3 x 10^9/L, or platelet count <50 x 10^9/L; coinfection hepatitis C, D, or HIV; previous treatment with antiviral, or corticosteroid therapy	Mean age 36 years. Men 71%. Race: Asian 49%; white 43%, Cirrhosis 20%. Prior HBV treatment: Interferon 37%	Liquid Hybridization (Abbott).	Allocation concealment: Partially double-blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes
Versus entecavir (see below)					
Versus telbivudine (see below)					
Versus pegylated interferon-α-2a monotherapy					
Lau, 2005[56] Multinational: Europe, Asia, Australasia, North and South America	Lamivudine 100 mg (n=272) Peginterferon α-2a 180 µg/ week plus placebo (n=271) Lamivudine 100 mg plus Peginterferon α-2a 180 µg/ week (n=271) x 48 weeks, plus 24 weeks followup.	**Inclusion**: HBsAg ≥6 months, were negative for antibodies to HBsAg (anti-HBs antibodies) and positive for HBeAg, had an HBV DNA level of > 500,000 copies per milliliter, serum ALT level that was >1 but ≤10 x ULN; findings on a liver biopsy within the previous 12 months that were consistent with the presence of chronic hepatitis B. **Exclusion**: Decompensated liver disease; coexisting serious medical or psychiatric illness; serum creatinine level >1.5 x ULN; history of alcohol or drug abuse within 1 year before entry; hepatitis C or D or HIV.	Mean age 32 years (range 17 to 77). Men 78%. Race: Asian 87%; white 10%; black 1%; other 2%. All subjects were HBeAg-positive. Prior HBV treatment: Interferon 11.5%; lamivudine 12%. Bridging fibrosis or cirrhosis 17%.	PCR-DNA Cobas Amplicor (Roche) and AxSYM test (Abbott)	Allocation concealment: unclear Partially double-blinded Pathologist blinded Intent-to-treat analyses: yes (one dose) Study withdrawals adequately described: yes Funding: pharmaceutical
Marcellin, 2004[57] Multinational: Europe, Asia	Lamivudine 100 mg (n=181) Peginterferon α -	**Inclusion**: Negative for HBeAg and positive for anti-HBe antibody and HBsAg ≥6 months; HBV DNA level of	Mean age 40 years (range 18 to 71). Men 85%. Race: Asian 61%; white 37%; black 1%.	PCR-DNA Cobas Amplicor (Roche)	Allocation concealment: unclear

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
	2a (180 µg/ week) plus placebo (n=177) Lamivudine 100 mg plus Peginterferon α - 2a 180 µg/ week (n=179) x 48 weeks, plus 24 weeks followup.	>100,000 copies/mL; serum ALT level >1 to ≤10 x ULN; findings on a liver biopsy within prior 2 years consistent with the presence of chronic hepatitis B, with evidence of prominent necroinflammatory activity. **Exclusion**: Decompensated liver disease; coexisting serious medical or psychiatric illness; serum creatinine level that was >1.5 x ULN; history of alcohol or drug abuse within 1 year before entry; treatment for chronic hepatitis B within the previous 6 months; hepatitis C, D virus or HIV.	All subjects were HBeAg-negative.		Partially double-blinded Pathologist blinded Intent-to-treat analyses: yes (one dose) Study withdrawals adequately described: yes Funding: pharmaceutical

C. Lamivudine versus combination therapy

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Versus combined lamivudine and adefovir (see above)					
Perrillo, 2004[58]	Lamivudine 100 mg (n=49) Lamivudine 100 mg plus adefovir 10 mg (n=46) x 52 weeks.	**Inclusion**: Compensated chronic hepatitis and be HBeAg+ at screening (patients in group B were allowed into the study if they were either HBeAg+ or - as well as elevated serum ALT levels >1.3 x ULN on at least 2 occasions in the previous 6 months): confirmed to have YMDD mutant HBV **Exclusion**: Hepatitis C or D or HIV; documented or suspected HCC; anemia; screening calculated creatinine clearance <50 mL/min or a serum creatinine value >1.5 mg/dL; pancreatitis; previously treatment with	Median age 43 years (range 24 to 68). Men 96%.	PCR assay (Roche)	Allocation concealment: unclear Double-blinded Intent-to-treat analyses: yes (one dose) Study withdrawals adequately described: yes Funding: not reported

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
		adefovir or other drugs with activity against HBV within the prior 3 months were not eligible.			
Versus combined Pegylated Interferon α-2a					
Lau, 2005[56]	*See under lamivudine monotherapy*				
Marcellin, 2004[57]	*See under lamivudine monotherapy*				
Versus combined Pegylated Interferon-α-2b and Lamivudine					
Chan, 2005[59] Multicenter study: China	Lamivudine 100 mg plus pegylated interferon-α-2b 1.5 microg/kg of body weight (patients <65 kg) or 100 mg per week for 32 weeks (n=50) Lamivudine 100 mg (n=50) x 52 weeks.	**Inclusion**: Age 18 to 65 years; HBsAg positive ≥6 months; serum HBV DNA level of at least 500,000 copies/mL; ALT level 1.3 to 5 x ULN. **Exclusion**: Decompensated liver disease or a history of interferon or antiviral agent use; hepatitis C or D, or HIV; HCC; other causes of liver disease, including autoimmune hepatitis; Wilson disease; hemochromatosis and a1-antitrypsin deficiency; serious medical or psychiatric illness; concurrent use of corticosteroid or immunosuppressive agents.	Mean age 33 years (range 16-68). Men 67%. All subjects were HBeAg-positive and treatment naïve.	Real-time PCR (TaqMan)	Allocation concealment: adequate Open-label Pathologist blinded Intent-to-treat analyses: yes (one dose) Study withdrawals adequately described: yes Funding: pharmaceutical
Versus combined Interferon-α-2b and lamivudine					
Akyuz 2007[60] Turkey	Lamivudine 100 mg for 24 months plus interferon-α-2b 10 MU/week for 6 months (n=21) Lamivudine 100 mg (n=24) x 24 months.	**Inclusion**: HBsAg-positive and HBeAg-negative ≥18 months; serum HBV DNA ≥6 months; ALT level 1.3 to 5 x ULN ≥3 months; biopsy proven HBV and compensated liver disease. **Exclusion:** hepatitis C or D, or HIV	Mean age 43 years (range 20-65). Men 71%. All subjects were HBeAg-negative and interferon resistant.	Molecular hybridization (Digene) and PCR	Allocation concealment: unclear Open-label Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: not reported

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Lu, 2007[61] China	Lamivudine x 8 months then interferon-α-2b from months 7 to 12 (n = 24) or interferon-α-2b 5 MU 3 times per week (n = 12). Lamivudine 100 mg (n=35) x 48 weeks, plus 24 weeks followup.	**Inclusion**: HBeAg-+ chronic hepatitis B **Exclusion**: Alcoholism; cirrhosis, chronic renal failure; concurrent autoimmune disease, serious neurological disorders, HIV infection or hepatitis A, C, D, or E; treatment with interferon or other anti-viral therapies for 6 months prior to enrollment in this study.	71 patients, mean age 32 ± 9 (range 19-47) years. 83% male.	PCR-RFLP.	Allocation concealment: unclear Blinding not reported Intent-to-treat analyses: yes Study withdrawals adequately described: no withdrawals reported Funding: not reported
Shi, 2006[62] China	Lamivudine 100 mg x 20 weeks, followed by interferon-α-2b 5 MU 3 times/ week plus lamivudine x 4 weeks, then interferon-α-2b x 24 weeks (n=64). Lamivudine 100 mg x 48 weeks (n=98). 24 weeks followup	**Inclusion**: >16 years of age; positive for HBsAg ≥6 months; negative for HBeAg and positive for hepatitis B e antibody (anti-HBe), and had HBV DNA levels of >100,000 copies/mL and serum ALT levels >1.5 to <10 x ULN. **Exclusion**: Hepatitis A, C, D, and E virus or HIV: decompensated liver diseases or HCC; history of alcohol or drug abuse within 1 year before entry; other possible causes of chronic liver damage; previous treatment of chronic hepatitis B.	Mean age 34 years (range 20 to 57). Men 72%. Race: Asian 100%. All subjects were HBeAg-negative.	Real-time PCR (Fosun)	Allocation concealment: unclear Open-label Intent-to-treat analyses: yes Study withdrawals adequately described: yes (none) Funding: foundations
Economou, 2005[63] Multicenter study Greece	Lamivudine 100 mg x 48 weeks plus interferon-α-2b 5 MU 3 times/week (n=24). Lamivudine 100 mg (n=26) x 104 weeks, plus 26 weeks followup.	**Inclusion**: HBsAg positive, anti-HBe positive and HBeAg negative serology ≥6 months before enrollment; serum HBV DNA concentrations >105 copies/mL; elevated ALT x 1.5 times the upper normal limit in three separate monthly occasions ≤6 months before randomization; liver biopsy with evidence of chronic hepatitis within	Median age 56 years (range 41 to 66). Men 66%. Prior HBV treatment: Interferon: 56%. Cirrhosis 48%. Median values: ALT 79; AST 59 Median values: ALT 59; AST 60	Microparticle enzyme immunoassay	Allocation concealment: adequate (Lottery cards) Open-label Intent-to-treat analyses: yes Study withdrawals adequately described: yes

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
		12 months before entering the study. **Exclusion**: Antibodies against hepatitis C or D or HIV; decompensated liver disease or received liver transplantation; treatment with any antiviral drug other than IFN and those who had received immunosuppressive therapy within 6 months before participation; alcohol consumption >50 g/d or suspected HCC and elevated α-fetoprotein.			Funding: not reported
Akarca, 2004[64] Turkey	Lamivudine 100 mg x 96 weeks plus interferon-α-2b 5 MU 3 times/week x 24 weeks (n=40). Lamivudine 100 mg x 96 weeks (n=40).	**Inclusion**: HBsAg positive, anti-HBe positive and HBeAg negative serology ≥6 months before enrollment.; elevated ALT x 1.5 times the upper normal limit on two occasions one month apart. **Exclusion**: other causes of liver disease (hepatitis C or D or HIV); decompensated liver disease	Mean age 42 years (range 19 to 67). Men 86%.	Hybridization assay (Digene)	Allocation concealment: adequate Open-label Intent-to-treat analyses: unclear Study withdrawals adequately described: no withdrawals reported Funding: not reported
Jang, 2004[65] South Korea	Lamivudine 100 mg plus interferon-α-2b 5 MU 3 times/week (n=41) Median duration 7 months Lamivudine 100 mg (n=42) Median duration 38 months	**Inclusion**: Positive for hepatitis B surface antigen (HBsAg), HBeAg, and HBV-DNA ≥ 6 months before the therapy; serum ALT levels >2 times upper limit of normal. **Exclusion**: Antibody for hepatitis C or D or HIV; liver cirrhosis by histological or clinical examination.	Mean age 37 years. Men 82%.	Solution hybridization assay	Allocation concealment: unclear Open-label Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: not reported
Schiff, 2003[47]	*See under lamivudine*				
Barbaro, 2001[66] Italy	Interferon-α-2b 9 MU 3 times/	**Inclusion**: Detectable hepatitis B surface antigen (HBsAg) and HBeAg	Mean age 41 years (range 32 to 50). Men 83%.	Solution hybridization	Allocation concealment:

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Multicenter	week plus Lamivudine 100 mg x 24 weeks (n=76) Lamivudine 100 mg x 52 weeks (n=75) 48 weeks followup.	in serum at the time of screening and for at least the previous 6 months, with serum HBV DNA levels ≥5 pg/ml and with ALT levels that were 1.3 to 10 times ULNfor at least the previous 3 months were eligible for the study. **Exclusion**: <18 years old; hepatitis C or D or HIV infection; decompensated liver disease; evidence of autoimmune hepatitis or metabolic liver disease; received an investigational drug within 30 days before enrollment or any systemic antiviral therapy, immunomodulators, cytotoxic agents, or corticosteroids within 6 months before enrollment; poor clinical condition and/or had serious medical diseases.	Cirrhosis 5%.	assay (Abbott)	adequate Open-label Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: none from pharmaceutical
Schalm, 2000[67] Multinational: Europe, Canada, Australia	Lamivudine 100 mg once daily followed by 16 weeks of lamivudine 100 mg plus interferon- α-2b 10 MU 3 times/week (n=75) Interferon-α-2b (n=69) Lamivudine 100 mg x 52 weeks (n=82) Treatment ranged from 24 to 52 weeks, depending on arm.	**Inclusion**: Ages 16-70 years; detectable HBsAg and HBeAg in serum at the time of screening and for at least 6 and 3 months, respectively, before study entry; serum HBV DNA levels of at least 5 pg/ml at screening; and evidence of inflammation by histology or by raised ALT levels (1.3 x 10 ULN) at screening and ≥3 months before screening with no value falling within the normal reference range in the intervening period. **Exclusion**: Previous interferon or antiviral treatment within 6 months; were co-infected with hepatitis C or D, or HIV; decompensated liver disease; evidence of liver disease of other etiology.	Median age 31 years (range 15-70). Men 74%. Race: white 63%; Asian 29%. All subjects were HBeAg-positive and treatment naïve. Cirrhosis 16%.	Solution-hybridization-assay (Abbott)	Allocation concealment: adequate Blinded up to week 8 Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: pharmaceutical

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Versus combined Interferon-α (type of alpha unclear) and lamivudine					
Scotto, 2006[68] Italy	Arm A Interferon-α 6 MU 3 times/week lamivudine 100 mg x 52 weeks (n=20) Arm B Interferon-α 6 MU 3 times/week lamivudine 100 mg x 40 weeks after pre-treatment with lamivudine x 12 weeks (n=18) Arm C Lamivudine 100 mg x 52 weeks (n=21)	**Inclusion**: Serum ALT >2 x normal level for >6 months; HBV infection based on the presence of HBsAg+; HBV DNA+ >5 pg/mL; positive histology for CHB/cirrhosis within 6 months of the study according to the Knodell-Ishak. **Exclusion**: Hepatitis C, D, or HIV; alcohol abuse; Wilson's disease; hemochromatosis; α-antitrypsin deficiency.	Mean age 44 years (range 23 to 63). Men 54%. All subjects were HBeAg-positive. Cirrhosis 12%.	Sandwich hybridization (Qunatiplex Chiron)	Allocation concealment: unclear Open-label Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: not reported
Sarin, 2005[69] India	Interferon-α 5 MU 3 times/week x 16 weeks plus Lamivudine 100 mg x 52 weeks (n=38) Lamivudine 100 mg once daily x 52 weeks (n=37)	**Inclusion**: Ages 16-70 years; HBsAg+; HBeAg+; anti-HBe antibody negative at the time of screening ≥6 months; quantifiable serum HBV DNA levels of >1.4 × 10^5 copies/mL; ALT levels >1.5 times ULN and <10 times UNL at screening and ≥ 3 months; liver biopsy proven HBV ≥12 months of inclusion. and (vi) **Exclusion**: Hepatitis C, D, or HIV; decompensated liver disease; evidence of liver disease due to other etiology; serum creatinine >1.5 times ULN; hemoglobin <10 g/dL; platelet count less than 70,000/mm^3; white-cell count <3,000/mm3; serious concurrent medical illnesses.	Mean age 31 years. Men 88%. All subjects were treatment naive. Cirrhosis 16%.	Hybrid capture assay (Digene) Detection limit = 1.4 × 105 copies/mL.	Allocation concealment: adequate Open-label Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: not reported

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Santantonio, 2002[70] Italy	Interferon-α 5 MU 3 times/week plus Lamivudine 100 mg x 52 weeks (n=24) Lamivudine 100 mg once daily (n=26) x 12 months	**Inclusion**: HBV DNA+; elevated ALT. All patients had a liver biopsy showing active disease within 24 months before admission to the study **Exclusion**: Decompensated liver cirrhosis, evidence of autoimmune hepatitis or markers of hepatitis C, D and HIV.	Mean age 45 years (range 25 to 63). Men 82%, All subjects were HBeAg-positive. Cirrhosis 32%. Prior HBV treatment: Interferon 42%.	PCR (Roche) Sensitivity of 400 copies/ml.	Allocation concealment: unclear Open-label Intent-to-treat analyses: yes Study withdrawals adequately described: none reported Funding: Authors stated they did not receive funding from pharmaceutical company involved with the drugs

D. Telbivudine (L-nucleoside analog)

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Versus adefovir (see above)					
Versus lamivudine					
Lai, 2007[71] Multinational: Asia, Europe, North America, Australia, and New Zealand	Telbivudine 600 mg (n=680) Lamivudine 100 mg (n=687) x 52 weeks	**Inclusion**: Patients 16 to 70 years; HBeAg-positive or HBeAg-negative chronic hepatitis B (detectable serum HBsAg, serum ALT level 1.3 to10 x ULN; serum HBV DNA level >6 log10 copies/mL; compatible pretreatment liver histologic findings. **Exclusion**: Coinfection with hepatitis C or D, or HIV; hepatic decompensation, pancreatitis, or HCC; previous treatment with	Mean age 36 years (range 16 to 68). Mean ages for HBeAg-positive and HBeAg-negative were 33 and 43 years, respectively. Men 76%. Race: Asian 76%; white 15%; black <1%; other 9%. 68% subjects were HBeAg-positive and 32% HBeAg-negative. All subjects had not previously received a nucleosides or nucleotides.	PCR-DNA Cobas Amplicor (Roche) Detection limit = 300 copies per mL	Allocation concealment: unclear Double-blinded Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding:

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
		nucleos(t)ide analogues; treatment with interferon or other immuno-modulators ≤12 months; other forms of liver disease; serum creatinine >1.5 mg/dL; serum amylase or lipase level >1.5 x ULN; serum albumin <3.3 g/dL deciliter; bilirubin level >2.0 mg/dL. Eligible patients with a serum α-fetoprotein level >50 ng/mL required exclusion of HCC.			pharmaceutical
Lai 2005[72] Gastroenterology Telbivudine Phase II Investigator Group	Telbivudine 400 mg (n=22) Telbivudine 600 mg (n=22) Telbivudine 400 mg plus Lamivudine 100 mg (n=21) Telbivudine 600 mg plus Lamivudine 100 mg (n=20) Lamivudine 100 mg (n=19 x 52 weeks	**Inclusion**: Ages 18 to 65 years; HBsAg seropositive ≥6 months; HBeAg seropositive at screening; serum HBV DNA level >6 log10 copies/mL; and serum ALT level 1.3 to 10 x ULN. **Exclusion**: Prior treatment with anti-HBV nucleos(t)ides; interferon treatment ≤12 months; HIV, hepatitis C or D; other known causes of liver disease; hepatic decompensation; history of pancreatitis; concurrent medical conditions that might confound safety or efficacy assessments during the study; history of alcohol or illicit substance abuse within ≤2 years.	Median ages ranged from 30 to 41 years (overall range was 18 to 68). Men 79%. Race: Asian 83%; white 8%; other 9% All subjects were HBeAg-positive and had not previously received a nucleosides or nucleotides. Prior HBV treatment: Interferon 4%.	PCR-DNA Cobas Amplicor (Roche)	Allocation concealment: unclear Double-blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: pharmaceutical

E. Entecavir monotherapy (<u>Acyclic guanosine derivative</u>)

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Chang, 2006[73] Multinational: North America, Europe, Australia, Asia,	Entecavir 0.5 mg (n=357, 354 included in analyses)	**Inclusion**: ≥16 years; HBeAg+ chronic hepatitis B and compensated liver function; a serum albumin level ≥3.0 g/dL; no history of variceal	Mean age 35 years (≥16 at study entry). Men 76%. Race: Asian 57%; white 40%; black 2%. All subjects were HBeAg-positive and	PCR-DNA Cobas Amplicor (Roche) Detection limit = 300 copies per mL	Allocation concealment: unclear Double-blinded

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
South America	Lamivudine 100 mg (n= 358, 355 included in analyses) x 52 weeks	bleeding or hepatic encephalopathy); detectable HBsAg ≥24 weeks before screening; evidence of chronic hepatitis on a baseline liver-biopsy specimen obtained within 52 weeks before randomization. **Exclusion**: Coinfection with hepatitis C or D, or HIV; other forms of liver disease; use of interferon-α, thymosin α, or antiviral agents with activity against hepatitis B ≤24 weeks before randomization; prior lamivudine therapy lasting >12 weeks; α-fetoprotein level >100 ng/mL; history of ascites requiring diuretics or paracentesis; previous treatment with entecavir.	had not previously received a nucleoside analog. Prior HBV treatment: Interferon 13%.		Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: pharmaceutical
Lai, 200 [74] Multinational: North America, Europe, Australia, Asia, South America	Entecavir 0.5 mg (n=331, 325 included in analyses) Lamivudine 100 mg (n=317, 313 included in analyses) x 52 weeks	**Inclusion**: ≥16 years; HBeAg-chronic hepatitis B and compensated liver function; serum albumin level ≥3.0 g/dL; no history of variceal bleeding or hepatic encephalopathy; HBsAg ≥24 weeks before screening, evidence of chronic hepatitis on a baseline liver biopsy specimen obtained ≤52 weeks before randomization; evidence of HBV DNA by any commercial assay ≥2 weeks before screening; undetectable HBeAg, detectable anti-HBe, serum HBV DNA level ≥ 0.7 MEq/mL; serum ALT level 1.3 to 10.0 x ULN. **Exclusion**: Coinfection with hepatitis C or D, or HIV; other forms of liver disease; use of interferon- α, thymosin α, or antiviral agents with activity against hepatitis B ≤24 weeks	Mean age 44 years (≥16 at study entry). Men 75%. Race: white 58%; Asian 39%; black 2%. All subjects were HBeAg-negative and had not previously received a nucleoside analog. Prior HBV treatment: Interferon 13%.	PCR assay (Roche). Detection limit = 300 copies per mL	Allocation concealment: unclear Double-blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: pharmaceutical

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
		before randomization; prior lamivudine therapy >12 weeks; α-fetoprotein level >100 ng/mL; history of ascites requiring diuretics or paracentesis; previous treatment with entecavir.			
Sherman, 2006[75] Multinational: North America, South America, Europe and the Middle East, Australia, and Asia	Entecavir 1 mg (n=147) continued Lamivudine 100 mg daily (n=146) x minimum of 52 weeks	**Inclusion**: ≥16 years; surface HBsAg+ men and women receiving ongoing lamivudine therapy and were refractory to that therapy; HBeAg+ and ALT levels 1.3 to 10 x ULN; HBV DNA levels ≥3.0 MEq/mL; compensated liver function; serum albumin ≥3.0 g/dL; no history of variceal bleeding, ascites requiring diuretics or paracentesis, or encephalopathy; evidence of chronic hepatitis upon liver biopsy that was performed at screening or ≤1 year prior to randomization and following clinical evidence of incomplete response to lamivudine. **Exclusion**: Hepatitis C or D, or HIV; other forms of liver disease; prior therapy with a nucleos(t)ide analogue with activity against HBV other than lamivudine for ≥12 weeks duration or given ≤6 months prior to random-ization; interferon α or thymosin-a1 use ≤6 months prior to random-ization; α-fetoprotein >100 ng/mL; prior treatment with entecavir.	Mean age 39years (range 16 to 74). Men 76%. Race: white 62%; Asian 37%. Subjects were HBeAg-positive and lamivudine resistant. Prior HBV treatment: Interferon 54%.	PCR assay (Roche). Detection limit = 300 copies per mL	Allocation concealment: adequate Double-blinded Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: unclear
Chang, 2005[76] Multinational: Australia, North America, Europe, Asia	Entecavir 1 mg (n=42) Entecavir 0.5 mg (n=47) Entecavir 0.1	**Inclusion**: Patients >16 years with chronic HBV infection considered to be lamivudine refractory on the basis of documented viremia after receiving ≥24 weeks of lamivudine therapy or	Mean age 46 years. Men 81%. Race: white 61%; Asian 32%; black 2%. All subjects were lamivudine resistant. Prior HBV treatment: Interferon 45%.	PCR assay	Allocation concealment: adequate Double-blinded Intent-to-treat

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
	mg (n=47) Lamivudine 100mg (n=45) Treatment: 24 to 52 weeks, plus 24 weeks followup.	documented evidence of a lamivudine resistance–associated substitution while receiving lamivudine. AST and ALT levels ≥10 x ULN and well-compensated liver function. **Exclusion**: Hepatitis C or D, or HIV; other form of liver disease or a liver transplant; received immuno-modulator therapy ≤24 weeks before randomization; received prior antiviral therapy.			analyses: yes Study withdrawals adequately described: yes Funding: not reported
Lai 2002[77] Multinational: Australia, North America, Europe, Asia	Entecavir 0.01 mg od (n=54) Entecavir 0.1 mg od (n=36) Entecavir 0.5 mg od (n=46) Lamivudine 100mg od (n=41) x 24 weeks	**Inclusion**: HBsAg+ for 24 weeks or more; either HBeAg+ or HBeAg-, but anti-HBe+ for 12 weeks or more before randomization; HBV DNA ≥40 MEQ/mL; baseline ALT ≤10 x ULN (patients with normal ALT were not excluded); well-compensated liver disease. **Exclusion**: Immunosuppressive therapy; IFN-α, thymosin-α, or nucleoside analogues ≤24 weeks of randomization; hepatitis C or D or HIV; serious medical illnesses; evidence of pancytopenia, alcohol or other drug abuse.	Mean age 31 years (range). Men 74%. Race: Asian 57%; white 32%; other 11%.	PCR-DNA Amplicor (Roche) and Quantiplex	Allocation concealment: adequate Double-blinded Intent-to-treat analyses: no Study withdrawals adequately described: yes Funding: several authors noted as receiving support from pharmaceutical

F. Combination Pegylated Interferon-α-2a and Lamivudine therapy (Interferon)

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Lau, 2005[56]	*See under lamivudine monotherapy*				
Marcellin, 2004[57]	*See under lamivudine monotherapy*				

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

G. Combination Pegylated interferon-α-2b and Lamivudine therapy (Interferon)

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Chan, 2005[59]	*See under lamivudine combination therapy*				
Janssen, 2005[78] Multinational	Pegylated interferon-α-2b 100microg/week plus lamivudine 100 mg (n=130) Pegylated interferon-α-2b and placebo (n=136) x 52 weeks, plus 26 weeks followup.	**Inclusion**: 16 years or older; HBsAg+ >6 months; positive for HBeAg on 2 occasions within 8 weeks before randomization; 2 episodes of raised serum concentrations of ALT (x 2 ULN) ≤8 weeks before randomization **Exclusion**: Serum antibodies against hepatitis C or D, or HIV; antiviral therapy or immunosuppressive therapy ≤ preceding 6 months; substance abuse ≤ previous 2 years; other acquired or inherited causes of liver disease; coexisting serious medical or psychiatric illness; uncontrolled thyroid disease; evidence of HCC; advanced liver; history of ascites, variceal bleeding, or hepatic encephalopathy.	Mean age 35 years (≥ 6 at study entry). Men 77%. Race: white 74%; Asian 20%; other 6%. All subjects were HBeAg-positive.	PCR assay based on the Eurohep standard	Allocation concealment: unclear Double-blinded Pathologist blinded Intent-to-treat analyses: yes (one dose) Study withdrawals adequately described: yes Funding: pharmaceutical

H. Interferon-α-2b and Lamivudine (Interferon)

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Shi, 2006[62]	*See under lamivudine*				
Economou, 2005[63]	*See under lamivudine*				
Akarca, 2004[64]	*See under lamivudine*				
Yalcin 2003[79] Turkey	Interferon-α-2b 10 MU 3 times/ week (n=17) x 52 weeks	**Inclusion**: Ages 18 to 60 years; positive HBsAg, and HBeAg; HBV DNA by liquid hybridization or PCR; elevated serum ALT level 11.5–10 x ULN on 3 occasions during the 6 months before enrollment; liver biopsy demonstrated histologic	Mean age 25 years. Men 69%	Hybridization assay (Digene) Detection limit = 2.8 x 10^5 copies/mL	Allocation concealment: unclear Open-label Pathologist blinded Intent-to-treat analyses: no Study withdrawals

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
		evidence of chronic HBV infection. **Exclusion**: Treated previously with IFN or had received antiviral or immunosuppressive medications; hepatitis C or D, or HIV; other causes of chronic liver disease; if they drank 140 g of alcohol per day; HCC; decompensated liver disease; history of ascites, variceal hemorrhage, or hepatic encephalopathy; any contraindications specified for use of IFN.			adequately described: yes Funding: not reported
Jang, 2004[65]	*See under lamivudine*				
Schiff, 2003[47]	*See under lamivudine*				
Barbaro, 2001[66]	*See under lamivudine*				
Schalm, 2000[67]	*See under lamivudine*				
Mutimer 1998[80]	Interferon-α-2b 10 MU 3 times/ week plus placebo x 4 weeks then lamivudine 100 mg x 12 weeks (n=6) Interferon-α-2b 10 MU 3 times/ week plus lamivudine 100 mg x 16 weeks (n=14) x 16 weeks, plus 16 weeks followup.	**Inclusion**: Ages 18–70; compensated liver disease; HBsAg, HBeAg and HBV DNA positive; failed to seroconvert (from HBeAg to anti-HBe) with at least one prior course of interferon at a minimum dose of 13.5 mega units per week ≥16 weeks; ≥6 months since the most recent interferon treatment. **Exclusion**: Co-infection with hepatitis D or C virus or HIV.	Mean age 39 years. Men 95%. Race: white 65%; Asian 35%. All subjects were interferon-α resistant. Cirrhosis 10%.	Real-time PCR assay (Roche) Detection limit = 1 x 103 copies per mL	Allocation concealment: adequate Double-blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: not reported

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

I. Pegylated interferon-α-2b versus Interferon-α-2b

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Zhao, 2007[81] China multicenter study	Pegylated interferon-α-2b (1.0 mg/ kg once per week; (n=115) Interferon-α-2b (3 MIU 3 times/ week (n=115) x 24 weeks, plus 24 weeks followup.	**Inclusion**: Age 18 to 70 years; HBsAg and HBeAg ≥6 months prior to enrollment; serum HBV DNA level >1 x10^5 copies/mL; and ALT level 2 to 10 x ULN. **Exclusion**: Any cause of liver disease other than chronic HBV infection; use of immune regulators during the previous 6 months, or individuals who have received antiviral therapy (nucleotide analogues and IFN) during the previous 3 months of the commencement of the study.	Median age 31 years. Men 82%. Race: Asian 100% Prior HBV treatment: Interferon 13%.	Real-time PCR assay (Roche) Detection limit = 1 x 103 copies per mL	Allocation concealment: adequate Open-label Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: not reported

J. Interferon-α-2b

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Chung, 2003[82] South Korea	"Individualized" Interferon-α-2b 5 MU 3 times/week (treatment duration varied) (n=30) Interferon-α-2b x 6 months (n=35)	**Inclusion**: Age ≥18 years; of HBsAg in serum ≥ 6 months with or without HBeAg; positive serum HBV-DNA; and serum ALT levels elevated >2 ULN >6 months before entry. Exclusion: mild activity and cirrhosis; serum bilirubin >2.0 mg/dl; serum albumin <3 g/dl; serum creatinine concentration >1.4 mg/dl; history of ascites or variceal hemorrhage; positive serum anti-hepatitis C or D.	Mean age 35 years (range). Men 88%. Race: Asian 100%	Liquid hybridization assay (Abbott) Detection limit = 1.6 pg/ml.	Allocation concealment: unclear Open-label Intent-to-treat analyses: not reported Study withdrawals adequately described: no withdrawals reported Funding: not reported
Janssen 1999[83]	Prolonged therapy (16 weeks of further Interferon-α-2b	**Inclusion**: Ages 18 to 70 years; HBsAg positivity in serum ≥6 months; presence of HBeAg and HBV DNA in serum; elevation of either serum AST	Mean age 34 years (range 16 to 70). Men 75%. Race: white 80%; Asian 14%; other 6% Cirrhosis 17%	Hybridization (Genostics, Abbott Laboratories). Cut-off = 1.7pg/mL	Allocation concealment: adequate Open-label

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
	(n=61) Standard therapy (no further Interferon-α-2b therapy) (n=57)	or ALT values ≥3 occasions in the 3 months before entry; histological evidence of chronic hepatitis on a liver biopsy taken in the 6 months preceding enrollment. **Exclusion**: Hepatitis C or D, or HIV; recent alcohol abuse or drug addiction; previous IFN-a course ≥12 weeks using at least 30 million units (MU) per week; any antiviral or immune modulatory therapy in the preceding 6 months; immuno-compromised patients; history of either ascites, bleeding esophageal varices, and hepatic encephalopathy.			Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: pharmaceutical
Lampertico 1997[84]	interferon-α-2b 6 MU 3 times/ week x 24 consecutive months (n=21) No therapy (n= 21)	**Inclusion**: Ages 18 to 65 years; presence of HBsAg and anti-HBe in serum ≥1 year: serum ALT levels >2 the ULN; HBV DNA either persist-ently or intermittently detectable by dot-blot assay on serum samples taken at 3-month intervals during year before enrollment; histologically documented chronic active hepatitis with or without cirrhosis. **Exclusion**: History of hepatic decompensation; hepatitis C or D and HIV; drug abuse, alcoholism; antiviral or immunosuppressive therapy in the previous 12 months	Mean age 46 years. Men 86%. Cirrhosis 17%	Dot-blot hybridization	Allocation concealment: unclear Open-label Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: private
Lopez-Alcorocho 1997[85]	Interferon-α-2b 10 MU (3 times/ week) x 2 months then 5 MU x 2 months then 10 MU x 2 months (n=19)	**Inclusion**: HBsAg+; elevated ALT; histologically confirmed disease. **Exclusion**: Hepatitis C or D and HIV.	Mean age 34 years (range 20-64). Men 87%. Intrafamilial exposure 16%. All subjects treatment-naïve.	Radioimmuno-assay	Allocation concealment: unclear Open-label Intent-to-treat analyses: yes Study withdrawals

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
	Interferon-α-2b 10 MU (3 times/ week) x 2 months then 5 MU x 2 months then 10 MU x 8 months (n=19) 52 weeks followup				adequately described: yes Funding: foundation
Di Bisceglie, 1993[86] United States	Interferon-α-2b 10 MU (3 times/ week) x 16 weeks (n=25) No therapy (n= 22) 6 month study duration	**Inclusion**: Elevated AST ≥6 months; HBeAg, HBsAg and HBV DNA+. **Exclusion**: Hepatitis D and HIV; decompensated liver disease	Mean age 44 years (range 23-72). Men 77%. Race: white 98%. Cirrhosis 38%	Quantitative liquid phase hybridization (Genostics, Abbott).	Allocation concealment: adequate Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: not reported
Műller 1990a[87] Germany	Interferon-α-2b 3 MU 3 times/ week x 4 months (n=25) No treatment (n=25) 26 weeks followup	**Inclusion**: Evidence of chronic hepatitis; seropositive for HBsAg and HBVDNA >6 months. **Exclusion**: Hepatitis D and HIV; decompensated cirrhosis; chronic renal insufficiency, or those requiring hemodialysis or immunosuppressive therapy; patients with previous organ transplantations or considered to be of poor general condition.	Mean age 41 years (range 18-65). Men 79%. Cirrhosis 44%	Spot molecular and solution hybridization	Allocation concealment: unclear Intent-to-treat analyses: ongoing Study withdrawals adequately described: not reported Funding: not reported
Hadziyannis 1990[88] Greece	Interferon-α-2b 2 MU 3 times/week x 14 to 16 weeks (n=25; 17 have finished this ongoing study). Untreated	**Inclusion**: HBsAg+; HBeAg- and HBV DNA+ >1 year; anti-HDV, anti-HIV. **Exclusion**: Decompensated cirrhosis; received therapy with corticosteroids, immunosuppressive drugs or antiviral agents ≤6 months	Mean age 49 years (range 26-66). Men 94% Cirrhosis 44%	Spot molecular hybridization (Genostics)	Allocation concealment: unclear Open-label Intent-to-treat analyses: ongoing Study withdrawals adequately

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
	controls (n=25)				described: no withdrawals reported Funding: not reported
Waked 1990[89]	Interferon-α-2b 5 MU 3 times/ week x 16 weeks (n=12) Interferon-α-2b 5 MU 3 times/ week x 16 weeks (n=12) 52 weeks followup	**Inclusion**: HBsAg+, and HBeAg+ ≥6 months; elevated ALT; histologically confirmed disease; compensated liver disease. **Exclusion**: Chronic persistent hepatitis (biopsy); inactive cirrhosis; serum albumin >3 gm/dL; serum bilirubin >4 gm/dL; serum creatinine concentration >1.5 mg/dl; history of ascites or variceal hemorrhage; corticosteroid or antiviral therapy ≤12 months.	Mean age 36 years (range 9-62). Men 78%. Cirrhosis 44%	Enzyme linked immunoassay	Allocation concealment: unclear Open-label Intent-to-treat analyses: no Study withdrawals adequately described: yes Funding: not reported

K. Interferon-α-2b plus prednisolone

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
Reichen 1994[90] Switzerland	Arm A prednisone 50 mg for 2 weeks followed by 25 mg for another 2 weeks. After 2 week drug-free interval, recombinant Interferon-α-2b 1.5 MU for 4 months (n=18) Arm B Same regimen w/ placebo replacing	**Inclusion**: 18-70 years; ALT ≥2 x ULN; replicating HBV documented for at least 6 months; chronic active HBV by biopsy no older than 3 months at study entry; positive for HBsAg and HBeAg. **Exclusion**: Lack of histological activity; alcohol abuse; spontaneous seroconversion during workup; suspicion of autoimmune liver disease; HIV+; alcohol consumption >80 g/day for men & 50 g/day for women; drug abuse; decompensated cirrhosis; HCC; previous Interferon therapy and immunosuppressive therapy within preceding 6 months.	Mean age 40 years. Male: 85%	Hybridization	Allocation concealment: adequate Blinding: unclear although study placebo-controlled Pathologist blinded Intent-to-treat analyses: no Study withdrawals adequately described: no Funding: not reported

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
	prednisone and followed by Interferon-α-2b 1.5 MU (n=19) Arm C Same regimen w/ placebo replacing prednisone and followed by Interferon-α-2b at 5 MU (n=19)				
Zarski 1994[91] France	Interferon α-2b 5 MU 3 times/ week x 24 weeks (n=25) Interferon-α-2b plus prednisolone, 60, 40, 20 mg x 6 weeks (n=31)	**Inclusion**: 18 to 75 years; serum HBsAg+ ≥6 months; HBeAg and HBV DNA+ documented on 3 or more occasions at last 1 month apart ≤6 months before entry; elevated ALT on at least 3 occasions before entry, with an average value ≥1.5 x ULN; compensated liver disease; evidence of HBV on biopsy. **Exclusion**: Corticosteroid or antiviral therapy ≤12 months; other serious medical illnesses that might preclude completion of the study; alcohol or drug abuse or other potential causes of liver disease; seropositivity for anti-hepatitis C or D or HIV type I and II.	Mean age 38 years. Male: 89%	Direct-spot hybridization	Allocation concealment: unclear Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: no withdrawals reported Funding: pharmaceutical
Perez 1993[92] Argentina	Prednisone 60, 40, 20 mg daily every 2 weeks, then 2 weeks' rest then interferon α-2b 10 MU 3 times/ week x 16 weeks (n=26)	**Inclusion**: Documented HBeAg and HBV-DNA positive ≥6 months, serum ALT activities ≥1 to 5 x ULN; liver biopsy specimens compatible with chronic hepatitis. **Exclusion**: Other causes of liver disease (other than CHB) were excluded.	Not reported		Allocation concealment: unclear Open-label Intent-to-treat analyses: yes Study withdrawals adequately described: yes

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
	No treatment x 24 weeks then interferon α-2b (n=24) x 24 weeks				Funding: not reported
Lok 1992[93] China	Prednisone, 45, 30, and 15 mg each for 2 weeks, then 2 weeks rest Interferon-α-2b 10 MU 3 times/ week x 16 weeks (n=21) Matching placebo then 2 weeks rest then Interferon α-2b 10 MU 3 times weekly x 16 weeks (n=18) No treatment (n=16)	**Inclusion**: 18-60 years; presence of HBsAg in serum >6 months; HBeAg+; HBV DNA+; stable serum HBV DNA and ALT levels on at least 3 occasions, 1 month apart, during the 6 months of entry. **Exclusion**: Decompensated liver disease; coagulopahy precluding liver biopsy; severe systemic illness; immunosuppressive or antiviral therapy within preceding 12 months; presence of other factors that may contribute to liver disease, such as alcoholism and seropositivity for antibody to hepatitis D or HIV.	Mean age 28 years (range). Men 62%. Race: Asian 100%. Cirrhosis 10%	Direct spot hybridization. Sensitivity of the assay 0.2pg HBV DNA/20uL serum.	Allocation concealment: unclear Blinding not stated Pathologist blinded Intent-to-treat analyses: ongoing Study withdrawals adequately described: yes Funding: pharmaceutical and other
Niederau 1992[94] Germany	Arm A Prednisone, 40 and 20 mg for 2 weeks, then Interferon-α-2b 2 MU 3 times/ week x 3 months (n=20). If no seroconversion Interferon-α-2b 5 MU given. Arm B Interferon-α-2b	**Exclusion**: absence of HBeAg or HBV DNA in serum; AST below required value; antibody to hepatitis D or HIV; thrombocytopenia; advanced cirrhosis; alcohol or drug abuse	Mean age 43 years. Men 91%.	Solution hybrid assay (Abbott)	Allocation concealment: unclear Open-label Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: pharmaceutical

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
	5 MU 3 times/ week x 4 months (n=20) Arm C No treatment (n=20)				
Perez 1990[95]	Prednisone 60, 40, 20 mg daily every 2 weeks, then 2 weeks' rest then interferon α-2b 10 MU 3 times/ week x 16 weeks (n=17) No treatment x 24 weeks then interferon α-2b (n=18) x 24 weeks	**Inclusion**: ≥18 years; presence of serum HBsAg, HBeAg, HBV DNA ≥6 months; ALT ≥1.3 x ULN on at least 3 occasions; compensated liver disease. **Exclusion**: Seropositivity for antibody to hepatitis D or HIV; inadequate hematocrit, platelet, white blood cell and granulocyte counts.	Mean age 39 years. Men 77%.	Molecular hybridization	Allocation concealment: unclear Open-label Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: not reported
Perillo 1990[96] United States	Arm A Prednisone, 60, 40, 20, 0 mg each, for 2 weeks at each dose) followed by Interferon-α-2b 5 MU daily x 16 weeks (n=44) Arm B Placebo plus Interferon-α-2b 5 MU daily x 16 weeks (n=41) Arm C Placebo plus Interferon-α-2b	**Inclusion**: ≥18 years; presence of HBsAg in serum ≥6 months; HBeAg+; HBV DNA+; stable serum HBV DNA and ALT levels on at least 3 occasions; ALT ≥1.3 x ULN on at least 3 occasions; compensated liver disease. **Exclusion**: Immunosuppressive or antiviral therapy within preceding 12 months; serious medical illness; low hematocrit, platelet and granulocyte counts; elevated serum creatinine; alcoholism or drug abuse; and seropositivity for antibody to hepatitis D or HIV.	Mean age 40 years. Men 85%.	Solution hybrid assay (Abbott)	Allocation concealment: unclear Partially double-blinded Pathologist blinded Intent-to-treat analyses: yes Study withdrawals adequately described: yes Funding: Government, pharmaceutical

Appendix E. Table 2. Evidence table: Randomized controlled trials for treatment of hepatitis B

Author / Country	Interventions/ Treatment Duration	Key Inclusion / Exclusion Criteria	Subject Characteristics	Assay	Study Quality
	1 MU daily x 16 weeks (n=41) Arm D No treatment (n=43)				

* Either coinfection or presence of antibodies

Appendix E. Table 3. Reported clinical and intermediate outcomes after comparisons of antiviral drugs for chronic hepatitis B (randomized controlled clinical trials)

Treatments	Mortality/ Liver-related Mortality	HCC	Cirrhosis	Liver Failure	Combined	Biochemical	Virological (DNA; HBe or HBs Ag Status)	Histological	Harm Effects
Adefovir dipivoxil+lamivudine vs. adefovir dipivoxil						2 studies[43,45]	2 studies[43,45]		1 study[43]
Adefovir dipivoxil+lamivudine vs. lamivudine						2 studies[43,58]	2 studies[43,58]		2 studies[43,58]
Adefovir dipivoxil (dose, time)	1 study[97]	1 study[97]				4 studies[40,42,44,98]	5 studies[40,42,44,97,98]	3 studies[42,97,98]	6 studies[40,42,44,97-99]
Adefovir dipivoxil vs. placebo						4 studies[40-42,98]	5 studies[40-42,98,100]	3 studies[41,42,98]	5 studies[40-42,98,99]
Entecavir (dose, time)	1 study[76]				2 studies[76,77]	2 studies[76,77]	2 studies[76,77]		2 studies[76,77]
Entecavir vs. lamivudine	5 studies[73-76,101]			2 studies[73,101]	4 studies[73,75-77]	7 studies[73-77,101]	6 studies[73-77,101]	3 studies[73-75]	6 studies[73-77,101]
Interferon alfa-2b+ corticosteroid vs. interferon alfa-2b	1 study[90]		1 study[91]			4 studies[90,92,95,96]	8 studies[90-96,102]	2 studies[90,91]	3 studies[92,93,95]
Interferon alfa-2b+ corticosteroid vs. no treatment						1 study[96]	3 studies[93,94,96]		
Interferon alfa-2b+ corticosteroid vs. symptomatic treatment	1 study[103]					1 study[103]	1 study[103]		1 study[103]
Interferon alfa-2b+ lamivudine					2 studies[61,79]	2 studies[67,79]	3 studies[67,79,104]	2 studies[67,79]	2 studies[67,79]
(dose, time)						80	80		
Interferon alfa-2b+ lamivudine vs. lamivudine					5 studies[60,61,64,66,68]	8 studies[47,62-67,69]	10 studies[47,60,62-66,68,69,104]	7 studies[47,60,64,66-69]	10 studies[47,60,62-69]
Interferon alfa-2b+ lamivudine vs. placebo						1 study[47]	2 studies[47,104]	1 study[47]	1 study[47]
Interferon alfa-2b+ placebo vs. lamivudine						1 study[67]	1 study[67]	1 study[67]	1 study[67]
Interferon alfa-2b+ placebo vs. no treatment							1 study[93]		

Appendix E. Table 3. Reported clinical and intermediate outcomes after comparisons of antiviral drugs for chronic hepatitis B (randomized controlled clinical trials)

Treatments	Mortality/ Liver-related Mortality	HCC	Cirrhosis	Liver Failure	Combined	Biochemical	Virological (DNA; HBe or HBs Ag Status)	Histological	Harm Effects
Interferon alfa-2b (dose, time)	2 studies[85,90]				1 study[85]	4 studies[82,85,90,96]	4 studies[82,85,90,96,104]		2 studies[82,85]
Interferon alfa-2b vs. lamivudine									
Interferon alfa-2b vs. no treatment	1 study[89]	1 study[84]	1 study[89]		4 studies[84,87,88,105]	4 studies[83,84,86,96]	7 studies[83,84,86,94,96,104]	2 studies[84,89]	5 studies[83,84,86,87,105]
Lamivudine vs. adefovir dipivoxil						1 study[43]	1 study[43]		1 study[43]
Lamivudine vs. baseline						2 studies[106,107]	4 studies[56,57,106,107]	1 study[107]	
Lamivudine (dose, time)						3 studies[50,55,108]	4 studies[50,108-110]	3 studies[50,107,111]	4 studies[50,55,108,110]
Lamivudine vs. no treatment				1 study[54]		1 study[54]	1 study[54]		
Lamivudine vs. placebo	1 study[51]			1 study[51]	3 studies[46,49,51]	7 studies[46-48,50,108,112,113]	11 studies[48-50]10861652[46,47,51,104,110,112,113]	6 studies[46-48,50,111,113]	9 studies[46-51,108,110,112]
Lamivudine vs. telbivudine					1 study[72]	1 study[72]	1 study[72]		1 study[72]
Lamivudine vs. usual care							1 study[53]		
Peginterferon alfa-2a+ lamivudine vs. baseline							2 studies[56,57]		
Peginterferon alfa-2a+ lamivudine vs. interferon alfa-2b					1 study[114]				
Peginterferon alfa-2a+ lamivudine vs. lamivudine	1 study[56]				4 studies[56,57,114,115]	2 studies[56,57]	2 studies[56,57]	2 studies[56,57]	2 studies[56,57]
Peginterferon alfa-2a+ lamivudine vs. peginterferon alfa-2a	1 study[56]				1 study[56]	1 study[56]	1 study[56]	1 study[56]	1 study[56]

Appendix E. Table 3. Reported clinical and intermediate outcomes after comparisons of antiviral drugs for chronic hepatitis B (randomized controlled clinical trials)

Treatments	Mortality/ Liver-related Mortality	HCC	Cirrhosis	Liver Failure	Combined	Biochemical	Virological (DNA; HBe or HBs Ag Status)	Histological	Harm Effects
Peginterferon alfa-2a+ placebo vs. baseline							1 study[56]		
Peginterferon alfa-2a+ placebo vs. lamivudine	1 study[56]				3 studies[56,57,114]	2 studies[56,57]	2 studies[56,57]	2 studies[56,57]	2 studies[56,57]
Peginterferon alfa-2a vs. baseline							1 study[57]		
Peginterferon alfa-2a vs. lamivudine					1 study[114]				
Peginterferon alfa-2a (dose, time)					1 study[116]	1 study[116]	1 study[116]		1 study[116]
Peginterferon alfa-2b+ lamivudine vs. lamivudine	1 study[117]			1 study[117]		2 studies[59,117]	3 studies[59,117,118]	1 study[59]	1 study[59]
Peginterferon alfa-2b+ lamivudine vs. peginterferon alfa-2b						4 studies[78,119-121]	6 studies[78,120-124]	2 studies[78,125]	2 studies[78,119]
Peginterferon alfa-2b vs. interferon alfa-2b					1 study[81]	1 study[81]	1 study[81]		1 study[81]
Telbivudine+lamivudine vs. lamivudine					1 study[72]	1 study[72]	1 study[72]		1 study[72]
Telbivudine+lamivudine vs. telbivudine					1 study[72]	1 study[72]			1 study[72]
Telbivudine vs. adefovir dipivoxil						1 study[44]	1 study[44]		1 study[44]
Telbivudine vs. lamivudine					1 study[71]	1 study[71]	1 study[71]	1 study[71]	1 study[71]
Telbivudine (dose, time)						2 studies[72]			1 study[72]

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

(A) Outcomes after antiviral drug therapy Interferon administration

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Niederau, 1992[94] Interferon-alpha (Intron A, Essex), 1/2 MU 3 times /week increasing to 5 MU in patients in whom therapy did not eliminate HBeAg and HBVDNA during 2 months of therapy Prednisolone, 2 weeks 40 mg/day and further 2 weeks 20 mg/day, 16 weeks	Interferon-alpha (Intron A, Essex), 2/ 5 MU 3 times per week, 16 weeks	Loss of HBV DNA	16/16	5/20 9/20	25/45	0.56 (0.23; 1.37)	-0.20 (-0.49; 0.09)	-5
	No treatment, 0, 16 weeks	Loss of HBV DNA	16/16	5/20 0/14	25/0	7.86 (0.47; 131.58)	**0.25 (0.04; 0.46)**	4
Niederau, 1992[94] Interferon-alpha (Intron A, Essex), 2/ 5 MU 3 times a week, 16 weeks	No treatment, 0, 16 weeks	Loss of HBV DNA	16/16	9/20 0/14	45/0	13.57 (0.85; 215.62)	**0.45 (0.22; 0.68)**	2
Niederau, 1992[94] Interferon-alpha (Intron A, Essex), 1/ 2 MU 3 times per week with increasing to 5 MU in patients in whom therapy did not eliminate HBe-Ag and HBV-DNA 2 months after its prednisolone, 2 weeks 40 mg/day and further 2 weeks 20 mg/day, 16 weeks	Interferon-alpha (Intron A, Essex), 2/ 5 MU 3 times per week, 16 weeks	Reduction in HBV DNA	16/16	10/20 10/20	50/50	1.00 (0.54; 1.86)	0.00 (-0.31; 0.31)	
		Unchanged HBV DNA	16/16	5/20 1/20	25/5	5.00 (0.64; 39.06)	0.20 (-0.01; 0.41)	5
		HBeAg negative	16/16	4/20 8/20	20/40	0.50 (0.18; 1.40)	-0.20 (-0.48; 0.08)	-5
		HBeAg positive	16/16	16/20 12/20	80/60	1.33 (0.88; 2.03)	0.20 (-0.08; 0.48)	5
		HBsAg negative	16/16	1/20 0/20	5/0	3.00 (0.13; 69.52)	0.05 (-0.08; 0.18)	20
		Loss of HBV DNA	40/40	5/20 9/20	25/45	0.56 (0.23; 1.37)	-0.20 (-0.49; 0.09)	-5
	No treatment, 0, 16 weeks	Loss of HBV DNA	40/40	5/20 1/14	25/5	3.50 (0.46; 26.80)	0.18 (-0.05; 0.41)	6

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Niederau, 1992[94] Interferon-alpha (Intron A, Essex), 2/ 5 MU 3 times a week, 16 weeks	No treatment, 0, 16 weeks	Loss of HBV DNA	40/40	9/20 1/14	45/5	6.30 (0.90; 44.27)	**0.38 (0.12; 0.63)**	3
Niederau, 1992[94] Interferon-alpha (Intron A, Essex), 1/ 2 MU 3 times per week with increasing to 5 MU in patients in whom therapy did not eliminate HBe-Ag and HBV-DNA 2 months after its prednisolone, 2 weeks 40 mg/day and further 2 weeks 20 mg/day, 16 weeks	Interferon-alpha (Intron A, Essex), 2/ 5 MU 3 times per week, 16 weeks	Reduction in HBV DNA	40/40	10/20 10/20	50/50	1.00 (0.54; 1.86)	0.00 (-0.31; 0.31)	
	No treatment, 16 weeks	Reduction in HBV DNA	40/40	10/20 2/14	50/15	3.50 (0.90; 13.58)	**0.36 (0.07; 0.64)**	3
Niederau, 1992[94] Interferon-alpha (Intron A, Essex), 2/ 5 MU 3 times a week, 16 weeks	No treatment, 16 weeks	Reduction in HBV DNA	40/40	10/20 2/14	50/15	3.50 (0.90; 13.58)	**0.36 (0.07; 0.64)**	3
Niederau, 1992[94] Interferon-alpha (Intron A, Essex), 1/ 2 MU 3 times per week with increasing to 5 MU in patients in whom therapy did not eliminate HBe-Ag and HBV-DNA 2 months after its prednisolone, 2 weeks 40 mg/day	Interferon-alpha (Intron A, Essex), 2/ 5 MU 3 times per week, 16 weeks	Unchanged HBV DNA	40/40	5/20 1/20	25/5	5.00 (0.64; 39.06)	0.20 (-0.01; 0.41)	5
	No treatment, 0, 16 weeks	Unchanged HBV DNA	40/40	5/20 11/14	25/80	0.32 (0.14; 0.71)	-0.54 (-0.82; -0.25)	-2

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
and further 2 weeks 20 mg/day, 16 weeks								
Niederau, 1992[94] Interferon-alpha (Intron A, Essex), 2/ 5 MU 3 times a week, 16 weeks	No treatment, 16 weeks	Unchanged HBV DNA	40/40	1/20 11/14	5/80	0.06 (0.01; 0.44)	**-0.74** **(-0.97; -0.50)**	-1
Robson, 1992[103] Interferon alpha-2b (Intron A; Scherag), 4 10MI 3 times/week after 6 weeks of prednisone and 2 weeks without treatment Prednisone, 60mg/day for 2 weeks then 40mg/day for 2 weeks, and then 20mg/day for 2 weeks, 24 weeks	Symptomatic treatment, 24 weeks	Death	72/72	0/10 1/10	0/10	0.33 (0.02; 7.32)	-0.10 (-0.34; 0.14)	-10
		Leucopenia	24/24	2/10 0/10	20/0	5.00 (0.27; 92.62)	0.20 (-0.08; 0.48)	5
		HBeAg loss, undetectable HBV DNA	24/24	6/10 1/10	60/10	6.00 (0.87; 41.21)	**0.50 (0.14; 0.86)**	2
		HBsAg loss	24/24	1/10 0/10	10/0	3.00 (0.14; 65.90)	0.10 (-0.14; 0.34)	10
Lok, 1992[93] Interferon alpha-2b (IntronA; Schering Plough, Kenilworth, NJ), 4 /10 MU 3 times per week Prednisone, 1545, 30, and 15 mg each for 2 weeks, followed by a 2-week rest, 24 weeks	Placebo for 6 weeks + 2 weeks rest then Interferon alpha 2b, 4 /10 MU 3 times per week, 24 weeks	Development of Interferon-neutralizing antibody	48/48	4/40 1/39	10/3	3.90 (0.46; 33.36)	0.07 (-0.03; 0.18)	13
	No treatment, 24 weeks	Partial antiviral response: sustained clearance of serum HBV DNA by direct spot hybridization (lower limit of detection of 10 pg/mL) and	48/48	9/40 3/36	22/8	2.70 (0.79; 9.21)	0.14 (-0.02; 0.30)	7

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		clearance of HBeAg but not HBsAg						
Lok, 1992[93] Interferon alpha 2b, 4/ 10 MU 3 times per week Placebo, 15 weeks Placebo for 6 weeks + 2 weeks rest, 24 weeks	No treatment, 24 weeks	Partial antiviral response: sustained clearance of serum HBV DNA by direct spot hybridization (lower limit of detection of 10 pg/mL) and clearance of HBeAg but not HBsAg	48/48	6/39 3/36	15/8	1.85 (0.50; 6.84)	0.07 (-0.07; 0.22)	14
Lok, 1992[93] Interferon alpha-2b (IntronA; Schering Plough, Kenilworth, NJ), 4 /10 MU 3 times per week Prednisone, 30, and 15 mg each for 2 weeks, followed by a 2-week rest, 24 weeks	Placebo for 6 weeks + 2 weeks rest then Interferon alpha 2b, 4 /10 MU 3 times per week, 24 weeks	Partial antiviral response: sustained clearance of serum HBV DNA by direct spot hybridization (lower limit of detection of 10 pg/mL) and clearance of HBeAg but not HBsAg	48/48	9/40 6/39	22/15	1.46 (0.57; 3.72)	0.07 (-0.10; 0.24)	14
	No treatment,, 24 weeks	Complete antiviral response: sustained clearance of serum HBV DNA by direct spot hybridization (lower limit of	48/48	0/40 0/36			0.00 (-0.05; 0.05)	

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		detection of 10 pg/mL) and clearance of HBeAg and HBsAg						
Lok,1992[93] Interferon alpha 2b, 4/ 10 MU three times per week Placebo for 6 weeks +2 weeks rest, 24 weeks	No treatment, 24 weeks	Complete antiviral response: sustained clearance of serum HBV DNA by direct spot hybridization (lower limit of detection of 10 pg/mL) and clearance of HBeAg and HBsAg	48/48	2/39 0/36	5/0	4.63 (0.23; 93.20)	0.05 (-0.03; 0.14)	19
Lok, 1992 [93] Interferon alpha-2b (IntronA; Schering Plough, Kenilworth, NJ), 4/ 10 MU 3 times per week Prednisone, 45, 30, and 15 mg each for 2 weeks, followed by a 2 week rest, 24 weeks	Placebo for 6 weeks + 2 weeks rest then Interferon alpha 2b, 4 /10 MU 3 times per week, 24 weeks	Complete antiviral response: sustained clearance of serum HBV DNA by direct spot hybridization (lower limit of detection of 10 pg/mL) and clearance of HBeAg and HBsAg	48/48	0/40 2/39	0/5	0.20 (0.01; 3.94)	-0.05 (-0.13; 0.03)	-19
Perez, 1990[95] Intron A, Schering-Plough Corporation, 4/ 10 MU 3 times/week for 16 weeks after 6 weeks of prednisone therapy and 2 weeks without	Intron A, Schering-Plough Corporation, 4 /10 MU 3 time/week for 16 weeks after 24 weeks of no treatment, 40 weeks	Normal ALT	48/64	2/17 1/18	12/6	2.12 (0.21; 21.27)	0.06 (-0.12; 0.25)	16
		Discontinuation due to adverse effects	22/40	0/17 1/18	0/6	0.35 (0.02; 8.09)	-0.06 (-0.20; 0.09)	-18
		Reduction in dose due to adverse effects	22/40	2/17 2/18	12/11	1.06 (0.17; 6.70)	0.01 (-0.20; 0.22)	153

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
treatment Prednisone, 60mg/day for 2 weeks then 40mg/day for 2 weeks, and then 20mg/day for 2 weeks, 24 weeks		Elimination of HBeAg	48/64	10/17 7/18	59/39	1.51 (0.75; 3.05)	0.20 (-0.13; 0.52)	5
		HBeAg seroconversion	48/64	8/17 6/18	47/33	1.41 (0.62; 3.22)	0.14 (-0.18; 0.46)	7
		Undetectable HBV DNA	48/64	9/17 6/18	53/33	1.59 (0.72; 3.51)	0.20 (-0.13; 0.52)	5
		Elimination of HBsAg	48/64	1/17 0/18	6/0	3.17 (0.14; 72.80)	0.06 (-0.09; 0.21)	17
Hadziyannis, 1990[88] Interferon Alfa 2b, 1/ 3 MU 3 times per week, 16 weeks	No treatment, 16 weeks	Complete response: loss of HBV DNA and normalization of ALT	16/16	10/25 0/25	40/0	21.00 (1.30; 340.02)	**0.40 (0.20; 0.60)**	2
			40/40	8/25 1/25	32/4	8.00 (1.08; 59.32)	**0.28 (0.08; 0.48)**	4
			64/64	11/25 2/25	44/8	5.50 (1.36; 22.32)	**0.36 (0.14; 0.58)**	3
		Partial response: reduction in HBV DNA and ALT by >50 from baseline level	16/16	7/25 4/25	28/16	1.75 (0.58; 5.24)	0.12 (-0.11; 0.35)	8
			40/40	6/25 5/25	24/20	1.20 (0.42; 3.43)	0.04 (-0.19; 0.27)	25
			64/64	3/25 6/25	12/24	0.50 (0.14; 1.78)	-0.12 (-0.33; 0.09)	-8
		Reappearance of HBV DNA and increase in ALT	112/112	4/25 2/25	16/8	2.00 (0.40; 9.95)	0.08 (-0.10; 0.26)	12
Műller, 1990[87] Recombinant interferon alfa-2b (Intron A, R Schering-Plough, Essex Corporation), 1/ 3 MU 3 times per week, 16 weeks	No treatment, 16 weeks	Complete response loss of HBs Ag, HBeAg, and HBV DNA, and normal-ization of ALT	40/40	1/30 0/28	3/0	2.81 (0.12; 66.17)	0.03 (-0.06; 0.12)	30
		Partial response: loss of HBeAg and HBV DNA, and normalization of ALT	40/40	8/30 0/28	27/0	15.90 (0.96; 263.32)	**0.27 (0.10; 0.43)**	4

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Loss HBV DNA and HBeAg seroconversion	40/40	9/30 3/28	30/11	2.80 (0.84; 9.30)	0.19 (-0.01; 0.39)	5
		Discontinuation due to overted depression	16/16	1/30 0/28	3/0	2.81 (0.12; 66.17)	0.03 (-0.06; 0.12)	30
		Developing of IFN neutralizing antibodies	16/16	2/30 0/28	7/0	4.68 (0.23; 93.37)	0.07 (-0.04; 0.17)	15
Waked, 1990[89] Intron A, Schering-Plough Inc, USA, 2/ 5 MU/m2 3 times weekly (n = 12) or daily (n = 8), outcomes reported after both doses together, 16 weeks	No treatment, 16 weeks	Death	16/16	3/20 1/20	15/5	3.00 (0.34; 26.45)	0.10 (-0.08; 0.28)	10
			64/80	0/20 2/20	0/10	0.20 (0.01; 3.92)	-0.10 (-0.25; 0.05)	-10
		Incident cirrhosis	64/80	1/20 2/20	5/10	0.50 (0.05; 5.08)	-0.05 (-0.21; 0.11)	-20
		Improved histology	64/80	4/20 1/20	20/5	4.00 (0.49; 32.72)	0.15 (-0.05; 0.35)	7
		Loss of HBeAg	16/16	16/20 5/20	80/25	3.20 (1.45; 7.05)	**0.55 (0.29; 0.81)**	2
		HBeAg seroconversion	16/16	11/20 4/20	55/20	2.75 (1.05; 7.20)	**0.35 (0.07; 0.63)**	3
		Loss of HBsAg	16/16	5/20 3/20	25/15	1.67 (0.46; 6.06)	0.10 (-0.15; 0.35)	10
		HBsAg seroconversion	16/16	4/20 1/20	20/5	4.00 (0.49; 32.72)	0.15 (-0.05; 0.35)	7
		Loss of HBeAg	64/80	13/20 5/20	65/25	2.60 (1.14; 5.93)	**0.40 (0.12; 0.68)**	2
		HBeAg seroconversion	64/80	10/20 5/20	50/25	2.00 (0.83; 4.81)	0.25 (-0.04; 0.54)	4
		Loss of HBsAg	64/80	6/20 3/20	30/15	2.00 (0.58; 6.91)	0.15 (-0.10; 0.40)	7
		HBsAg seroconversion	64/80	4/20 1/20	20/5	4.00 (0.49; 32.72)	0.15 (-0.05; 0.35)	7

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Perrillo, 1990[96] Interferon Alfa 2b (Intron-A, Schering-Plough), 5 MU daily Prednisone, decreasing daily doses of 60, 40, and 20mg each for 2 weeks followed by 2 weeks rest, 24 weeks	Placebo oral for 6 weeks followed by 2 weeks rest then Intron-A 5 MU daily, 24 weeks	Normalization of ALT and AST	48/48	19/44 18/41	43/44	0.98 (0.61; 1.60)	-0.01 (-0.22; 0.20)	-139
	Placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 1 MU daily, 24 weeks	Normalization of ALT and AST	48/48	19/44 11/41	43/27	1.61 (0.88; 2.96)	0.16 (-0.04; 0.36)	6
	No treatment, 24 weeks	Normalization of ALT and AST	48/48	19/44 8/43	43/19	2.32 (1.14; 4.73)	**0.25 (0.06; 0.43)**	4
Perrillo, 1990[96] Interferon Alfa 2b (Intron-A, Schering-Plough), 5 MU daily placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 5 MU daily, 24 weeks	Placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 1 MU daily, 24 weeks	Normalization of ALT and AST	48/48	18/41 11/41	44/27	1.64 (0.89; 3.02)	0.17 (-0.03; 0.37)	6
	No treatment, 24 weeks	Normalization of ALT and AST	48/48	18/41 8/43	44/19	2.36 (1.15; 4.82)	**0.25 (0.06; 0.44)**	4
				11/41 8/43	27/19	1.44 (0.65; 3.22)	0.08 (-0.10; 0.26)	12
Perrillo, 1990[96] Interferon Alfa 2b (Intron-A, Schering-Plough), 5 MU daily Prednisone, decreasing daily doses of 60, 40, and 20mg each for 2 weeks followed by 2 weeks rest, 24 weeks	Placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 5 MU daily, 24 weeks	Loss of HBV DNA and HBeAg	24/24	16/44 15/41	36/37	0.99 (0.57; 1.74)	0.00 (-0.21; 0.20)	-451
	Placebo oral for 6 weeks followed by 2 weeks rest than Intron-A 1 MU daily, 24 weeks	Loss of HBV DNA and HBeAg	24/24	16/44 7/41	36/17	2.13 (0.98; 4.64)	**0.19 (0.01; 0.38)**	5
	No treatment, 24 weeks	Loss of HBV DNA and HBeAg	24/24	16/44 3/43	36/7	5.21 (1.64; 16.61)	**0.29 (0.13; 0.46)**	3

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Perrillo, 1990[96] Interferon Alfa 2b (Intron-A, Schering-Plough), placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 5 MU daily, 24 weeks	Placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 1 MU daily, 24 weeks	Loss of HBV DNA and HBeAg	24/24	15/41 7/41	37/17	2.14 (0.98; 4.70)	**0.20 (0.01; 0.38)**	5
	No treatment, 24 weeks	Loss of HBV DNA and HBeAg	24/24	15/41 3/43	37/7	5.24 (1.64; 16.79)	**0.30 (0.13; 0.46)**	3
				7/41 3/43	17/7	2.45 (0.68; 8.83)	0.10 (-0.04; 0.24)	10
Perrillo 1990 2195346 Interferon Alfa 2b (Intron-A, Schering-Plough), 5 MU daily Prednisone, decreasing daily doses of 60, 40, and 20mg each for 2 weeks followed by 2 weeks rest, 24 weeks	Placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 5 MU daily, 24 weeks	Loss of HBV DNA	48/48	4/44 3/41	9/7	1.24 (0.30; 5.22)	0.02 (-0.10; 0.13)	56
Perrillo, 1990[96] Interferon Alfa 2b (Intron-A, Schering-Plough), 5 MU daily Prednisone, 40 decreasing daily doses of 60, 40, and 20mg each for 2 weeks followed by 2 weeks rest, 24 weeks	Interferon Alfa 2b (placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 1 MU daily, 24 weeks	Loss of HBV DNA	48/48	4/44 4/41	9/10	0.93 (0.25; 3.48)	-0.01 (-0.13; 0.12)	-150
	No treatment, 24 weeks	Loss of HBV DNA	48/48	4/44 2/43	9/5	1.95 (0.38; 10.12)	0.04 (-0.06; 0.15)	23
Perrillo, 1990[96] Interferon Alfa 2b (Intron-A, Schering-Plough), placebo orally for 6	Placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 1 MU daily, 24 weeks	Loss of HBV DNA	48/48	3/41 4/41	7/10	0.75 (0.18; 3.14)	-0.02 (-0.15; 0.10)	-41

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
weeks followed by 2 weeks rest then Intron-A 5 MU daily, 24 weeks	No treatment, 24 weeks	Loss of HBV DNA	48/48	3/41 2/43	7/5	1.57 (0.28; 8.94)	0.03 (-0.07; 0.13)	38
				4/41 2/43	10/5	2.10 (0.41; 10.84)	0.05 (-0.06; 0.16)	20
Perrillo, 1990[96] Interferon Alfa 2b (Intron-A, Schering-Plough), 5 MU daily Prednisone, decreasing daily doses of 60, 40, and 20mg each for 2 weeks followed by 2 weeks rest, 24 weeks	Placebo oral for 6 weeks followed by 2 weeks rest than Intron-A 5 MU daily, 24 weeks	Loss of HBsAg	24/24	5/44 5/41	11/12	0.93 (0.29; 2.99)	-0.01 (-0.15; 0.13)	-120
	Placebo oral for 6 weeks followed by 2 weeks rest than Intron-A 1 MU daily, 24 weeks	Loss of HBsAg	24/24	5/44 1/41	11/2	4.66 (0.57; 38.22)	0.09 (-0.02; 0.19)	11
	No treatment, 24 weeks	Loss of HBsAg	24/24	5/44 0/43	11/0	10.76 (0.61; 188.77)	**0.11 (0.01; 0.21)**	9
Perrillo, 1990[96] Interferon Alfa 2b (Intron-A, Schering-Plough), placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 5 MU daily, 24 weeks	Placeboorally for 6 weeks followed by 2 weeks rest then Intron-A 1 MU daily, 24 weeks	Loss of HBsAg	24/24	5/41 1/41	12/2	5.00 (0.61; 40.95)	0.10 (-0.01; 0.21)	10
	No treatment, 24 weeks	Loss of HBsAg	24/24	5/41 0/43	12/0	11.52 (0.66; 202.03)	**0.12 (0.02; 0.23)**	8
				1/41 0/43	2/0	3.14 (0.13; 75.02)	0.02 (-0.04; 0.09)	41
Perrillo, 1990[96] Interferon Alfa 2b (Intron-A, Schering-Plough), 5 MU daily Prednisone, decreasing daily doses of 60,40, and 20mg each for 2 weeks followed by 2	Placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 5 MU daily, 24 weeks	Reactivation of HBeAg or reappearance of HBV DNA	48/48	1/44 0/41	2/0	2.80 (0.12; 66.85)	0.02 (-0.04; 0.08)	44
	Placebo orally for 6 weeks followed by 2 weeks rest then	Reactivation of HBeAg or reappearance of	48/48	1/44 1/41	2/2	0.93 (0.06; 14.42)	0.00 (-0.07; 0.06)	-601

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
weeks rest, 24 weeks	Intron-A 1 MU daily, 24 weeks	HBV DNA						
	No treatment, 24 weeks	Reactivation of HBeAg or reappearance of HBV DNA	48/48	1/44 0/43	2/0	2.93 (0.12; 70.08)	0.02 (-0.04; 0.08)	44
Perrillo, 1990[96] Interferon Alfa 2b (Intron-A, Schering-Plough), placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 5 MU daily, 24 weeks	Placebo orally for 6 weeks followed by 2 weeks rest then Intron-A 1 MU daily, 24 weeks	Reactivation of HBeAg or reappearance of HBV DNA	48/48	0/41 1/41	0/2	0.33 (0.01; 7.95)	-0.02 (-0.09; 0.04)	-41
	No treatment, 24 weeks	Reactivation of HBeAg or reappearance of HBV DNA	48/48	0/41 0/43			0.00 (-0.05; 0.05)	
					2/0	3.14 (0.13; 75.02)	0.02 (-0.04; 0.09)	41
Zarski, 1994[91] interferon alpha-2b (Intron A, Schering-Plough Corporation), 2 /5 MU 3 times a week Prednisone, decreasing doses of 60, 40, 20 mg for 6 weeks, 24 weeks	Interferon alpha-2b (Intron A, Schering-Plough Corporation), 2/ 5 MU 3 times per week, 24 weeks	Chronic active hepatitis	48/48	18/31 15/25	58/60	0.97 (0.62; 1.50)	-0.02 (-0.28; 0.24)	-52
		Cirrhosis	48/48	3/31 4/25	10/16	0.60 (0.15; 2.46)	-0.06 (-0.24; 0.11)	-16
		Sustained clearance of HBV DNA during therapy + HBeAg seroconversion during or after therapy	48/48	7/31 10/25	23/40	0.56 (0.25; 1.27)	-0.17 (-0.42; 0.07)	-6
		Sustained clearance of HBV DNA during therapy	48/48	4/31 2/25	13/8	1.61 (0.32; 8.10)	0.05 (-0.11; 0.21)	20
		HBsAg loss	48/48	5/31 1/25	16/4	4.03 (0.50; 32.32)	0.12 (-0.03; 0.27)	8
		Transient	48/48	5/31	16/24	0.67 (0.23; 1.95)	-0.08	-13

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		clearance of HBV DNA and HBeAg during therapy but reappearance by the end of the study		6/25			(-0.29; 0.13)	
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1.5 MU three times per week Prednisone, 50mg for 2 weeks, 25 mg for 2 weeks, then 2 week drug free interval, 24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed 5 MU 3 times per week, 24 weeks	Death from hepatorenal syndrome	24/24	0/18 2/19	0/11	0.21 (0.01; 4.11)	-0.11 (-0.27; 0.06)	-9
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 1.5 MU 3 times per week, 24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed 5 MU 3 times per week, 24 weeks	Death from hepatorenal syndrome	48/48	0/19 2/19	0/11	0.20 (0.01; 3.91)	-0.11 (-0.27; 0.06)	-9
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1.5 MU 3 times per week Prednisone, 50mg for 2 weeks, 25 mg for two weeks, then 2 week drug free interval, 24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 1.5 MU 3 times per week, 24 weeks	Loss of HBeAg	24/24	11/18 16/19	61/84	0.73 (0.48; 1.10)	-0.23 (-0.51; 0.05)	-4
	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed	Loss of HBeAg	24/24	11/18 7/19	61/37	1.66 (0.83; 3.32)	0.24 (-0.07; 0.56)	4

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	by 5 MU 3 times per week, 24 weeks							
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), placebo withdrawal followed 1.5 MU 3 times per week, 24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed 5 MU 3 times per week, 24 weeks	Loss of HBeAg	24/24	16/19 7/19	84/37	2.29 (1.23; 4.25)	**0.47 (0.20; 0.75)**	2
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1.5 MU three times per week Prednisone, 50mg for 2 weeks, 25 mg for two weeks, then 2 week drug free interval, 24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 1.5 MU 3 times per week, 24 weeks	Loss of HBeAg	48/48	10/18 12/19	56/63	0.88 (0.51; 1.51)	-0.08 (-0.39; 0.24)	-13
	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 5 MU 3 times per week, 24 weeks	Loss of HBeAg	48/48	10/18 13/19	56/68	0.81 (0.49; 1.36)	-0.13 (-0.44; 0.18)	-8
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 1.5 MU 3 times per week, 24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 5 MU 3 times per week, 24 weeks	Loss of HBeAg	48/48	12/19 13/19	63/68	0.92 (0.58; 1.46)	-0.05 (-0.35; 0.25)	-19
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1.5 MU three	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed	Loss of HBeAg	96/96	5/18 9/19	28/47	0.59 (0.24; 1.42)	-0.20 (-0.50; 0.11)	-5

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
times per week Prednisone, 50mg for 2 weeks, 25 mg for 2 weeks, then 2 week drug free interval, 24 weeks	by 1.5 MU 3 times per week, 24 weeks							
	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 5 MU 3 times per week, 24 weeks	Loss of HBeAg	96/96	5/18 11/19	28/58	0.48 (0.21; 1.11)	-0.30 (-0.60; 0.00)	-3
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 1.5 MU 3 times per week, 24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 5 MU 3 times per week, 24 weeks	Loss of HBeAg	96/96	9/19 11/19	47/58	0.82 (0.44; 1.51)	-0.11 (-0.42; 0.21)	-9
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1.5 MU 3 times per week Prednisone, 50mg for 2 weeks, 25 mg for 2 weeks, then 2 week drug free interval,24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 1.5 MU three times per week, 24 weeks	Loss of HBV DNA	24/24	10/18 11/19	56/58	0.96 (0.55; 1.69)	-0.02 (-0.34; 0.30)	-43
	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 5 MU 3 times per week, 24 weeks	Loss of HBV DNA	24/24	10/18 10/19	56/53	1.06 (0.58; 1.91)	0.03 (-0.29; 0.35)	34
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 1.5 MU 3 times per	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 5 MU 3 times per week, 24 weeks	Loss of HBV DNA	24/24	11/19 10/19	58/53	1.10 (0.62; 1.95)	0.05 (-0.26; 0.37)	19

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
week, 24 weeks								
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1.5 MU 3 times per week Prednisone, 50mg for 2 weeks, 25 mg for 2 weeks, then 2 week drug free interval, 24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 1.5 MU 3 times per week, 24 weeks	Loss of HBV DNA	48/48	10/18 13/19	56/68	0.81 (0.49; 1.36)	-0.13 (-0.44; 0.18)	-8
	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 5 MU 3 times per week, 24 weeks	Loss of HBV DNA	48/48	10/18 11/19	56/58	0.96 (0.55; 1.69)	-0.02 (-0.34; 0.30)	-43
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 1.5 MU 3 times per week, 24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 5 MU 3 times per week, 24 weeks	Loss of HBV DNA	48/48	13/19 11/19	68/58	1.18 (0.72; 1.93)	0.11 (-0.20; 0.41)	9
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1.5 MU 3 times per week Prednisone, 50mg for 2 weeks, 25 mg for two weeks, then 2 week drug free interval, 24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 1.5 MU 3 times per week, 24 weeks	Loss of HBV DNA	96/96	5/18 10/19	28/53	0.53 (0.22; 1.25)	-0.25 (-0.55; 0.06)	-4
	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 5 MU 3 times per week, 24 weeks	Loss of HBV DNA	96/96	5/18 6/19	28/32	0.88 (0.32; 2.38)	-0.04 (-0.33; 0.26)	-26

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 1.5 MU 3 times per week, 24 weeks	Recombinant interferon alpha 2b (Intron), placebo withdrawal followed by 5 MU 3 times per week, 24 weeks	Loss of HBV DNA	96/96	10/19 6/19	53/32	1.67 (0.76; 3.66)	0.21 (-0.10; 0.52)	5
Di Bisceglie, 1993[86] "IFN-a2b (Intron A, Schering-Plough, NJ)", 4 /10 MU 3 times per week, 16 weeks	No treatment, 16 weeks	Normalization of ALT	24/24	9/25 0/22	36/0	16.81 (1.03; 73.08)	**0.36 (0.17; 0.55)**	3
		Discontinuation of therapy due to adverse effects	39794	3/25 0/22	12/0	6.19 (0.34; 113.62)	0.12 (-0.02; 0.26)	8
		Reduction in dose due to adverse effects	39794	16/25 0/22	64/0	29.19 (1.85; 59.85)	**0.64 (0.45; 0.83)**	2
		Fatigue	39794	12/25 0/22	48/0	22.12 (1.39; 53.09)	**0.48 (0.28; 0.68)**	2
		Marrow suppression	39794	2/25 0/22	8/0	4.42 (0.22; 87.44)	0.08 (-0.05; 0.21)	12
		Nausea	39794	3/25 0/22	12/0	6.19 (0.34; 113.62)	0.12 (-0.02; 0.26)	8
		Infections	39794	2/25 0/22	8/0	4.42 (0.22; 87.44)	0.08 (-0.05; 0.21)	12
		Arthralgia	39794	2/25 0/22	8/0	4.42 (0.22; 87.44)	0.08 (-0.05; 0.21)	12
		Jaundice	39794	1/25 0/22	4/0	2.65 (0.11; 62.00)	0.04 (-0.07; 0.15)	25
		Depression	39794	1/25 0/22	4/0	2.65 (0.11; 62.00)	0.04 (-0.07; 0.15)	25
		HBV DNA and HBeAg negative	24/24	11/25 1/22	44/5	9.68 (1.36; 69.09)	**0.39 (0.18; 0.61)**	3
		Loss of HBsAg	24/24	4/25 0/22	16/0	7.96 (0.45; 140.05)	**0.16 (0.00; 0.32)**	6

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		HBV DNA undetectable	24/24	13/25 1/22	52/5	11.44 (1.63; 80.54)	**0.47 (0.26; 0.69)**	2
		Loss of HBeAg	24/24	11/25 1/22	44/5	9.68 (1.36; 69.09)	**0.39 (0.18; 0.61)**	3
Perez, 1993[92] Interferon alfa-2b (INTRON A, Schering-Plough Corporation), 4 /10 MU 3 times weekly Prednisone, pretreatment with 60, 40, 20 mg daily every 2 weeks, followed by 2 week free drug period, 24 weeks	Interferon alfa-2b (INTRON A, Schering-Plough Corporation), 4/ 10 MU 3 times per week, 16 weeks	ALT normalization	48/40	16/26 14/24	62/58	1.05 (0.67; 1.66)	0.03 (-0.24; 0.30)	31
		Reduction in dose because of severe side effects	48/40	2/26 2/24	8/8	0.92 (0.14; 6.05)	-0.01 (-0.16; 0.14)	-156
		HBeAg loss	48/40	16/26 14/24	62/58	1.05 (0.67; 1.66)	0.03 (-0.24; 0.30)	31
		Undetectable HBV DNA	48/40	16/26 14/24	62/58	1.05 (0.67; 1.66)	0.03 (-0.24; 0.30)	31
		HBsAg loss	48/40	14/26 11/24	54/46	1.17 (0.67; 2.06)	0.08 (-0.20; 0.36)	12
		HBeAg seroconversion	48/40	14/26 11/24	54/46	1.17 (0.67; 2.06)	0.08 (-0.20; 0.36)	12
Műller, 1993[105] Interferon alfa-2b, 1/ 3 MU 3 times per week, 16 weeks	No treatment, 16 weeks	Complete response: elimination of HBsAg, HBeAg and HBV-DNA and normal ALT	40/40	1/30 0/28	3/0	2.81 (0.12; 66.17)	0.03 (-0.06; 0.12)	30
		Partial response: elimination of HBeAg and HBV-DNA, while HBsAg persisted, and normal ALT	40/40	8/30 3/28	27/11	2.49 (0.73; 8.45)	0.16 (-0.04; 0.35)	6
		Discontinuation due to psychosis	16/16	1/30 0/28	3/0	2.81 (0.12; 66.17)	0.03 (-0.06; 0.12)	30

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Lopez-Alcorocho, 1997[85] Intron A, Schering-Plough Inc, USA, 6/ 10 MU 3 times per week for 2 months, 5 MU 3 times per week for 2 months and then 3 MU 2 times per week for 2 months, 24 weeks	Intron A, Schering-Plough Inc, USA, 2/ 10 MU 3 times per week for 2 months, 5 MU 3 times per week for 2 months and then 3 MU 3 times per week for 8 months, 48 weeks	ALT normalization	18/18	4/19 2/19	21/11	2.00 (0.41; 9.65)	0.11 (-0.12; 0.33)	9
			24/24	3/19 10/19	16/53	0.30 (0.10; 0.92)	-0.37 (-0.65; -0.09)	-3
			24/48	10/19 5/19	53/26	2.00 (0.84; 4.75)	0.26 (-0.04; 0.56)	4
			72/96	9/19 8/19	47/42	1.13 (0.55; 2.29)	0.05 (-0.26; 0.37)	19
		Abnormal ALT, >45IU/L	72/96	3/19 3/19	16/16	1.00 (0.23; 4.34)	0.00 (-0.23; 0.23)	
		Death not related to IFN therapy	24/48	0/19 1/19	0/5	0.33 (0.01; 7.70)	-0.05 (-0.19; 0.08)	-19
		Loss HBV DNA and ALT normalization	48/72	0/19 4/19	0/21	0.11 (0.01; 1.93)	**-0.21 (-0.41; -0.02)**	-5
		Loss HBV DNA and ALT normalization	72/96	2/19 4/19	11/21	0.50 (0.10; 2.41)	-0.11 (-0.33; 0.12)	-9
		Discontinuation due to neuropsychiatric disorder	24/48	0/19 1/19	0/5	0.33 (0.01; 7.70)	-0.05 (-0.19; 0.08)	-19
		Development of anti IFN antibodies	72/96	0/19 0/19			0.00 (-0.10; 0.10)	
		Loss HBV DNA	24/48	4/19 5/19	21/26	0.80 (0.25; 2.53)	-0.05 (-0.32; 0.22)	-19
			48/72	0/19 6/19	0/32	0.08 (0.00; 1.28)	**-0.32 (-0.53; -0.10)**	-3
			72/96	2/19 5/19	11/26	0.40 (0.09; 1.81)	-0.16 (-0.40; 0.08)	-6
			72/96	2/19 3/19	11/16	0.67 (0.13; 3.55)	-0.05 (-0.27; 0.16)	-19

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lampertico, 1997[84] "IFN-a2b (Intron A, Schering-Plough, Milan, Italy)", 3/ 6 MU 3 times per week, 96 weeks	No treatment, 96 weeks	Flare as rise in ALT levels >> 5 times ULN and/or rise in serum levels of HBV DNA > 100 picograms/mL	96/96	4/21 15/21	19/71	0.27 (0.11; 0.67)	**-0.52 (-0.78; -0.27)**	-2
		Hepatocellular carcinoma	56/56	1/21 0/21	5/0	3.00 (0.13; 69.70)	0.05 (-0.07; 0.17)	21
		Loss of HBV DNA by dot-blot assay and normal ALT	96/96	8/21 2/21	38/10	4.00 (0.96; 16.66)	**0.29 (0.04; 0.53)**	3
			144/144	6/21 0/21	29/0	13.00 (0.78; 17.03)	**0.29 (0.09; 0.49)**	3
		Discontinuation due to adverse effects	96/96	5/21 0/21	24/0	11.00 (0.65; 87.17)	**0.24 (0.05; 0.43)**	4
		Persistent headache	96/96	1/21 0/21	5/0	3.00 (0.13; 69.70)	0.05 (-0.07; 0.17)	21
		Persistent myalgia or arthralgia	96/96	3/21 0/21	14/0	7.00 (0.38; 127.69)	0.14 (-0.02; 0.31)	7
		Moderate psychological depression	96/96	1/21 0/21	5/0	3.00 (0.13; 69.70)	0.05 (-0.07; 0.17)	21
		Histology index score improved: 50 reduction of the total histology activity index	96/96	7/21 2/21	33/10	3.50 (0.82; 14.93)	**0.24 (0.00; 0.48)**	4
		Histology index score remained unchanged	96/96	6/21 7/21	29/33	0.86 (0.35; 2.12)	-0.05 (-0.33; 0.23)	-21
		Histology index score worsened	96/96	0/21 4/21	0/19	0.11 (0.01; 1.94)	**-0.19 (-0.37; -0.01)**	-5

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Loss of HBsAg	96/96	0/21 0/21			0.00 (-0.09; 0.09)	
			144/144	2/21 0/21	10/0	5.00 (0.25; 98.27)	0.10 (-0.05; 0.24)	10
		Loss of HBsAg and/or HBV-DNA	144/144	7/21 0/21	33/0	15.00 (0.91; 46.93)	**0.33 (0.13; 0.54)**	3
		HBsAg seroconversion	144/144	2/21 0/21	10/0	5.00 (0.25; 98.27)	0.10 (-0.05; 0.24)	10
		Relapse-any increase in ALT above ULNand/or detection of serum HBV DNA in the followup period	144/144	2/21 2/21	10/10	1.00 (0.16; 6.45)	0.00 (-0.18; 0.18)	
Mutimer, 1997[80] Intron A, Schering-Plough Inc, USA, 4/ 10 MU 3 times per week Lamivudine, 150mg daily, 16 weeks	Intron A, Schering-Plough Inc, USA + lamivudine, 4 /10 MU 3 times weekly + 4 weeks placebo then 12 weeks lamivudine 100mg/day, 16 weeks	ALT normalization	16/16	11/14 5/6	79/83	0.94 (0.60; 1.48)	-0.05 (-0.42; 0.32)	-21
		Loss of HBV DNA	16/16	14/14 6/6	100/100		0.00 (-0.21; 0.21)	
		HBeAg negativity	16/16	4/14 0/6	29/0	4.20 (0.26; 67.74)	0.29 (-0.01; 0.59)	3
		Sustained loss of HBV DNA	32/32	1/14 0/6	7/0	1.40 (0.06; 30.23)	0.07 (-0.17; 0.32)	14
		HBeAg seroconversion	32/32	4/14 0/6	29/0	4.20 (0.26; 67.74)	0.29 (-0.01; 0.59)	3
Janssen, 1999[83] Recombinant IFN-a (alfa-2b, Intron-A; Schering-Plough, Kenilworth, NJ), 4/ 10 MU 3 times per week, 32 weeks	Discontinuation of treatment of Interferon Alfa 2b (10 MU IFN-a 3 times/week for 16 weeks)	Dose reduction due to depression, fatigue, hair loss, and headache	32/32	7/61 0/57	11/0	14.03 (0.82; 40.23)	**0.11 (0.03; 0.20)**	9
		Discontinuation due to adverse effects	32/32	3/61 0/57	5/0	6.55 (0.35; 124.05)	0.05 (-0.01; 0.11)	20

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Collapse after dizziness	32/32	1/61 0/57	2/0	2.81 (0.12; 67.52)	0.02 (-0.03; 0.06)	61
		Sustained HBeAg and HBV-DNA negativity	52/52	17/61 7/57	28/12	2.27 (1.02; 5.06)	**0.16 (0.01; 0.30)**	6
		Clearance of HBeAg with subsequent HBeAg reappearance	52/52	1/61 2/57	2/4	0.47 (0.04; 5.01)	-0.02 (-0.08; 0.04)	-53
		Lost HBsAg	52/52	3/61 0/57	5/0	6.55 (0.35; 124.05)	0.05 (-0.01; 0.11)	20
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly 8 weeks lamivudine 100 mg/day followed by 16 weeks of lamivudine 100 mg/day and alpha interferon, 24 weeks	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times per week, 24 weeks	ALT normalization <1.0 ULN	24/24	62/75 58/69	83/84	0.98 (0.85; 1.14)	-0.01 (-0.14; 0.11)	-72
			52/52	55/75 55/69	73/80	0.92 (0.77; 1.10)	-0.06 (-0.20; 0.07)	-16
			64/64	50/75 50/69	67/72	0.92 (0.74; 1.14)	-0.06 (-0.21; 0.09)	-17
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	ALT normalization<1.0 ULN	24/24	62/75 72/82	83/88	0.94 (0.83; 1.07)	-0.05 (-0.16; 0.06)	-19
			52/52	55/75 58/82	73/71	1.04 (0.85; 1.26)	0.03 (-0.11; 0.17)	38
			64/64	50/75 63/82	67/77	0.87 (0.71; 1.06)	-0.10 (-0.24; 0.04)	-10

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/ 10 MU 3 times weekly, 8 weeks of oral placebo once daily followed by 16 weeks of placebo once daily and interferon, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	ALT normalization <1.0 ULN	24/24	58/69 72/82	84/88	0.96 (0.84; 1.09)	-0.04 (-0.15; 0.07)	-27
			52/52	55/69 58/82	80/71	1.13 (0.94; 1.35)	0.09 (-0.05; 0.23)	11
			64/64	50/69 63/82	72/77	0.94 (0.78; 1.14)	-0.04 (-0.18; 0.10)	-23
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/ 10 MU 3 times weekly 8 weeks of oral lamivudine 100 mg once daily followed by 16 weeks of lamivudine 100 mg once daily and alpha interferon mg/day, 24 weeks	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU three times per week, 24 weeks	Viral respiratory infections	52/52	32/76 37/70	42/53	0.80 (0.56; 1.12)	-0.11 (-0.27; 0.05)	-9
		Headache	52/52	71/76 47/70	93/67	1.39 (1.17; 1.66)	**0.26 (0.14; 0.39)**	4
		Muscle pain	52/52	36/76 40/70	47/57	0.83 (0.61; 1.13)	-0.10 (-0.26; 0.06)	-10
		Abdominal dis-comfort and pain	52/52	11/76 23/70	14/33	0.44 (0.23; 0.84)	**-0.18 (-0.32; -0.05)**	-5
		Diarrhea	52/52	14/76 16/70	18/23	0.81 (0.43; 1.53)	-0.04 (-0.18; 0.09)	-23
		Malaise and fatigue	52/52	66/76 70/70	87/100	0.87 (0.79; 0.95)	**-0.13 (-0.21; -0.05)**	-8
		Arthralgia	52/52	9/76 23/70	12/33	0.36 (0.18; 0.72)	**-0.21 (-0.34; -0.08)**	-5
		Anorexia	52/52	30/76 33/70	39/47	0.84 (0.58; 1.22)	-0.08 (-0.24; 0.08)	-13
		Dizziness	52/52	9/76 19/70	12/27	0.44 (0.21; 0.90)	**-0.15 (-0.28; -0.03)**	-7
		Nausea and vomiting	52/52	33/76 34/70	43/49	0.89 (0.63; 1.27)	-0.05 (-0.21; 0.11)	-19
		Fever/chills	52/52	46/76 43/70	61/61	0.99 (0.76; 1.28)	-0.01 (-0.17; 0.15)	-111

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Hair loss and alopecia	52/52	30/76 21/70	39/30	1.32 (0.84; 2.07)	0.09 (-0.06; 0.25)	11
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/ 10 MU 3 times weekly lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Viral respiratory infections	52/52	32/76 25/84	42/30	1.41 (0.93; 2.16)	0.12 (-0.02; 0.27)	8
		Headache	52/52	71/76 27/84	93/32	2.91 (2.12; 3.99)	**0.61 (0.50; 0.73)**	2
		Muscle pain	52/52	36/76 11/84	47/13	3.62 (1.99; 6.59)	**0.34 (0.21; 0.48)**	3
		Abdominal discomfort and pain	52/52	11/76 13/84	14/15	0.94 (0.45; 1.96)	-0.01 (-0.12; 0.10)	-100
		Diarrhea	52/52	14/76 13/84	18/15	1.19 (0.60; 2.37)	0.03 (-0.09; 0.15)	34
		Malaise and fatigue	52/52	66/76 35/84	87/42	2.08 (1.59; 2.72)	**0.45 (0.32; 0.58)**	2
		Arthralgia	52/52	9/76 4/84	12/5	2.49 (0.80; 7.75)	0.07 (-0.01; 0.16)	14
		Anorexia	52/52	30/76 4/84	39/5	8.29 (3.06; 22.44)	**0.35 (0.23; 0.47)**	3
		Dizziness	52/52	9/76 8/84	12/10	1.24 (0.51; 3.06)	0.02 (-0.07; 0.12)	43
		Nausea and vomiting	52/52	33/76 19/84	43/23	1.92 (1.20; 3.08)	**0.21 (0.07; 0.35)**	5
		Fever/chills	52/52	46/76 6/84	61/7	8.47 (3.84; 18.71)	**0.53 (0.41; 0.66)**	2
		Hair loss and alopecia	52/52	30/76 8/84	39/10	4.14 (2.03; 8.48)	**0.30 (0.17; 0.43)**	3
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly, 8	Lamivudine, 100 mg/day, 52 weeks	Viral respiratory infections	52/52	37/70 25/84	53/30	1.78 (1.20; 2.64)	**0.23 (0.08; 0.38)**	4
		Headache	52/52	47/70 27/84	67/32	2.09 (1.47; 2.97)	**0.35 (0.20; 0.50)**	3
		Muscle pain	52/52	40/70 11/84	57/13	4.36 (2.43; 7.85)	**0.44 (0.30; 0.58)**	2

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
weeks of oral placebo once daily followed by 16 weeks of placebo once daily and interferon, 24 weeks		Abdominal discomfort and pain	52/52	23/70 13/84	33/15	2.12 (1.16; 3.87)	**0.17 (0.04; 0.31)**	6
		Diarrhea	52/52	16/70 13/84	23/15	1.48 (0.76; 2.86)	0.07 (-0.05; 0.20)	14
		Malaise and fatigue	52/52	70/70 35/84	100/42	2.38 (1.85; 3.06)	**0.58 (0.48; 0.69)**	2
		Arthralgia	52/52	23/70 4/84	33/5	6.90 (2.50; 19.01)	**0.28 (0.16; 0.40)**	4
		Anorexia	52/52	33/70 4/84	47/5	9.90 (3.69; 26.59)	**0.42 (0.30; 0.55)**	2
		Dizziness	52/52	19/70 8/84	27/10	2.85 (1.33; 6.11)	**0.18 (0.05; 0.30)**	6
		Nausea and vomiting	52/52	34/70 19/84	49/23	2.15 (1.35; 3.41)	**0.26 (0.11; 0.41)**	4
		Fever/chills	52/52	43/70 6/84	61/7	8.60 (3.89; 19.01)	**0.54 (0.42; 0.67)**	2
		Hair loss and alopecia	52/52	21/70 8/84	30/10	3.15 (1.49; 6.67)	**0.20 (0.08; 0.33)**	5
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/ 10 MU 3 times weekly 8 weeks of oral lamivudine 100 mg once daily followed by 16 weeks of lamivudine 100 mg once daily and alpha interferon mg/day, 24 weeks	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times per week, 24 weeks	Discontinuation due to adverse effects	24/24	2/76 0/70	3/0	4.61 (0.23; 94.40)	0.03 (-0.02; 0.07)	38

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Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Discontinuation due to adverse effects	24/52	2/76 3/84	3/4	0.74 (0.13; 4.29)	-0.01 (-0.06; 0.04)	-106
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/ 10 MU 3 times weekly, 8 weeks of oral placebo once daily followed by 16 weeks of placebo once daily and interferon, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Discontinuation due to adverse effects	24/52	0/70 3/84	0/4	0.17 (0.01; 3.26)	-0.04 (-0.08; 0.01)	-28
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly 8 weeks of oral lamivudine 100 mg once daily followed by 16 weeks of lamivudine 100 mg once daily and alpha interferon mg/day, 24 weeks	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times per week, 24 weeks	Hepatitis flares (ALT levels >500 IU/l and >2time from baseline)	24/24	0/76 8/70	0/11	0.05 (0.00; 0.92)	**-0.11** **(-0.19; -0.04)**	-9

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Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/ 10 MU 3 times weekly lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Hepatitis flares (ALT levels >500 IU/l and >2 times from baseline)	24/52	0/76 10/84	0/12	0.05 (0.00; 0.88)	**-0.12** **(-0.19; -0.05)**	-8
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly, 8 weeks of oral placebo once daily followed by 16 weeks of placebo once daily and interferon, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Hepatitis flares (ALT levels >500 IU/l and >2 times from baseline)	24/52	8/70 10/84	11/12	0.96 (0.40; 2.30)	0.00 (-0.11; 0.10)	-210
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly lamivudine, 8 weeks of oral lamivudine 100 mg once daily followed by 16 weeks of lamivudine 100 mg once daily and alpha interferon mg/day, 24 weeks	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times per week, 24 weeks	Hepatitis flares (ALT levels >500 IU/l and >2 times from baseline)	52/52	5/76 6/70	7/9	0.77 (0.25; 2.40)	-0.02 (-0.11; 0.07)	-50

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Hepatitis flares (ALT levels >500 IU/l and >2times from baseline)	52/52	5/76 10/84	7/12	0.55 (0.20; 1.54)	-0.05 (-0.14; 0.04)	-19
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly, 8 weeks of oral placebo once daily followed by 16 weeks of placebo once daily and interferon, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Hepatitis flares (ALT levels >500 IU/l and >2 times from baseline)	52/52	6/70 10/84	9/12	0.72 (0.28; 1.88)	-0.03 (-0.13; 0.06)	-30
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly lamivudine, 8 weeks lamivudine 100 mg/day followed by 16 weeks of lamivudine 100 mg/day and alpha interferon, 24 weeks	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times per week, 24 weeks	Histological response (reduction in Knodell score by at least 2 points)	52/52	21/75 25/69	28/36	0.77 (0.48; 1.25)	-0.08 (-0.23; 0.07)	-12

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Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Histological response (reduction in Knodell score by at least 2 points)	52/52	21/75 31/82	28/38	0.74 (0.47; 1.17)	-0.10 (-0.24; 0.05)	-10
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly, 8 weeks of oral placebo once daily followed by 16 weeks of placebo once daily and interferon, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Histological response (reduction in Knodell score by at least 2 points)	52/52	25/69 31/82	36/38	0.96 (0.63; 1.46)	-0.02 (-0.17; 0.14)	-64
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly lamivudine, 8 weeks lamivudine 100 mg/day followed by 16 weeks of lamivudine 100 mg/day and alpha interferon , 24 weeks	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times per week, 24 weeks	Histological relapse (increase in Knodell score by at least 2 points)	52/52	17/75 17/69	23/25	0.92 (0.51; 1.66)	-0.02 (-0.16; 0.12)	-51

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly Lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Histological relapse (increase in Knodell score by at least 2 points)	52/52	17/75 7/82	23/9	2.66 (1.17; 6.04)	**0.14 (0.03; 0.25)**	7
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly, 8 weeks of oral placebo once daily followed by 16 weeks of placebo once daily and interferon, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Histological relapse (increase in Knodell score by at least 2 points)	52/52	17/69 7/82	25/9	2.89 (1.27; 6.55)	**0.16 (0.04; 0.28)**	6
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/ 10 MU 3 times weekly Lamivudine, 8 weeks lamivudine 100 mg/day followed by 16 weeks of lamivudine 100 mg/day and alpha interferon, 24 weeks	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/ 10 MU 3 times per week, 24 weeks	HBeAg seroconversion: loss of HBeAg, development of antibodies to HBeAg, and undetectable HBV DNA	24/24	68/75 64/69	91/93	0.98 (0.89; 1.08)	-0.02 (-0.11; 0.07)	-48

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly Lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	HBeAg seroconversion : loss of HBeAg, development of antibodies to HBeAg, and undetectable HBV DNA	24/24	68/75 80/82	91/98	0.93 (0.86; 1.01)	-0.07 (-0.14; 0.00)	-15
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly, 8 weeks lamivudine 100 mg/day followed by 16 weeks of lamivudine 100 mg/day and alpha interferon, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	HBeAg seroconversion : loss of HBeAg, development of antibodies to HBeAg, and undetectable HBV DNA	24/24	64/69 80/82	93/98	0.95 (0.88; 1.02)	-0.05 (-0.12; 0.02)	-21
	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/ 10 MU 3 times per week, 24 weeks	HBeAg seroconversion: loss of HBeAg, development of antibodies to HBeAg, and undetectable HBV DNA	52/52	68/75 64/69	91/93	0.98 (0.89; 1.08)	-0.02 (-0.11; 0.07)	-48
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU three times weekly Lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	HBeAg seroconversion : loss of HBeAg, development of antibodies to HBeAg, and undetectable HBV DNA.	52/52	68/75 80/82	91/98	0.93 (0.86; 1.01)	-0.07 (-0.14; 0.00)	-15

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Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly, 8 weeks of oral placebo once daily followed by 16 weeks of placebo once daily and interferon, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	HBeAg seroconversion : loss of HBeAg, development of antibodies to HBeAg, and undetectable HBV DNA	52/52	64/69 80/82	93/98	0.95 (0.88; 1.02)	-0.05 (-0.12; 0.02)	-21
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly lamivudine, 8 weeks lamivudine 100 mg/day followed by 16 weeks of lamivudine 100 mg/day and alpha interferon, 24 weeks	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times per week, 24 weeks	HBeAg seroconversion: loss of HBeAg, development of antibodies to HBeAg, and undetectable HBV DNA	64/64	68/75 64/69	91/93	0.98 (0.89; 1.08)	-0.02 (-0.11; 0.07)	-48
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	HBeAg seroconversion : loss of HBeAg, development of antibodies to HBeAg, and undetectable HBV DNA	64/64	68/75 80/82	91/98	0.93 (0.86; 1.01)	-0.07 (-0.14; 0.00)	-15

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly, 8 weeks of oral placebo once daily followed by 16 weeks of placebo once daily and interferon, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	HBeAg seroconversion : loss of HBeAg, development of antibodies to HBeAg, and undetectable HBV DNA	64/64	64/69 80/82	93/98	0.95 (0.88; 1.02)	-0.05 (-0.12; 0.02)	-21
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly lamivudine, 8 weeks lamivudine 100 mg/day followed by 16 weeks of lamivudine 100 mg/day and alpha interferon, 24 weeks	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times per week, 24 weeks	HBeAg loss	24/24	62/75 57/69	83/83	1.00 (0.86; 1.16)	0.00 (-0.12; 0.12)	1725
			52/52	55/75 56/69	73/81	0.90 (0.76; 1.08)	-0.08 (-0.21; 0.06)	-13
			64/64	55/75 48/69	73/70	1.05 (0.86; 1.30)	0.04 (-0.11; 0.19)	27
		HBV DNA loss, <3 pg/ml, Abbott HBV DNA test	24/24	62/75 57/69	83/83	1.00 (0.86; 1.16)	0.00 (-0.12; 0.12)	1725
			52/52	55/75 55/69	73/80	0.92 (0.77; 1.10)	-0.06 (-0.20; 0.07)	-16
			64/64	55/75 49/69	73/71	1.03 (0.84; 1.27)	0.02 (-0.12; 0.17)	43
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4 /10 MU 3 times weekly lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	HBeAg loss	24/24	62/75 70/82	83/85	0.97 (0.84; 1.11)	-0.03 (-0.14; 0.09)	-37
			52/52	55/75 60/82	73/73	1.00 (0.83; 1.21)	0.00 (-0.14; 0.14)	615
			64/64	55/75 62/82	73/76	0.97 (0.81; 1.17)	-0.02 (-0.16; 0.11)	-44
		HBV DNA loss, <3 pg/ml, Abbott HBV DNA test	24/24	62/75 70/82	83/85	0.97 (0.84; 1.11)	-0.03 (-0.14; 0.09)	-37
			52/52	55/75 60/82	73/73	1.00 (0.83; 1.21)	0.00 (-0.14; 0.14)	615

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
			64/64	55/75 63/82	73/77	0.95 (0.80; 1.14)	-0.03 (-0.17; 0.10)	-29
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly, 8 weeks of oral placebo once daily followed by 16 weeks of placebo once daily and interferon, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	HBeAg loss	24/24	57/69 70/82	83/85	0.97 (0.84; 1.11)	-0.03 (-0.15; 0.09)	-36
			52/52	56/69 60/82	81/73	1.11 (0.93; 1.32)	0.08 (-0.05; 0.21)	13
			64/64	48/69 62/82	70/76	0.92 (0.75; 1.12)	-0.06 (-0.20; 0.08)	-17
		HBV DNA loss, <3 pg/ml, Abbott HBV DNA test	24/24	57/69 70/82	83/85	0.97 (0.84; 1.11)	-0.03 (-0.15; 0.09)	-36
			52/52	55/69 60/82	80/73	1.09 (0.91; 1.30)	0.07 (-0.07; 0.20)	15
			64/64	49/69 63/82	71/77	0.92 (0.76; 1.12)	-0.06 (-0.20; 0.08)	-17
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly lamivudine, 8 weeks of oral lamivudine 100 mg once daily followed by 16 weeks of lamivudine 100 mg once daily and alpha interferon, 24 weeks	Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times per week, 24 weeks	Incidence of YMDD	52/52	0/75 0/69			0.00 (-0.03; 0.03)	
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly lamivudine, 100mg/day, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Incidence of YMDD	52/52	0/75 19/82	0/23	0.03 (0.00; 0.46)	**-0.23** **(-0.32; -0.14)**	-4

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Schalm, 2000[67] Alpha interferon (Intron A, Schering Plough, Kenilworth, USA), 4/10 MU 3 times weekly, 8 weeks of oral placebo once daily followed by 16 weeks of placebo once daily and interferon, 24 weeks	Lamivudine, 100 mg/day, 52 weeks	Incidence of YMDD	52/52	0/69 19/82	0/23	0.03 (0.00; 0.49)	**-0.23** **(-0.33; -0.14)**	-4
Barbaro, 2001[66] Recombinant interferon alpha-2b (Intron A, Schering Plough, Kenilworth, NJ, USA), 4/ 9 MU 3 times per week Lamivudine (Glaxo-Wellcome Inc, Research Triangle Park, NC), 100mg/day,24 weeks	Lamivudine (Glaxo-Wellcome Inc, Research Triangle Park, NC), 100 mg/day, 52 weeks	ALT :3.1 to 10 times the baseline value and > 10 times the baseline value, respectively	72/100	15/76 9/75	20/12	1.64 (0.77; 3.53)	0.08 (-0.04; 0.19)	13
		Albumin: 2.0-2.4 g/dl and < 2.0 g/dl	72/100	2/76 2/75	3/3	0.99 (0.14; 6.82)	0.00 (-0.05; 0.05)	-2850
		Amylase: value 3.1 to 10 times the baseline value and >10 times the baseline value	72/100	2/76 1/75	3/1	1.97 (0.18; 21.31)	0.01 (-0.03; 0.06)	77
		Lipase: value 2.6 to 5 times ULNand more >5 times the upper limit of normal	72/100	4/76 2/75	5/3	1.97 (0.37; 10.45)	0.03 (-0.04; 0.09)	39
		Creatine kinase: value 7 to 9.9 times the baseline value and at least 10 times the	72/100	6/76 5/75	8/7	1.18 (0.38; 3.71)	0.01 (-0.07; 0.10)	81

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		baseline value						
		Platelets: value of 20,000–49,000/mm3 and < 20,000/mm3	72/100	2/76 2/75	3/3	0.99 (0.14; 6.82)	0.00 (-0.05; 0.05)	-2850
		ALT levels returned to normal during treatment and remained so during the followup period	72/100	28/76 17/75	37/23	1.63 (0.97; 2.71)	**0.14 (0.00; 0.29)**	7
		Influenza-like symptoms	72/100	47/76 12/75	62/16	3.87 (2.23; 6.68)	**0.46 (0.32; 0.60)**	2
		Malaise or fatigue	72/100	8/76 8/75	11/11	0.99 (0.39; 2.49)	0.00 (-0.10; 0.10)	-713
		Nausea or vomiting	72/100	7/76 5/75	9/7	1.38 (0.46; 4.16)	0.03 (-0.06; 0.11)	39
		Headache	72/100	8/76 7/75	11/9	1.13 (0.43; 2.95)	0.01 (-0.08; 0.11)	84
		Abdominal discomfort	72/100	5/76 4/75	7/5	1.23 (0.34; 4.42)	0.01 (-0.06; 0.09)	80
		Skin rash	72/100	6/76 5/75	8/7	1.18 (0.38; 3.71)	0.01 (-0.07; 0.10)	81
		Diarrhea	72/100	4/76 5/75	5/7	0.79 (0.22; 2.83)	-0.01 (-0.09; 0.06)	-71
		Withdrawal from the study because of side effects	39731	3/76 4/75	4/5	0.74 (0.17; 3.20)	-0.01 (-0.08; 0.05)	-72
		improvement of the inflammation score defined as a reduction of at	24/52	35/76 20/75	46/27	1.73 (1.10; 2.70)	**0.19 (0.04; 0.34)**	5

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		least 2 points in the score as compared to baseline						
		Improvement of fibrosis score defined as a reduction of at least 2 points in the score as compared to baseline	24/52	32/76 18/75	42/24	1.75 (1.08; 2.84)	**0.18 (0.03; 0.33)**	6
		HBeAg seroconversion and undetectable levels of HBV DNA	24/52	27/76 14/75	36/19	1.90 (1.09; 3.34)	**0.17 (0.03; 0.31)**	6
		Undetectable HBV DNA on at least one occasion	24/52	65/76 51/75	85/68	1.26 (1.05; 1.51)	**0.18 (0.04; 0.31)**	6
		Viral breakthrough: HBV DNA initially became negative but reappeared after 16 and 24 weeks of therapy	24/52	3/76 2/75	4/3	1.48 (0.25; 8.61)	0.01 (-0.04; 0.07)	78
		Relapse: detectable levels of HBeAg and HBV DNA within 12 weeks after treatment	39794	2/76 3/75	3/4	0.66 (0.11; 3.83)	-0.01 (-0.07; 0.04)	-73
		HBeAg seroconversion	72/100	25/76 11/75	33/15	2.24 (1.19; 4.23)	**0.18 (0.05; 0.31)**	5

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		and undetectable levels of HBV DNA						
		Undetectable levels of HBsAg	72/100	0/76 0/75			0.00 (-0.03; 0.03)	
		Median reduction in the HBsAg concentrations	72/100	18/76 9/75	24/12	1.97 (0.95; 4.11)	**0.12 (0.00; 0.24)**	9
		Genotypic mutations in the YMDD locus assessed in HBV DNA amplified by polymerase chain reaction	24/52	9/76 11/75	12/15	0.81 (0.36; 1.84)	-0.03 (-0.14; 0.08)	-35
Perrillo, 2002[104] Intron A; Schering-Plough, Kenilworth, NJ, 4/10 MU 3 times per week for 16 weeks Lamivudine, 100mg/day for 8 weeks, then combined with Interferon until week 24, 24 weeks	Intron A; Schering-Plough, Kenilworth, NJ, 8 weeks of oral placebo then Placebo+ interferon 10 MU 3 times weekly for 16 weeks, 24 weeks	HBeAg loss rrespective of HBV-DNA status	52/52	35/135 15/68	26/22	1.18 (0.69; 2.00)	0.04 (-0.08; 0.16)	26
	Lamivudine, 100 mg/day, 52 weeks	HBeAg loss irrespective of HBV-DNA status	52/52	35/135 102/406	26/25	1.03 (0.74; 1.44)	0.01 (-0.08; 0.09)	125
	Placebo, 52 weeks	HBeAg loss irrespective of HBV-DNA status	52/52	35/135 20/196	26/10	2.54 (1.54; 4.20)	**0.16 (0.07; 0.24)**	6
Perrillo, 2002[104] Intron A; Schering-Plough, Kenilworth, NJ, 8 weeks of oral placebo then Placebo+ interferon	Lamivudine, 100 mg/day, 24 weeks	HBeAg loss irrespective of HBV-DNA status	52/52	15/68 102/406	22/25	0.88 (0.54; 1.42)	-0.03 (-0.14; 0.08)	-33
	Placebo, 52 weeks	HBeAg loss irrespective of HBV-DNA status	52/52	15/68 20/196	22/10	2.16 (1.17; 3.98)	**0.12 (0.01; 0.23)**	8

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10 MU 3 times weekly for 16 weeks, 24 weeks								
Perrillo, 2002[104] Intron A; Schering-Plough, Kenilworth, NJ, 4/ 10 MU 3 times weekly for 16 weeks Lamivudine , 100mg/day for 8 weeks, then combined with Interferon until week 24, 24 weeks	Intron A; Schering-Plough, Kenilworth, NJ, 8 weeks of oral placebo then placebo+ interferon 10 MU 3 times weekly for 16 weeks, 24 weeks	HBeAg seroconversionand HBV DNA loss	52/52	27/135 12/68	20/18	1.13 (0.61; 2.09)	0.02 (-0.09; 0.14)	43
	Lamivudine, 100 mg/day, 52 weeks	HBeAg seroconversion and HBV DNA loss	52/52	27/135 66/406	20/16	1.23 (0.82; 1.84)	0.04 (-0.04; 0.11)	27
	Placebo, 0, 52 weeks	HBeAg seroconversion and HBV DNA loss	52/52	27/135 14/196	20/7	2.80 (1.53; 5.14)	**0.13 (0.05; 0.21)**	8
Perrillo, 2002[104] Intron A; Schering-Plough, Kenilworth, NJ, 8 weeks of oral placebo then placebo+ interferon 10 MU 3 times weekly for 16 weeks, 24 weeks	Lamivudine, 100 mg/day, 24 weeks	HBeAg seroconversion and HBV DNA loss	52/52	12/68 66/406	18/16	1.09 (0.62; 1.90)	0.01 (-0.08; 0.11)	72
	Placebo, 52 weeks	HBeAg seroconversion and HBV DNA loss	52/52	12/68 14/196	18/7	2.47 (1.20; 5.08)	**0.11 (0.01; 0.20)**	10
Chung, 2003[82] Recombinant IFN-Alfa 2b (Intron A; Schering-Plough, Kenilworth, NJ, USA), 4 /5 MU/m2 3 times a week for 6 months +	Recombinant IFN-Alfa 2b (Intron A; Schering-Plough, Kenilworth, NJ, USA), 4/ 5 MU/m2 three times per week, 24 weeks	Normalization of ALT	48/24	20/30 28/35	67/80	0.83 (0.62; 1.13)	-0.13 (-0.35; 0.08)	-8
			96/72	14/30 9/35	47/26	1.81 (0.92; 3.58)	0.21 (-0.02; 0.44)	5
		Discontinuation due to adverse effects	48/24	0/30 0/35			0.00 (-0.06; 0.06)	

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prolonged to maintain negative serum HBV-DNA levels for the next 6 months in patients who became HBV-DNA-negative following IFN therapy, 48 weeks		Loss of HBV-DNA	48/24	16/30 18/35	53/51	1.04 (0.65; 1.65)	0.02 (-0.22; 0.26)	53
		Loss of HBeAg	48/24	6/30 12/35	20/34	0.58 (0.25; 1.36)	-0.14 (-0.36; 0.07)	-7
		Appearance of anti-HBe	48/24	8/30 13/35	27/37	0.72 (0.34; 1.49)	-0.10 (-0.33; 0.12)	-10
		Loss of HBV-DNA	96/72	15/30 10/35	50/29	1.75 (0.93; 3.30)	0.21 (-0.02; 0.45)	5
		Loss of HBeAg	96/72	8/30 9/35	27/26	1.04 (0.46; 2.35)	0.01 (-0.20; 0.22)	105
		Appearance of anti-HBe	96/72	8/30 10/35	27/29	0.93 (0.42; 2.06)	-0.02 (-0.24; 0.20)	-53
		Loss of serum HBsAg	96/72	0/30 0/35			0.00 (-0.06; 0.06)	
Schiff, 2003[47] lamivudine 100 mg/day for 8 weeks followed by 16 weeks of IFN a-2b, 4 /10 MU 3 times/wee + continued lamivudine to week 24, 52 weeks	Placebo, 52 weeks	Normal ALT	52/52	11/63 8/56	17/14	1.22 (0.53; 2.82)	0.03 (-0.10; 0.16)	32
	Lamivudine, 100 mg/daily, 52 weeks	Normal ALT	52/52	11/63 51/119	17/43	0.41 (0.23; 0.72)	**-0.25 (-0.38; -0.12)**	-4
	Placebo, 52 weeks	Discontinuation due to adverse effects	52/52	1/63 5/56	2/9	0.18 (0.02; 1.48)	-0.07 (-0.15; 0.01)	-14
	Lamivudine, 100 mg/daily, 52 weeks	Discontinuation due to adverse effects	52/52	1/63 3/119	2/3	0.63 (0.07; 5.93)	-0.01 (-0.05; 0.03)	-107
	Placebo, 52 weeks	Malaise/fatigue	52/52	60/63 18/56	95/32	2.96 (2.02; 4.35)	**0.63 (0.50; 0.76)**	2
		Fever	52/52	60/63 0/56	95/0	107.77 (6.82; 1703.11)	**0.95 (0.89; 1.01)**	1
		Headache	52/52	48/63 13/56	76/23	3.28 (2.00; 5.39)	**0.53 (0.38; 0.68)**	2
		Nausea/vomiting	52/52	37/63 11/56	59/20	2.99 (1.69; 5.28)	**0.39 (0.23; 0.55)**	3
		Hair loss/alopecia	52/52	30/63	48/4	13.33 (3.34; 53.28)	**0.44 (0.31; 0.57)**	2

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
				2/56				
		Muscle pain	52/52	29/63 5/56	46/9	5.16 (2.14; 12.41)	**0.37 (0.23; 0.51)**	3
		Viral respiratory infections	52/52	22/63 0/56	35/0	40.08 (2.49; 645.77)	**0.35 (0.23; 0.47)**	3
		Feeding problems	52/52	19/63 2/56	30/4	8.44 (2.06; 34.65)	**0.27 (0.14; 0.39)**	4
		Depression	52/52	17/63 2/56	27/4	7.56 (1.83; 31.27)	**0.23 (0.11; 0.35)**	4
		Decreased WBCs	52/52	16/63 0/56	25/0	29.39 (1.80; 478.87)	**0.25 (0.14; 0.36)**	4
		Rheumatism	52/52	16/63 2/56	25/4	7.11 (1.71; 29.57)	**0.22 (0.10; 0.34)**	5
		Diarrhea	52/52	13/63 0/56	21/0	24.05 (1.46; 395.45)	**0.21 (0.10; 0.31)**	5
		Abnormal ALT/AST	52/52	10/63 9/56	16/16	0.99 (0.43; 2.25)	0.00 (-0.13; 0.13)	-504
		Pain	52/52	10/63 4/56	16/7	2.22 (0.74; 6.69)	0.09 (-0.03; 0.20)	11
		Musculoskeletal pain	52/52	10/63 2/56	16/4	4.44 (1.02; 19.42)	**0.12 (0.02; 0.23)**	8
		Abnormal enzymes (amylase/CPK)	52/52	8/63 4/56	13/7	1.78 (0.57; 5.59)	0.06 (-0.05; 0.16)	18
	Lamivudine, 100 mg/daily, 52 weeks	Malaise/fatigue	52/52	60/63 32/119	95/27	3.54 (2.62; 4.79)	**0.68 (0.59; 0.78)**	1
		Fever	52/52	60/63 9/119	95/8	12.59 (6.70; 23.66)	**0.88 (0.81; 0.95)**	1
		Headache	52/52	48/63 18/119	76/15	5.04 (3.22; 7.88)	**0.61 (0.49; 0.73)**	2
		Nausea/vomiting	52/52	37/63 20/119	59/17	3.49 (2.23; 5.48)	**0.42 (0.28; 0.56)**	2
		Hair loss/alopecia	52/52	30/63 2/119	48/2	28.33 (7.00; 114.71)	**0.46 (0.33; 0.58)**	2

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Muscle pain	52/52	29/63 22/119	46/18	2.49 (1.57; 3.95)	**0.28 (0.13; 0.42)**	4
		Viral respiratory infections	52/52	22/63 3/119	35/3	13.85 (4.31; 44.50)	**0.32 (0.20; 0.45)**	3
		Feeding problems	52/52	19/63 2/119	30/2	17.94 (4.32; 74.59)	**0.28 (0.17; 0.40)**	4
		Depression	52/52	17/63 5/119	27/4	6.42 (2.49; 16.59)	**0.23 (0.11; 0.34)**	4
		Decreased WBCs	52/52	16/63 1/119	25/1	30.22 (4.10; 222.66)	**0.25 (0.14; 0.35)**	4
		Rheumatism	52/52	16/63 6/119	25/5	5.04 (2.07; 12.23)	**0.20 (0.09; 0.32)**	5
		Diarrhea	52/52	13/63 15/119	21/13	1.64 (0.83; 3.22)	0.08 (-0.04; 0.20)	12
		Abnormal ALT/AST	52/52	10/63 22/119	16/18	0.86 (0.43; 1.70)	-0.03 (-0.14; 0.09)	-38
		Pain	52/52	10/63 1/119	16/1	18.89 (2.47; 144.23)	**0.15 (0.06; 0.24)**	7
		Musculoskeletal pain	52/52	10/63 1/119	16/1	18.89 (2.47; 144.23)	**0.15 (0.06; 0.24)**	7
		Abnormal enzymes (amylase/CPK)	52/52	8/63 19/119	13/16	0.80 (0.37; 1.71)	-0.03 (-0.14; 0.07)	-31
	Placebo, 52 weeks	ALT >2 at baseline and >500U/l	52/52	0/63 4/56	0/7	0.10 (0.01; 1.80)	-0.07 (-0.14; 0.00)	-14
	Lamivudine, 100 mg/daily, 52 weeks	ALT >2 at baseline and >500U/l	52/52	0/63 9/119	0/8	0.10 (0.01; 1.67)	**-0.08 (-0.13; -0.02)**	-13
	Placebo, 52 weeks	ALT >2 at baseline and >500U/l	68/68	1/63 2/56	2/4	0.44 (0.04; 4.77)	-0.02 (-0.08; 0.04)	-50
	Lamivudine, 100 mg/daily, 52 weeks	ALT >2 at baseline and >500U/l	68/68	1/63 3/119	2/3	0.63 (0.07; 5.93)	-0.01 (-0.05; 0.03)	-107
	Placebo, 52 weeks	Histological response:	52/52	20/63 14/56	32/25	1.27 (0.71; 2.27)	0.07 (-0.09; 0.23)	15

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		reduction in HAI score >2						
	Lamivudine, 100 mg/daily, 52 weeks	Histological response: reduction in HAI score >2	52/52	20/63 62/119	32/52	0.61 (0.41; 0.91)	**-0.20 (-0.35; -0.06)**	-5
	Placebo, 52 weeks	Worsening in histology: increase in HAI by >2 scores	52/52	13/63 9/56	21/16	1.28 (0.59; 2.77)	0.05 (-0.09; 0.18)	22
	Lamivudine, 100 mg/daily, 52 weeks	Worsening in histology: increase in HAI by >2 scores	52/52	13/63 8/119	21/7	3.07 (1.34; 7.01)	**0.14 (0.03; 0.25)**	7
	Placebo, 52 weeks	Improved necroinflammatory activity	52/52	21/63 16/56	33/29	1.17 (0.68; 2.01)	0.05 (-0.12; 0.21)	21
	Lamivudine, 100 mg/daily, 52 weeks	Improved necroin-flammatory activity	52/52	21/63 63/119	33/53	0.63 (0.43; 0.93)	**-0.20 (-0.34; -0.05)**	-5
	Placebo, 52 weeks	Worsening of fibrosis	52/52	8/63 3/56	13/5	2.37 (0.66; 8.50)	0.07 (-0.03; 0.17)	14
	Lamivudine, 100 mg/daily, 52 weeks	Worsening of fibrosis	52/52	8/63 4/119	13/3	3.78 (1.18; 12.06)	**0.09 (0.01; 0.18)**	11
	Placebo, 52 weeks	HBeAg loss	52/52	13/63 7/56	21/12	1.65 (0.71; 3.84)	0.08 (-0.05; 0.21)	12
	Lamivudine, 100 mg/daily, 52 weeks	HBeAg loss	52/52	13/63 38/119	21/32	0.65 (0.37; 1.12)	-0.11 (-0.24; 0.02)	-9
	Placebo, 52 weeks	HBeAg loss	68/68	11/63 9/56	17/16	1.09 (0.49; 2.43)	0.01 (-0.12; 0.15)	72
	Lamivudine, 100 mg/daily, 52 weeks	HBeAg loss	68/68	11/63 40/119	17/34	0.52 (0.29; 0.94)	**-0.16 (-0.29; -0.04)**	-6
	Placebo, 52 weeks	HBeAg seroconversion	52/52	7/63 7/56	11/12	0.89 (0.33; 2.38)	-0.01 (-0.13; 0.10)	-72

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

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	Lamivudine, 100 mg/daily, 52 weeks	HBeAg seroconversion	52/52	7/63 19/119	11/16	0.70 (0.31; 1.57)	-0.05 (-0.15; 0.05)	-21
	Placebo, 52 weeks	HBeAg seroconversion	68/68	5/63 7/56	8/12	0.63 (0.21; 1.89)	-0.05 (-0.15; 0.06)	-22
	Lamivudine, 100 mg/daily, 52 weeks	HBeAg seroconversion	68/68	5/63 21/119	8/18	0.45 (0.18; 1.14)	-0.10 (-0.19; 0.00)	-10
	Placebo, 52 weeks	HBV DNA response <3pg/ml	52/52	56/63 23/56	89/41	2.16 (1.56; 3.00)	**0.48 (0.33; 0.63)**	2
	Lamivudine, 100 mg/daily, 52 weeks	HBV DNA response: <3pg/ml	52/52	56/63 102/119	89/86	1.04 (0.93; 1.16)	0.03 (-0.07; 0.13)	32
	Placebo, 52 weeks	Sustained HBV DNA response: no 2 consecutive detectable HBV DNA	52/52	13/63 9/56	21/16	1.28 (0.59; 2.77)	0.05 (-0.09; 0.18)	22
	Lamivudine, 100 mg/daily, 52 weeks	Sustained HBV DNA response: no 2 consecutive detectable HBV DNA	52/52	13/63 60/119	21/50	0.41 (0.24; 0.69)	**-0.30 (-0.43; -0.16)**	-3
	Placebo, 52 weeks	HBV DNA undetectable by PCR (<750 genomes/ml)	24/52	26/63 8/56	41/14	2.89 (1.43; 5.85)	**0.27 (0.12; 0.42)**	4
	Lamivudine, 100 mg/daily, 52 weeks	HBV DNA undetectable by PCR (<750 genomes/ml)	24/52	26/63 34/119	41/29	1.44 (0.96; 2.17)	0.13 (-0.02; 0.27)	8
	Placebo, 52 weeks	HBsAg loss	52/52	4/63 0/56	6/0	8.02 (0.44; 145.66)	**0.06 (0.00; 0.13)**	16
	Lamivudine, 100 mg/daily, 52 weeks	HBsAg loss	52/52	4/63 2/119	6/2	3.78 (0.71; 20.06)	0.05 (-0.02; 0.11)	21

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	Placebo, 52 weeks	HBsAg loss	68/68	3/63 0/56	5/0	6.23 (0.33; 118.12)	0.05 (-0.01; 0.11)	21
	Lamivudine, 100 mg/daily, 52 weeks	HBsAg loss	68/68	3/63 3/119	5/3	1.89 (0.39; 9.09)	0.02 (-0.04; 0.08)	45
	Placebo, 52 weeks	Detectable YMDD-variant virus	52/52	0/63 0/56			0.00 (-0.03; 0.03)	
	Lamivudine, 100 mg/daily, 52 weeks	Detectable YMDD-variant virus	52/52	0/63 52/119	0/44	0.02 (0.00; 0.28)	**-0.44 (-0.53; -0.35)**	-2
Yalcin, 2003[79] IFN-a-2b, 4/10 MU 3 times per week Lamivudine, 100mg daily, 48 weeks	IFN-a-2b, 4/10 MU 3 times per week, 48 weeks	ALT level normalization	26/26	18/33 5/16	55/31	1.75 (0.79; 3.85)	0.23 (-0.05; 0.52)	4
			52/52	28/33 11/16	85/69	1.23 (0.86; 1.77)	0.16 (-0.10; 0.42)	6
			104/104	16/33 3/16	48/19	2.59 (0.88; 7.61)	**0.30 (0.04; 0.55)**	3
		Sudden flares - intermittent elevations of ALT to 110 times >ULN and >2 from baseline value	48/48	0/33 1/16	0/6	0.17 (0.01; 3.88)	-0.06 (-0.20; 0.08)	-16
		Reversion of HBeAg, detection of HBV DNA in serum by PCR, or as an increase in serum ALT level to greater than the ULN (35 IU/L)	44/44	3/33 1/16	9/6	1.45 (0.16; 12.91)	0.03 (-0.13; 0.18)	35
		Mouth dryness	48/48	25/33 3/16	76/19	4.04 (1.43; 11.41)	**0.57 (0.33; 0.81)**	2

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		Histological response as improved Knodell HAI score	48/48	26/33 4/16	79/25	3.15 (1.32; 7.50)	**0.54 (0.28; 0.79)**	2
		HBeAg seroconversion	26/26	18/33 5/16	55/31	1.75 (0.79; 3.85)	0.23 (-0.05; 0.52)	4
			52/52	22/33 7/16	67/44	1.52 (0.83; 2.79)	0.23 (-0.06; 0.52)	4
			104/104	18/33 3/16	55/19	2.91 (1.00; 8.45)	**0.36 (0.10; 0.61)**	3
		HBV DNA undetectable	26/26	32/33 6/16	97/38	2.59 (1.37; 4.88)	**0.59 (0.35; 0.84)**	2
			52/52	33/33 9/16	100/56	1.76 (1.15; 2.70)	**0.44 (0.20; 0.68)**	2
			104/104	15/33 3/16	45/19	2.42 (0.82; 7.18)	**0.27 (0.01; 0.52)**	4
		HBsAg sero-conversion and loss of HBV DNA	28/28	2/33 0/16	6/0	2.50 (0.13; 49.22)	0.06 (-0.06; 0.18)	16
Akarca, 2004[64] Interferon Alfa, 4 /10 MU three times per week for 24 weeks Lamivudine, 150mg daily, 96 weeks	Lamivudine, 150 mg/day, 96 weeks	Re-elevation of ALT	96/96	2/40 5/40	5/12	0.40 (0.08; 1.94)	-0.08 (-0.20; 0.05)	-13
		Flare as elevation in ALT >10 to normal level	96/96	3/40 1/40	8/2	3.00 (0.33; 27.63)	0.05 (-0.04; 0.14)	20
		HBV DNA negativity and ALT normalization	96/96	32/40 34/40	80/85	0.94 (0.77; 1.15)	-0.05 (-0.22; 0.12)	-20
		Reappearance of HBV DNA and increase in ALT	96/96	1/40 3/40	2/8	0.33 (0.04; 3.07)	-0.05 (-0.14; 0.04)	-20
		Dose reduction due to adverse effects	96/96	4/40 0/40	10/0	9.00 (0.50; 161.86)	**0.10 (0.00; 0.20)**	10

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Thrombocytopenia	96/96	11/40 3/40	28/8	3.67 (1.11; 12.16)	**0.20 (0.04; 0.36)**	5
		Undetectable HBV DNA	24/24	34/40 37/40	85/92	0.92 (0.79; 1.08)	-0.08 (-0.21; 0.06)	-13
		Undetectable HBV DNA	96/96	39/40 36/40	98/90	1.08 (0.97; 1.21)	0.08 (-0.03; 0.18)	13
		HBs Ag negative	96/96	0/40 0/40			0.00 (-0.05; 0.05)	
Jang, 2004[65] Interferon -a 2b, 2/ 5 MU 3 times weekly, monotherapy for at least 4 months then combined therapy Lamivudine, 100mg/day, 176 weeks	Lamivudine, 100 mg/daily after Interferon therapy for at least 4 months, 174 weeks	ALT normalization	200/198	37/41 41/42	90/97	0.92 (0.83; 1.03)	-0.07 (-0.18; 0.03)	-14
			224/222	41/41 42/42	100/100		0.00 (-0.05; 0.05)	
			272/270	41/41 42/42	100/100		0.00 (-0.05; 0.05)	
		Discontinuation due to adverse effects	368/366	3/41 0/42	7/0	7.17 (0.38; 134.55)	0.07 (-0.02; 0.16)	14
		Severe myalgia	368/366	2/41 0/42	5/0	5.12 (0.25; 103.48)	0.05 (-0.03; 0.13)	20
		Depression	368/366	1/41 0/42	2/0	3.07 (0.13; 73.29)	0.02 (-0.04; 0.09)	41
		Undetectable serum HBV-DNA	200/198	40/41 42/42	97/100	0.98 (0.91; 1.04)	-0.02 (-0.09; 0.04)	-41
			224/222	41/41 42/42	100/100		0.00 (-0.05; 0.05)	
			272/270	41/41 42/42	100/100		0.00 (-0.05; 0.05)	
		HBeAg loss	200/198	9/41 9/42	22/21	1.02 (0.45; 2.32)	0.01 (-0.17; 0.18)	191
			224/222	19/41 12/42	46/29	1.62 (0.91; 2.90)	0.18 (-0.03; 0.38)	6
			272/270	25/41 17/42	61/41	1.51 (0.97; 2.34)	0.20 (-0.01; 0.42)	5

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

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			320/318	27/41 18/42	67/44	1.54 (1.02; 2.32)	**0.23 (0.02; 0.44)**	4
		Viral breakthrough as the reappearance of serum HBV-DNA by solution hybridization assay in at least 2 consecutive tests during lamivudine therapy following the disappearance of the serum HBV DNA	200/198	2/41 2/42	5/5	1.02 (0.15; 6.93)	0.00 (-0.09; 0.09)	861
			224/222	2/41 4/42	5/10	0.51 (0.10; 2.65)	-0.05 (-0.16; 0.06)	-22
			272/270	8/41 23/42	20/55	0.36 (0.18; 0.70)	-**0.35** **(-0.55; -0.16)**	-3
			320/318	12/41 24/42	30/58	0.51 (0.30; 0.88)	**-0.28** **(-0.48; -0.07)**	-4
			368/366	1/41 3/42	2/7	0.34 (0.04; 3.15)	-0.05 (-0.14; 0.04)	-21
Economou, 2005[63] IFN-α-2b (Shering-Plough, Athens, Greece), 2/ 5 MU 3 times per week lamivudine (GSK, Athens, Greece), 100mg/day, 96 weeks	Lamivudine (GSK, Athens, Greece), 100 mg/day, 96 weeks	Normalization of ALT	24/24	14/24 12/26	58/46	1.26 (0.74; 2.16)	0.12 (-0.15; 0.40)	8
			48/48	18/24 21/26	75/81	0.93 (0.69; 1.25)	-0.06 (-0.29; 0.17)	-17
			72/72	19/24 19/26	79/73	1.08 (0.79; 1.48)	0.06 (-0.17; 0.30)	16
			96/96	19/24 16/26	79/62	1.29 (0.89; 1.86)	0.18 (-0.07; 0.42)	6
			120/120	6/24 5/26	25/19	1.30 (0.46; 3.71)	0.06 (-0.17; 0.29)	17
		Increase of ALT or AST levels to greater than 1.5 times the upper normal limit after an initial bio-chemical response	96/96	2/24 5/26	8/19	0.43 (0.09; 2.03)	-0.11 (-0.30; 0.08)	-9
		ALT >10 times the upper normal limit	96/96	0/24 2/26	0/8	0.22 (0.01; 4.28)	-0.08 (-0.20; 0.05)	-13

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		Discontinuation due to adverse effects	39731	3/24 0/26	12/0	7.56 (0.41; 139.17)	0.13 (-0.02; 0.27)	8
		Sustained virological response (undetectable serum HBV DNA concentrations)	120/120	5/24 3/26	21/12	1.81 (0.48; 6.76)	0.09 (-0.11; 0.30)	11
		HBsAg clearance	120/120	0/24 0/26			0.00 (-0.07; 0.07)	
		HBV DNA below detection	24/24	21/24 19/26	88/73	1.20 (0.91; 1.58)	0.14 (-0.07; 0.36)	7
			48/48	21/24 20/26	88/77	1.14 (0.88; 1.47)	0.11 (-0.10; 0.31)	9
			72/72	20/24 17/26	83/65	1.27 (0.91; 1.78)	0.18 (-0.06; 0.42)	6
			96/96	18/24 13/26	75/50	1.50 (0.96; 2.35)	0.25 (-0.01; 0.51)	4
		Virologic breakthrough - the reappearance of detectable serum HBV DNA by PCR after an initial virologic response	96/96	3/24 11/26	12/42	0.30 (0.09; 0.93)	**-0.30 (-0.53; -0.07)**	-3
		YMDD mutations	96/96	2/24 12/26	8/46	0.18 (0.04; 0.73)	**-0.38 (-0.60; -0.16)**	-3
Sarin, 2005[69] IFN-α, 5 MU daily 16 weeks added after the first 8 weeks	Lamivudine , 100 mg/day, 52 weeks	Normal ALT	52/52	18/38 15/37	47/41	1.17 (0.70; 1.95)	0.07 (-0.16; 0.29)	15
			76/76	15/38 5/37	39/14	2.92 (1.18; 7.22)	**0.26 (0.07; 0.45)**	4

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lamivudine , 100mg/day, 52 weeks		>10 times rise in ALT	76/76	2/38 0/37	5/0	4.87 (0.24; 98.18)	0.05 (-0.03; 0.14)	19
		Withdrawal due to side effects	39731	2/38 0/37	5/0	4.87 (0.24; 98.18)	0.05 (-0.03; 0.14)	19
		Influenza-like symptoms	76/76	26/38 7/37	68/19	3.62 (1.79; 7.29)	0**.50 (0.30; 0.69)**	2
		Malaise or fatigue	76/76	4/38 5/37	11/14	0.78 (0.23; 2.68)	-0.03 (-0.18; 0.12)	-33
		Nausea or vomiting	76/76	3/38 2/37	8/5	1.46 (0.26; 8.25)	0.02 (-0.09; 0.14)	40
		Headache	76/76	5/38 4/37	13/11	1.22 (0.35; 4.18)	0.02 (-0.12; 0.17)	43
		Abdominal discomfort	76/76	4/38 3/37	11/8	1.30 (0.31; 5.41)	0.02 (-0.11; 0.16)	41
		Diarrhea	76/76	4/38 3/37	11/8	1.30 (0.31; 5.41)	0.02 (-0.11; 0.16)	41
		Reduction of at least 2 points in the HAI score	52/52	14/38 12/37	37/32	1.14 (0.61; 2.12)	0.04 (-0.17; 0.26)	23
		increase of at least 2 points in the HAI score	52/52	2/38 2/37	5/5	0.97 (0.14; 6.56)	0.00 (-0.10; 0.10)	-703
		HBeAg loss	52/52	15/38 14/37	39/38	1.04 (0.59; 1.85)	0.02 (-0.20; 0.24)	61
		Undetectable HBV DNA	52/52	16/38 13/37	42/35	1.20 (0.67; 2.13)	0.07 (-0.15; 0.29)	14
		HBeAg seroconversion	52/52	10/38 5/37	26/14	1.95 (0.74; 5.15)	0.13 (-0.05; 0.31)	8
		HBeAg loss, loss of detectable HBV DNA, and seroconversion to anti-HBe	52/52	10/38 5/37	26/14	1.95 (0.74; 5.15)	0.13 (-0.05; 0.31)	8
			76/76	9/38 1/37	24/3	8.76 (1.17; 65.78)	**0.21 (0.06; 0.35)**	5

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Relapse	76/76	1/38 4/37	3/11	0.24 (0.03; 2.08)	-0.08 (-0.19; 0.03)	-12
		HBeAg loss	76/76	17/38 7/37	45/19	2.36 (1.11; 5.03)	**0.26 (0.06; 0.46)**	4
		Undetectable HBV DNA	76/76	15/38 6/37	39/16	2.43 (1.06; 5.59)	**0.23 (0.04; 0.43)**	4
		HBeAg loss, loss of detectable HBV DNA, and sero-conversion to anti-HBe	76/76	14/38 4/37	37/11	3.41 (1.24; 9.40)	**0.26 (0.08; 0.44)**	4
		YM552I/VDD-resistant mutants	52/52	6/38 3/37	16/8	1.95 (0.53; 7.22)	0.08 (-0.07; 0.22)	13
Shi, 2006[62] Lamivudine (Glaxo Wellcome, Suzhou, China), 100mg/day for 20 weeks, then combined with interferon-alfa-2b (Schering-Plough, Shanghai, China), 2/ 5 MU 3 times per week for 4 weeks and then treated for another 24 weeks with interferon-alpha-2b alone	Lamivudine (Glaxo Wellcome, Suzhou, China), 100 mg/day, 48 weeks	Normalization of ALT	24/24	28/64 72/98	44/73	0.60 (0.44; 0.81)	**-0.30 (-0.45; -0.15)**	-3
			48/48	38/64 54/98	59/55	1.08 (0.82; 1.41)	0.04 (-0.11; 0.20)	23
			72/72	34/64 36/98	53/37	1.45 (1.02; 2.05)	**0.16 (0.01; 0.32)**	6
		Serious adverse events including pyrexia, fatigue, myalgia and headache	48/48	6/64 0/98	9/0	19.80 (1.13; 345.52)	**0.09 (0.02; 0.17)**	11
		HBV DNA <1000 copies/mL	24/24	52/64 76/98	81/78	1.05 (0.89; 1.23)	0.04 (-0.09; 0.16)	27
			48/48	36/64 54/98	56/55	1.02 (0.77; 1.35)	0.01 (-0.14; 0.17)	87
			72/72	9/64 18/98	14/18	0.77 (0.37; 1.60)	-0.04 (-0.16; 0.07)	-23
		HBsAg loss or seroconversion	72/72	0/64 0/98			0.00 (-0.03; 0.03)	
		YMDD mutants	24/24	2/64	3/6	0.51 (0.11; 2.45)	-0.03 (-0.09; 0.03)	-33

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
				6/98				
			48/48	0/64 22/98	0/22	0.03 (0.00; 0.55)	**-0.22 (-0.31; -0.14)**	-4
		YMDD mutants, YIDD variant	24/24	2/64 4/98	3/4	0.77 (0.14; 4.06)	-0.01 (-0.07; 0.05)	-105
		YMDD mutants, YVDD variants	24/24	0/64 2/98	0/2	0.30 (0.01; 6.24)	-0.02 (-0.06; 0.02)	-49
		YMDD mutants, YIDD variant	48/48	0/64 12/98	0/12	0.06 (0.00; 1.01)	**-0.12 (-0.19; -0.05)**	-8
		YMDD mutants, YVDD variants	48/48	0/64 8/98	0/8	0.09 (0.01; 1.53)	**-0.08 (-0.14; -0.02)**	-12
		YMDD mutants, YVDD+YIDD variants	48/48	0/64 2/98	0/2	0.30 (0.01; 6.24)	-0.02 (-0.06; 0.02)	-49
Scotto, 2006[68] Alpha-interferon, 3/6 MU 3 times weekly Lamivudine, 100mg/day, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Response: normal ALT (<40U/L) and undetectable HBV DNA (<5pg/ml)	39794	14/20 13/21	70/62	1.13 (0.73; 1.76)	0.08 (-0.21; 0.37)	12
	Lamivudine, 100 mg/day, pre-treatment with lamivudine for 12 weeks, then combined therapy with Interferon, 52 weeks	Response: normal ALT (<40U/L) and undetectable HBV DNA (<5pg/ml)	39794	14/20 13/18	70/72	0.97 (0.65; 1.45)	-0.02 (-0.31; 0.27)	-45
Scotto, 2006[68] Pre-treatment with lamivudine for 12 weeks, lamivudine 100 mg/day plus alpha-interferon 6 MU three times weekly,	Lamivudine, 100 mg/day, 52 weeks	Response: normal ALT (<40U/L) and undetectable HBV DNA (<5pg/ml)	39794	13/18 13/21	72/62	1.17 (0.75; 1.81)	0.10 (-0.19; 0.40)	10

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
52 weeks								
Scotto, 2006[68] Alpha-interferon, 3 /6 MU 3 times weekly Lamivudine, 100mg/day, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Response: normal ALT (<40U/L) and undetectable HBV DNA (<5pg/ml)	52/52	14/20 13/21	70/62	1.13 (0.73; 1.76)	0.08 (-0.21; 0.37)	12
	Lamivudine, 100 mg/day, pre-treatment with lamivudine for 12 weeks, then combined therapy with Interferon, 52 weeks	Response: normal ALT (<40U/L) and undetectable HBV DNA (<5pg/ml)	52/52	14/20 13/18	70/72	0.97 (0.65; 1.45)	-0.02 (-0.31; 0.27)	-45
Scotto, 2006[68] Pre-treatment with lamivudine for 12 weeks, lamivudine 100 mg/day plus alpha-interferon 6 MU three times weekly, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Response: normal ALT (<40U/L) and undetectable HBV DNA (<5pg/ml)	52/52	13/18 13/21	72/62	1.17 (0.75; 1.81)	0.10 (-0.19; 0.40)	10
Scotto, 2006[68] Alpha-interferon, 3/ 6 MU 3 times weekly Lamivudine, 100mg/day, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Response: normal ALT (<40U/L) and undetectable HBV DNA (<5pg/ml)	104/104	7/20 7/21	35/33	1.05 (0.45; 2.46)	0.02 (-0.27; 0.31)	60
	Lamivudine, 100 mg/day, pre-treatment with lamivudine for 12 weeks, then combined therapy with Interferon, 52 weeks	Response: normal ALT (<40U/L) and undetectable HBV DNA (<5pg/ml)	104/104	7/20 6/18	35/33	1.05 (0.43; 2.54)	0.02 (-0.29; 0.32)	60

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Scotto, 2006[68] Pre-treatment with lamivudine for 12 weeks, lamivudine 100 mg/day plus alpha-interferon 6 MU three times weekly, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Response: normal ALT (<40U/L) and undetectable HBV DNA (<5pg/ml)	104/104	6/18 7/21	33/33	1.00 (0.41; 2.44)	0.00 (-0.30; 0.30)	
Scotto, 2006[68] Alpha-interferon, 3/ 6 MU 3 times weekly Lamivudine, 100mg/day, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Discontinuation due to adverse effects	52/52	2/20 3/21	10/14	0.70 (0.13; 3.76)	-0.04 (-0.24; 0.16)	-23
	Lamivudine, 100 mg/day, pre-treatment with lamivudine for 12 weeks, then combined therapy with Interferon, 52 weeks	Discontinuation due to adverse effects	52/52	2/20 2/18	10/11	0.90 (0.14; 5.74)	-0.01 (-0.21; 0.18)	-90
Scotto, 2006[68] Pre-treatment with lamivudine for 12 weeks, lamivudine 100 mg/day plus alpha-interferon 6 MU three times weekly, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Discontinuation due to adverse effects	52/52	2/18 3/21	11/14	0.78 (0.15; 4.15)	-0.03 (-0.24; 0.18)	-32
Scotto, 2006[68] Alpha-interferon, 3/ 6 MU 3 times weekly Lamivudine, 100mg/day, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Reduction in HAI score >2 points below baseline	52/52	6/20 5/21	30/24	1.26 (0.46; 3.48)	0.06 (-0.21; 0.33)	16
	Lamivudine, 100 mg/day, pre-treatment with lamivudine for 12	Reduction in HAI score >2 points below baseline	52/52	6/20 5/18	30/28	1.08 (0.40; 2.94)	0.02 (-0.27; 0.31)	45

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	weeks, then combined therapy with Interferon, 52 weeks							
Scotto, 2006[68] Pre-treatment with lamivudine for 12 weeks, lamivudine 100 mg/day plus alpha-interferon 6 MU three times weekly, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Reduction in HAI score >2 points below baseline	52/52	5/18 5/21	28/24	1.17 (0.40; 3.39)	0.04 (-0.24; 0.32)	25
Scotto, 2006[68] Alpha-interferon, 3 /6 MU 3 times weekly Lamivudine, 100mg/day, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Unchanged HAI score	52/52	11/20 13/21	55/62	0.89 (0.53; 1.49)	-0.07 (-0.37; 0.23)	-14
	Lamivudine, 100 mg/day, pre-treatment with lamivudine for 12 weeks, then combined therapy with Interferon, 52 weeks	Unchanged HAI score	52/52	11/20 11/18	55/61	0.90 (0.52; 1.55)	-0.06 (-0.37; 0.25)	-16
Scotto, 2006[68] Pre-treatment with lamivudine for 12 weeks, lamivudine 100 mg/day plus alpha-interferon 6 MU three times weekly, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Unchanged HAI score	52/52	11/18 13/21	61/62	0.99 (0.60; 1.62)	-0.01 (-0.31; 0.30)	-126
Scotto, 2006[68] Alpha-interferon, 3/ 6 MU 3 times weekly Lamivudine,	Lamivudine, 100 mg/day, 52 weeks	Worsening in HAI score	52/52	3/20 3/21	15/14	1.05 (0.24; 4.61)	0.01 (-0.21; 0.22)	140
	Lamivudine, 100 mg/day, pre-	Worsening in HAI score	52/52	3/20 2/18	15/11	1.35 (0.25; 7.19)	0.04 (-0.17; 0.25)	26

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
100mg/day, 52 weeks	treatment with lamivudine for 12 weeks, then combined therapy with Interferon, 52 weeks							
Scotto, 2006[68] Pre-treatment with lamivudine for 12 weeks, lamivudine 100 mg/day plus alpha-interferon 6 MU three times weekly, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Worsening in HAI score	52/52	2/18 3/21	11/14	0.78 (0.15; 4.15)	-0.03 (-0.24; 0.18)	-32
Scotto, 2006[68] Alpha-interferon, 3 /6 MU 3 times weekly Lamivudine, 100mg/day, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Undetectable HBV DNA (<6pg/ml)	52/52	14/20 14/21	70/67	1.05 (0.69; 1.59)	0.03 (-0.25; 0.32)	30
	Lamivudine, 100 mg/day, pre-treatment with lamivudine for 12 weeks, then combined therapy with Interferon, 52 weeks	Undetectable HBV DNA (<6pg/ml)	52/52	14/20 13/18	70/72	0.97 (0.65; 1.45)	-0.02 (-0.31; 0.27)	-45

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Scotto, 2006[68] Pre-treatment with lamivudine for 12 weeks, lamivudine 100 mg/day plus alpha-interferon 6 MU three times weekly, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Undetectable HBV DNA (<6pg/ml)	52/52	13/18 14/21	72/67	1.08 (0.71; 1.64)	0.06 (-0.23; 0.34)	18
Lu, 2007[61] Interferon alpha 2b, 2/ 5 MU 3 times per week after first 8 months of Lamivudine monotherapy Lamivudine, 100mg/day during the first 8 months, then combination with Interferon, 48 weeks	Interferon alpha 2b, 1 /5 MU 3 times per week, 48 weeks	HBV DNA level ≤1 × 103 and normalization of serum ALT	48/48	0/24 0/12				
	Lamivudine, 100 mg/day, 48 weeks	HBV DNA level ≤1 × 103 and normalization of serum ALT	48/48	0/24 0/35				
Akyuz, 2007[60] Interferon Alfa 2b, 4/ 10 MU 3 times per week for 24 weeks Lamivudine, 100mg/day, 96 weeks	Lamivudine, 100 mg/day, 96 weeks	Undetected HBV DNA and normal-ization of ALT	96/96	11/21 16/24	52/67	0.79 (0.48; 1.29)	-0.14 (-0.43; 0.14)	-7
		Undetected HBV DNA and normal-ization of ALT	120/120	4/21 7/24	19/29	0.65 (0.22; 1.92)	-0.10 (-0.35; 0.15)	-10
		Reappearance of HBV DNA and elevation of ALT (>1.5 times normal level)	96/96	4/21 6/24	19/25	0.76 (0.25; 2.34)	-0.06 (-0.30; 0.18)	-17
		Discontinuation due to adverse events	96/96	3/21 0/24	14/0	7.95 (0.43; 145.62)	0.14 (-0.02; 0.31)	7
		YMDD mutations	96/96	10/21 13/24	48/54	0.88 (0.49; 1.57)	-0.07 (-0.36; 0.23)	-15

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Cooksley, 2003[116] PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 13 /90 mg weekly, 24 weeks	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 26/ 180 mg weekly, 24 weeks	Normalization of ALT	48/48	21/49 16/46	43/35	1.23 (0.74; 2.05)	0.08 (-0.11; 0.28)	12
	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 39/ 270 mg weekly, 24 weeks	Normalization of ALT	48/48	21/49 15/48	43/31	1.37 (0.81; 2.33)	0.12 (-0.07; 0.31)	9
Cooksley, 2003[116] PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 26 /180 mg weekly, 24 weeks	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 39/ 270 mg weekly, 24 weeks	Normalization of ALT	48/48	16/46 15/48	35/31	1.11 (0.63; 1.98)	0.04 (-0.15; 0.23)	28
Cooksley, 2003[116] PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 13 /90 mg weekly, 24 weeks	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 26 /180 mg weekly, 24 weeks	HBeAg loss, HBV DNA suppression, and ALT normalization	48/48	13/49 13/46	27/28	0.94 (0.49; 1.81)	**-0.02 (-0.20; 0.16)**	-58
	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 39/ 270 mg weekly, 24 weeks	HBeAg loss, HBV DNA suppression, and ALT normalization	48/48	13/49 9/48	27/19	1.41 (0.67; 3.00)	0.08 (-0.09; 0.24)	13
Cooksley, 2003[116] PEGASYS, F. Hoffmann-La Roche	PEGASYS, F. Hoffmann-La Roche Ltd., Basel,	HBeAg loss, HBV DNA suppression, and ALT	48/48	13/46 9/48	28/19	1.51 (0.71; 3.18)	0.10 (-0.08; 0.27)	11

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Ltd., Basel, Switzerland 40 kDa, 26 180 mg weekly, 24 weeks	Switzerland, 40 kDa, 39/ 270 mg weekly, 24 weeks	normalization						
Cooksley, 2003[116] PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 13 /90 mg weekly, 24 weeks	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 26 /180 mg weekly, 24 weeks	Pyrexia	48/48	25/49 27/46	52/58	0.87 (0.60; 1.25)	-0.08 (-0.28; 0.12)	-13
		Myalgia	48/48	19/49 17/46	38/36	1.05 (0.63; 1.76)	0.02 (-0.18; 0.21)	55
		Fatigue	48/48	14/49 10/46	29/22	1.31 (0.65; 2.66)	0.07 (-0.11; 0.24)	15
		Headache	48/48	23/49 17/46	46/38	1.27 (0.79; 2.05)	0.10 (-0.10; 0.30)	10
		Alopecia	48/48	8/49 15/46	17/33	0.50 (0.23; 1.07)	-0.16 (-0.33; 0.01)	-6
		Anorexia	48/48	4/49 8/46	8/18	0.47 (0.15; 1.45)	-0.09 (-0.23; 0.04)	-11
		Insomnia	48/48	8/49 9/46	17/20	0.83 (0.35; 1.98)	-0.03 (-0.19; 0.12)	-31
		Dizziness	48/48	9/49 7/46	19/16	1.21 (0.49; 2.97)	0.03 (-0.12; 0.18)	32
		Diarrhea	48/48	4/49 8/46	8/18	0.47 (0.15; 1.45)	-0.09 (-0.23; 0.04)	-11
		Nausea	48/48	5/49 8/46	10/18	0.59 (0.21; 1.66)	-0.07 (-0.21; 0.07)	-14
		Upper respiratory infection	48/48	11/49 6/46	23/13	1.72 (0.69; 4.27)	0.09 (-0.06; 0.25)	11
		Cough	48/48	7/49 3/46	15/7	2.19 (0.60; 7.97)	0.08 (-0.04; 0.20)	13
	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 39/ 270 mg weekly, 24 weeks	Pyrexia	48/48	25/49 34/48	52/71	0.72 (0.52; 1.00)	**-0.20 (-0.39; -0.01)**	-5
		Myalgia	48/48	19/49 22/48	38/46	0.85 (0.53; 1.35)	-0.07 (-0.27; 0.13)	-14
		Fatigue	48/48	14/49 13/48	29/27	1.05 (0.56; 2.00)	0.01 (-0.16; 0.19)	67

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Headache	48/48	23/49 22/48	46/46	1.02 (0.67; 1.57)	0.01 (-0.19; 0.21)	90
		Alopecia	48/48	8/49 21/48	17/44	0.37 (0.18; 0.76)	**-0.27 (-0.45; -0.10)**	-4
		Anorexia	48/48	4/49 9/48	8/19	0.44 (0.14; 1.32)	-0.11 (-0.24; 0.03)	-9
		Insomnia	48/48	8/49 5/48	17/10	1.57 (0.55; 4.45)	0.06 (-0.08; 0.19)	17
		Dizziness	48/48	9/49 7/48	19/15	1.26 (0.51; 3.11)	0.04 (-0.11; 0.19)	26
		Diarrhea	48/48	4/49 8/48	8/17	0.49 (0.16; 1.52)	-0.09 (-0.22; 0.05)	-12
		Nausea	48/48	5/49 7/48	10/15	0.70 (0.24; 2.05)	-0.04 (-0.17; 0.09)	-23
		Upper respiratory infection	48/48	11/49 4/48	23/8	2.69 (0.92; 7.88)	**0.14 (0.00; 0.28)**	7
		Cough	48/48	7/49 4/48	15/8	1.71 (0.54; 5.48)	0.06 (-0.07; 0.18)	17
Cooksley, 2003[116] PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 26 /180 mg weekly, 24 weeks	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 39 /270 mg weekly, 24 weeks	Pyrexia	48/48	27/46 34/48	58/71	0.83 (0.61; 1.12)	-0.12 (-0.31; 0.07)	-8
		Myalgia	48/48	17/46 22/48	36/46	0.81 (0.50; 1.31)	-0.09 (-0.29; 0.11)	-11
		Fatigue	48/48	10/46 13/48	22/27	0.80 (0.39; 1.65)	-0.05 (-0.23; 0.12)	-19
		Headache	48/48	17/46 22/48	38/46	0.81 (0.50; 1.31)	-0.09 (-0.29; 0.11)	-11
		Alopecia	48/48	15/46 21/48	33/44	0.75 (0.44; 1.26)	-0.11 (-0.31; 0.08)	-9
		Anorexia	48/48	8/46 9/48	18/19	0.93 (0.39; 2.20)	-0.01 (-0.17; 0.14)	-74
		Insomnia	48/48	9/46 5/48	20/10	1.88 (0.68; 5.19)	0.09 (-0.05; 0.24)	11
		Dizziness	48/48	7/46	16/15	1.04 (0.40; 2.74)	0.01 (-0.14; 0.15)	158

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
				7/48				
		Diarrhea	48/48	8/46 8/48	18/17	1.04 (0.43; 2.55)	0.01 (-0.14; 0.16)	138
		Nausea	48/48	8/46 7/48	18/15	1.19 (0.47; 3.02)	0.03 (-0.12; 0.18)	36
		Upper respiratory infection	48/48	6/46 4/48	13/8	1.57 (0.47; 5.19)	0.05 (-0.08; 0.17)	21
		Cough	48/48	3/46 4/48	7/8	0.78 (0.19; 3.31)	-0.02 (-0.12; 0.09)	-55
Cooksley, 2003[116] PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 13/ 90 mg weekly, 24 weeks	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 26/180 mg weekly, 24 weeks	Loss of HBeAg	48/48	18/49 16/46	37/35	1.06 (0.62; 1.81)	0.02 (-0.17; 0.21)	51
	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 39/270 mg weekly, 24 weeks	Loss of HBeAg	48/48	18/49 14/48	37/29	1.26 (0.71; 2.24)	0.08 (-0.11; 0.26)	13
Cooksley, 2003[116] PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 26/180 mg weekly, 24 weeks	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 39/270 mg weekly, 24 weeks	loss of HBeAg	48/48	16/46 14/48	35/29	1.19 (0.66; 2.16)	0.06 (-0.13; 0.24)	18
PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 39 270 mg weekly, 24 weeks	Seroconversion HBeAg	Seroconversion HBeAg	48/48	18/49 15/46	37/33	1.13 (0.65; 1.96)	0.04 (-0.15; 0.23)	24
				18/49 13/48	37/27	1.36 (0.75; 2.45)	0.10 (-0.09; 0.28)	10

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

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Cooksley, 2003[116] PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland 40 kDa, 26 180 mg weekly, 24 weeks	PEGASYS , F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 39/ 270 mg weekly, 24 weeks	Seroconversion HBeAg	48/48	15/46 13/48	33/27	1.20 (0.65; 2.24)	0.06 (-0.13; 0.24)	18
Cooksley, 2003[116] PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland 40 kDa, 13 /90 mg weekly, 24 weeks	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 26/ 180 mg weekly, 24 weeks	Suppression of HBV DNA levels to <500 000 copies/mL	48/48	21/49 18/46	43/39	1.10 (0.67; 1.78)	0.04 (-0.16; 0.23)	27
	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 39/ 270 mg weekly, 24 weeks	Suppression of HBV DNA levels to <500 000 copies/mL	48/48	21/49 13/48	43/27	1.58 (0.90; 2.79)	0.16 (-0.03; 0.34)	6
Cooksley, 2003[116] PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland 40 kDa, 26/ 180 mg weekly, 24 weeks	PEGASYS, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 40 kDa, 39/ 270 mg weekly, 24 weeks	Suppression of HBV DNA levels to <500 000 copies/mL	48/48	18/46 13/48	39/27	1.44 (0.80; 2.60)	0.12 (-0.07; 0.31)	8
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT	48/48	87/181 132/181	48/73	0.66 (0.55; 0.79)	**-0.25** **(-0.35; -0.15)**	-4

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT	48/48	67/181 132/181	37/73	0.51 (0.41; 0.63)	**-0.36** **(-0.45; -0.26)**	-3
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT	72/72	107/181 80/181	59/44	1.34 (1.09; 1.64)	**0.15 (0.05; 0.25)**	7
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT	72/72	105/181 80/181	58/44	1.31 (1.07; 1.61)	**0.14 (0.04; 0.24)**	7
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT and HBV DNA <20,000 copies/ml	48/48	87/181 125/181	48/69	0.70 (0.58; 0.83)	**-0.21** **(-0.31; -0.11)**	-5
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT and HBV DNA <20,000 copies/ml	48/48	63/181 125/181	35/69	0.50 (0.40; 0.63)	**-0.34** **(-0.44; -0.25)**	-3

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT and HBV DNA <20,000 copies/ml	72/72	68/181 42/181	38/23	1.62 (1.17; 2.24)	**0.14 (0.05; 0.24)**	7
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT and HBV DNA <20,000 copies/ml	72/72	63/181 42/181	35/23	1.50 (1.08; 2.09)	**0.12 (0.02; 0.21)**	9
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT and HBV DNA <400 copies/ml	48/48	82/181 109/181	45/60	0.75 (0.62; 0.92)	**-0.15 (-0.25; -0.05)**	-7
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT and HBV DNA <400 copies/ml	48/48	47/181 109/181	26/60	0.43 (0.33; 0.57)	**-0.34 (-0.44; -0.25)**	-3
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT and HBV DNA <400 copies/ml	72/72	29/181 11/181	16/6	2.64 (1.36; 5.11)	**0.10 (0.04; 0.16)**	10

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks								
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Normalization of ALT and HBV DNA <400 copies/ml	72/72	26/181 11/181	14/6	2.36 (1.20; 4.64)	**0.08 (0.02; 0.14)**	12
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Discontinuation for safety reasons	48/48	7/181 0/181	4/0	15.00 (0.86; 260.70)	**0.04 (0.01; 0.07)**	26
		Discontinuation for other reasons	48/48	3/181 4/181	2/2	0.75 (0.17; 3.30)	-0.01 (-0.03; 0.02)	-181
		Dose modification	48/48	86/181 0/181	48/0	173.00 (10.82; 2766.94)	**0.48 (0.40; 0.55)**	2
		Dose modification due to adverse event	48/48	23/181 0/181	13/0	47.00 (2.88; 767.96)	**0.13 (0.08; 0.18)**	8
		Dose modification due to laboratory abnormality	48/48	64/181 0/181	35/0	129.00 (8.04; 2068.85)	**0.35 (0.28; 0.42)**	3
		Dose modification due to alanine aminotransferase elevation	48/48	6/181 0/181	3/0	13.00 (0.74; 229.07)	**0.03 (0.01; 0.06)**	30
		Dose modification due to neutropenia	48/48	44/181 0/181	24/0	89.00 (5.52; 1434.24)	**0.24 (0.18; 0.31)**	4
		Dose modification due to thrombo-cytopenia	48/48	22/181 0/181	12/0	45.00 (2.75; 736.24)	**0.12 (0.07; 0.17)**	8
		≥1 reported serious adverse event	48/48	12/181 5/181	7/3	2.40 (0.86; 6.67)	**0.04 (0.00; 0.08)**	26
		Death	48/48	0/181			0.00 (-0.01; 0.01)	

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
				0/181				
		≥1 reported adverse event	48/48	155/181 86/181	86/48	1.80 (1.53; 2.12)	**0.38 (0.29; 0.47)**	3
		Pyrexia	48/48	98/181 8/181	54/4	12.25 (6.14; 24.44)	**0.50 (0.42; 0.58)**	2
		Fatigue	48/48	75/181 33/181	41/18	2.27 (1.60; 3.24)	**0.23 (0.14; 0.32)**	4
		Myalgia	48/48	49/181 11/181	27/6	4.45 (2.39; 8.29)	**0.21 (0.14; 0.28)**	5
		Headache	48/48	34/181 14/181	19/8	2.43 (1.35; 4.37)	**0.11 (0.04; 0.18)**	9
		Decreased appetite	48/48	26/181 6/181	14/3	4.33 (1.83; 10.28)	**0.11 (0.05; 0.17)**	9
		Arthralgia	48/48	27/181 6/181	15/3	4.50 (1.90; 10.64)	**0.12 (0.06; 0.17)**	9
		Alopecia	48/48	20/181 1/181	11/1	20.00 (2.71; 147.45)	**0.10 (0.06; 0.15)**	10
		Diarrhea	48/48	10/181 5/181	6/3	2.00 (0.70; 5.74)	0.03 (-0.01; 0.07)	36
		Dizziness	48/48	12/181 8/181	7/4	1.50 (0.63; 3.58)	0.02 (-0.02; 0.07)	45
		Insomnia	48/48	15/181 5/181	8/3	3.00 (1.11; 8.08)	**0.06 (0.01; 0.10)**	18
		Nausea	48/48	13/181 9/181	7/5	1.44 (0.63; 3.29)	0.02 (-0.03; 0.07)	45
		Irritability	48/48	8/181 4/181	4/2	2.00 (0.61; 6.52)	0.02 (-0.01; 0.06)	45
		Sore throat	48/48	5/181 8/181	3/4	0.63 (0.21; 1.87)	-0.02 (-0.05; 0.02)	-60
		Rigors	48/48	5/181 0/181	3/0	11.00 (0.61; 197.48)	**0.03 (0.00; 0.05)**	36
		Injection-site reaction	48/48	21/181 0/181	12/0	43.00 (2.62; 704.52)	**0.12 (0.07; 0.16)**	9

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Cough	48/48	5/181 2/181	3/1	2.50 (0.49; 12.72)	0.02 (-0.01; 0.04)	60
		Upper respiratory tract infection	48/48	4/181 7/181	2/4	0.57 (0.17; 1.92)	-0.02 (-0.05; 0.02)	-60
		Pruritus	48/48	11/181 4/181	6/2	2.75 (0.89; 8.48)	**0.04 (0.00; 0.08)**	26
		Upper abdominal pain	48/48	12/181 14/181	7/8	0.86 (0.41; 1.80)	-0.01 (-0.06; 0.04)	-91
		Back pain	48/48	11/181 6/181	6/3	1.83 (0.69; 4.85)	0.03 (-0.02; 0.07)	36
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Discontinuation for safety reasons	48/48	13/181 0/181	7/0	27.00 (1.62; 450.80)	**0.07 (0.03; 0.11)**	14
		Discontinuation for other reasons	48/48	2/181 4/181	1/2	0.50 (0.09; 2.70)	-0.01 (-0.04; 0.02)	-91
		Dose modification	48/48	83/181 0/181	46/0	167.00 (10.44; 2671.74)	**0.46 (0.39; 0.53)**	2
		Dose modification due to adverse event	48/48	13/181 0/181	7/0	27.00 (1.62; 450.80)	**0.07 (0.03; 0.11)**	14
		Dose modification due to laboratory abnormality	48/48	65/181 0/181	36/0	131.00 (8.17; 2100.58)	**0.36 (0.29; 0.43)**	3
		Dose modification due to alanine aminotransferase elevation	48/48	15/181 0/181	8/0	31.00 (1.87; 514.22)	**0.08 (0.04; 0.12)**	12
		Dose modification due to neutropenia	48/48	30/181 0/181	17/0	61.00 (3.76; 990.04)	**0.17 (0.11; 0.22)**	6
		Dose modification due to thrombocytopenia	48/48	34/181 0/181	19/0	69.00 (4.26; 1116.95)	**0.19 (0.13; 0.25)**	5
		≥1 reported	48/48	9/181	5/3	1.80 (0.62; 5.27)	0.02 (-0.02; 0.06)	45

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		serious adverse event		5/181				
		Death	48/48	1/181 0/181	1/0	3.00 (0.12; 73.16)	0.01 (-0.01; 0.02)	181
		≥1 reported adverse event	48/48	155/181 86/181	86/48	1.80 (1.53; 2.12)	**0.38 (0.29; 0.47)**	3
		Pyrexia	48/48	105/181 8/181	58/4	13.13 (6.59; 26.13)	**0.54 (0.46; 0.61)**	2
		Fatigue	48/48	74/181 33/181	41/18	2.24 (1.57; 3.20)	**0.23 (0.14; 0.32)**	4
		Myalgia	48/48	47/181 11/181	26/6	4.27 (2.29; 7.97)	**0.20 (0.13; 0.27)**	5
		Headache	48/48	42/181 14/181	23/8	3.00 (1.70; 5.30)	**0.15 (0.08; 0.23)**	6
		Decreased appetite	48/48	31/181 6/181	17/3	5.17 (2.21; 12.08)	**0.14 (0.08; 0.20)**	7
		Arthralgia	48/48	27/181 6/181	15/3	4.50 (1.90; 10.64)	**0.12 (0.06; 0.17)**	9
		Alopecia	48/48	24/181 1/181	13/1	24.00 (3.28; 175.53)	**0.13 (0.08; 0.18)**	8
		Diarrhea	48/48	20/181 5/181	11/3	4.00 (1.53; 10.43)	**0.08 (0.03; 0.13)**	12
		Dizziness	48/48	15/181 8/181	8/4	1.88 (0.82; 4.31)	0.04 (-0.01; 0.09)	26
		Insomnia	48/48	15/181 5/181	8/3	3.00 (1.11; 8.08)	**0.06 (0.01; 0.10)**	18
		Nausea	48/48	14/181 9/181	8/5	1.56 (0.69; 3.50)	0.03 (-0.02; 0.08)	36
		Irritability	48/48	12/181 4/181	7/2	3.00 (0.99; 9.13)	**0.04 (0.00; 0.09)**	23
		Sore throat	48/48	11/181 8/181	6/4	1.38 (0.57; 3.34)	0.02 (-0.03; 0.06)	60
		Rigors	48/48	10/181	6/0	21.00	**0.06 (0.02; 0.09)**	18

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
				0/181		(1.24; 355.71)		
		Injection site reaction	48/48	10/181 0/181	6/0	21.00 (1.24; 355.71)	**0.06 (0.02; 0.09)**	18
		Cough	48/48	10/181 2/181	6/1	5.00 (1.11; 22.50)	**0.04 (0.01; 0.08)**	23
		Upper respiratory tract infection	48/48	9/181 7/181	5/4	1.29 (0.49; 3.38)	0.01 (-0.03; 0.05)	91
		Pruritus	48/48	9/181 4/181	5/2	2.25 (0.71; 7.17)	0.03 (-0.01; 0.07)	36
		Upper abdominal pain	48/48	9/181 14/181	5/8	0.64 (0.29; 1.45)	-0.03 (-0.08; 0.02)	-36
		Back pain	48/48	4/181 6/181	2/3	0.67 (0.19; 2.32)	-0.01 (-0.04; 0.02)	-91
		Histological response - reduction of at least 2 points in the modified HAI score	72/72	68/181 72/181	38/40	0.94 (0.73; 1.22)	-0.02 (-0.12; 0.08)	-45
				85/181 72/181	47/40	1.18 (0.93; 1.50)	**0.07 (-0.03; 0.17)**	14
		Improved necroinflammatory activity graded from 0 (none) to 18 (severe)	72/72	66/181 57/181	36/31	1.16 (0.87; 1.54)	0.05 (-0.05; 0.15)	20
				79/181 57/181	44/31	1.39 (1.06; 1.82)	**0.12 (0.02; 0.22)**	8
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Worse necroinflammatory activity graded from 0 (none) to 18 (severe)	72/72	23/181 21/181	13/12	1.10 (0.63; 1.91)	0.01 (-0.06; 0.08)	91

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Worse necroinflammatory activity graded from 0 (none) to 18 (severe)	72/72	16/181 21/181	9/12	0.76 (0.41; 1.41)	-0.03 (-0.09; 0.03)	-36
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day,48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Improved fibrosis graded from 0 (none) to 18 (severe)	72/72	18/181 22/181	10/12	0.82 (0.45; 1.47)	-0.02 (-0.09; 0.04)	-45
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Improved fibrosis graded from 0 (none) to 18 (severe)	72/72	21/181 22/181	12/12	0.95 (0.54; 1.67)	-0.01 (-0.07; 0.06)	-181
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Worse fibrosis graded from 0 (none) to 18 (severe)	72/72	15/181 6/181	8/3	2.50 (0.99; 6.30)	**0.05 (0.00; 0.10)**	20
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	Worse fibrosis graded from 0 (none) to 18 (severe)	72/72	11/181 6/181	6/3	1.83 (0.69; 4.85)	0.03 (-0.02; 0.07)	36

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	HBV DNA <20,000 copies/ml	48/48	164/181 154/181	91/85	1.06 (0.99; 1.15)	0.06 (-0.01; 0.12)	18
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Placebo, 48 weeks	Lamivudine, 100 mg/day, 48 weeks	HBV DNA <20,000 copies/ml	48/48	144/181 154/181	80/85	0.94 (0.85; 1.03)	-0.06 (-0.13; 0.02)	-18
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine, 100mg/day, 48 weeks	Lamivudine, 100 mg/day, 48 weeks	HBV DNA <400 copies/ml	48/48	156/181 133/181	86/73	1.17 (1.06; 1.30)	**0.13 (0.05; 0.21)**	8
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Placebo, 48 weeks	Lamivudine, 100 mg/day, 48 weeks	HBV DNA <400 copies/ml	48/48	112/181 133/181	62/73	0.84 (0.73; 0.97)	**-0.12 (-0.21; -0.02)**	-9
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	HBV DNA <20,000 copies/m	72/72	79/181 53/181	44/29	1.49 (1.13; 1.97)	**0.14 (0.05; 0.24)**	7

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks								
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	HBV DNA <20,000 copies/m	72/72	76/181 53/181	42/29	1.43 (1.08; 1.90)	**0.13 (0.03; 0.22)**	8
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100mg/day, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	HBV DNA <400 copies/ml	72/72	35/181 12/181	19/7	2.92 (1.57; 5.44)	**0.13 (0.06; 0.20)**	8
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26/ 180 mg once weekly, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg/day, 48 weeks	HBV DNA <400 copies/ml	72/72	34/181 12/181	19/7	2.83 (1.52; 5.29)	**0.12 (0.05; 0.19)**	8
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26 180 mg weekly and placebo, 48 weeks	Normalization of ALT	48/48	126/271 105/271	46/39	1.20 (0.99; 1.46)	0.08 (-0.01; 0.16)	13
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Normalization of ALT	48/48	126/271 168/272	46/62	0.75 (0.64; 0.88)	**-0.15 (-0.24; -0.07)**	-7

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Normalization of ALT	48/48	105/271 168/272	39/62	0.63 (0.53; 0.75)	**-0.23 (-0.31; -0.15)**	-4
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26 180 mg weekly and placebo, 48 weeks	Normalization of ALT	72/72	106/271 111/271	39/41	0.95 (0.78; 1.17)	-0.02 (-0.10; 0.06)	-54
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Normalization of ALT	72/72	106/271 76/272	39/28	1.40 (1.10; 1.78)	**0.11 (0.03; 0.19)**	9
Lau, 2005[56] peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Normalization of ALT	72/72	111/271 76/272	41/28	1.47 (1.15; 1.86)	**0.13 (0.05; 0.21)**	8
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26 180 mg weekly and placebo, 48 weeks	ALT elevations, defined as a peak value at least 5 times as great as the baseline value	48/48	16/271 14/271	6/5	1.14 (0.57; 2.30)	0.01 (-0.03; 0.05)	135
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	ALT elevations, defined as a peak value at least 5 times as great as the baseline value	48/48	16/271 12/272	6/4	1.34 (0.65; 2.78)	0.01 (-0.02; 0.05)	67

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Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	ALT elevations, defined as a peak value at least 5 times as great as the baseline value	48/48	14/271 12/272	5/4	1.17 (0.55; 2.49)	0.01 (-0.03; 0.04)	133
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26 180 mg weekly and placebo, 48 weeks	Deaths (unrelated to hepatitis)	56/56	3/271 0/271	1/0	7.00 (0.36; 134.87)	**0.01 (0.00; 0.03)**	90
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Deaths (unrelated to hepatitis)	56/56	3/271 0/272	1/0	7.03 (0.36; 135.37)	**0.01 (0.00; 0.03)**	90
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Deaths (unrelated to hepatitis)	56/56	0/271 0/272			0.00 (-0.01; 0.01)	
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	HBeAg seroconversion, normalization of ALT, and HBV DNA <100,000	48/48	42/271 27/271	15/10	1.56 (0.99; 2.45)	**0.06 (0.00; 0.11)**	18
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg seroconversion, normalization of ALT, and HBV DNA <100,000	48/48	42/271 50/272	15/18	0.84 (0.58; 1.23)	-0.03 (-0.09; 0.03)	-35

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Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg seroconversion, normalization of ALT, and HBV DNA <100,000	48/48	27/271 50/272	10/18	0.54 (0.35; 0.84)	**-0.08 (-0.14; -0.03)**	-12
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26 180 mg weekly and placebo, 48 weeks	HBeAg seroconversion, normalization of ALT, and HBV DNA <100,000	72/72	56/271 62/271	21/23	0.90 (0.66; 1.24)	-0.02 (-0.09; 0.05)	-45
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg seroconversion, normalization of ALT, and HBV DNA <100,000	72/72	56/271 28/272	21/10	2.01 (1.32; 3.06)	**0.10 (0.04; 0.16)**	10
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg seroconversion, normalization of ALT, and HBV DNA <100,000	72/72	62/271 28/272	23/10	2.22 (1.47; 3.36)	**0.13 (0.06; 0.19)**	8
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/180 mg weekly and placebo, 48 weeks	Discontinuation due to adverse effects	48/48	12/271 8/271	4/3	1.50 (0.62; 3.61)	0.01 (-0.02; 0.05)	68
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Discontinuation due to adverse effects	48/48	12/271 2/272	4/1	6.02 (1.36; 26.65)	**0.04 (0.01; 0.06)**	27

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Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Discontinuation due to adverse effects	48/48	8/271 2/272	3/1	4.01 (0.86; 18.73)	**0.02 (0.00; 0.04)**	45
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	Dose modification due to adverse effects	48/48	23/271 20/271	8/7	1.15 (0.65; 2.04)	0.01 (-0.03; 0.06)	90
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Dose modification due to adverse effects	48/48	23/271 0/272	8/0	47.17 (2.88; 772.72)	**0.08 (0.05; 0.12)**	12
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Dose modification due to adverse effects	48/48	20/271 0/272	7/0	41.15 (2.50; 676.96)	**0.07 (0.04; 0.11)**	14
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	Dose modification due to laboratory abnormality: ALT elevation, neutropenia, and thrombocytopenia	48/48	102/271 99/271	38/37	1.03 (0.83; 1.28)	0.01 (-0.07; 0.09)	90
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Dose modification due to laboratory abnormality: ALT elevation, neutropenia, and thrombocytopenia	48/48	102/271 0/272	38/0	205.75 (12.85; 3295.00)	**0.38 (0.32; 0.43)**	3

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Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Dose modification due to laboratory abnormality: ALT elevation, neutropenia, and thrombocytopenia	48/48	99/271 0/272	37/0	199.73 (12.47; 3199.21)	**0.37 (0.31; 0.42)**	3
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26 180 mg weekly and placebo, 48 weeks	≥1 reported serious adverse event	56/56	16/271 12/271	6/4	1.33 (0.64; 2.76)	0.01 (-0.02; 0.05)	68
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	≥1 reported serious adverse event	56/56	16/271 5/272	6/2	3.21 (1.19; 8.64)	**0.04 (0.01; 0.07)**	25
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	≥1 reported serious adverse event	56/56	12/271 5/272	4/2	2.41 (0.86; 6.74)	**0.03 (0.00; 0.06)**	39
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/180 mg weekly and placebo, 48 weeks	≥1 reported adverse event	56/56	240/271 240/271	89/89	1.00 (0.94; 1.06)	0.00 (-0.05; 0.05)	
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	≥1 reported adverse event	56/56	240/271 152/272	89/56	1.58 (1.41; 1.78)	**0.33 (0.26; 0.40)**	3

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Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	≥1 reported adverse event	56/56	240/271 152/272	89/56	1.58 (1.41; 1.78)	**0.33 (0.26; 0.40)**	3
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	Pyrexia	56/56	148/271 133/271	55/49	1.11 (0.95; 1.31)	0.06 (-0.03; 0.14)	18
		Fatigue	56/56	101/271 108/271	37/40	0.94 (0.76; 1.16)	-0.03 (-0.11; 0.06)	-39
		Headache	56/56	81/271 76/271	30/28	1.07 (0.82; 1.39)	0.02 (-0.06; 0.09)	54
		Myalgia	56/56	77/271 70/271	28/26	1.10 (0.83; 1.45)	0.03 (-0.05; 0.10)	39
		Alopecia	56/56	78/271 55/271	29/20	1.42 (1.05; 1.92)	**0.08 (0.01; 0.16)**	12
		Decreased appetite	56/56	34/271 40/271	13/15	0.85 (0.56; 1.30)	-0.02 (-0.08; 0.04)	-45
		Rash	56/56	22/271 27/271	8/10	0.81 (0.48; 1.39)	-0.02 (-0.07; 0.03)	-54
		Pruritus	56/56	26/271 26/271	10/10	1.00 (0.60; 1.68)	0.00 (-0.05; 0.05)	
		Dizziness	56/56	32/271 25/271	12/9	1.28 (0.78; 2.10)	0.03 (-0.03; 0.08)	39
		Diarrhea	56/56	26/271 25/271	10/9	1.04 (0.62; 1.75)	0.00 (-0.05; 0.05)	271
		Nausea	56/56	27/271 24/271	10/9	1.13 (0.67; 1.90)	0.01 (-0.04; 0.06)	90
		Injection-site reaction	56/56	15/271 24/271	6/9	0.63 (0.34; 1.17)	-0.03 (-0.08; 0.01)	-30
		Arthralgia	56/56	24/271 24/271	9/9	1.00 (0.58; 1.72)	0.00 (-0.05; 0.05)	
		Upper respiratory	56/56	15/271	6/8	0.71 (0.38; 1.36)	-0.02 (-0.06; 0.02)	-45

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		tract infection		21/271				
		Insomnia	56/56	23/271 20/271	8/7	1.15 (0.65; 2.04)	0.01 (-0.03; 0.06)	90
		Rigors	56/56	27/271 19/271	10/7	1.42 (0.81; 2.49)	0.03 (-0.02; 0.08)	34
		Upper abdominal pain	56/56	14/271 19/271	5/7	0.74 (0.38; 1.44)	-0.02 (-0.06; 0.02)	-54
		Sore throat	56/56	21/271 15/271	8/6	1.40 (0.74; 2.66)	0.02 (-0.02; 0.06)	45
		Gingival bleeding	56/56	15/271 15/271	6/6	1.00 (0.50; 2.00)	0.00 (-0.04; 0.04)	
		Cough	56/56	19/271 14/271	7/5	1.36 (0.69; 2.65)	0.02 (-0.02; 0.06)	54
		Dyspepsia	56/56	6/271 14/271	2/5	0.43 (0.17; 1.10)	-0.03 (-0.06; 0.00)	-34
		Depression	56/56	16/271 13/271	6/5	1.23 (0.60; 2.51)	0.01 (-0.03; 0.05)	90
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Pyrexia	56/56	148/271 12/272	55/4	12.38 (7.04; 21.75)	**0.50 (0.44; 0.57)**	2
		Fatigue	56/56	101/271 37/272	37/14	2.74 (1.96; 3.84)	**0.24 (0.17; 0.31)**	4
		Headache	56/56	81/271 27/272	30/10	3.01 (2.01; 4.50)	**0.20 (0.13; 0.26)**	5
		Myalgia	56/56	77/271 8/272	28/3	9.66 (4.76; 19.62)	**0.25 (0.20; 0.31)**	4
		Alopecia	56/56	78/271 6/272	29/2	13.05 (5.79; 29.42)	**0.27 (0.21; 0.32)**	4
		Decreased appetite	56/56	34/271 5/272	13/2	6.83 (2.71; 17.19)	**0.11 (0.06; 0.15)**	9
		Rash	56/56	22/271 10/272	8/4	2.21 (1.07; 4.57)	**0.04 (0.00; 0.08)**	23
		Pruritus	56/56	26/271 5/272	10/2	5.22 (2.03; 13.39)	**0.08 (0.04; 0.12)**	13

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Dizziness	56/56	32/271 11/272	12/4	2.92 (1.50; 5.67)	**0.08 (0.03; 0.12)**	13
		Diarrhea	56/56	26/271 9/272	10/3	2.90 (1.38; 6.07)	**0.06 (0.02; 0.10)**	16
		Nausea	56/56	27/271 6/272	10/2	4.52 (1.90; 10.76)	**0.08 (0.04; 0.12)**	13
		Injection-site reaction	56/56	15/271 0/272	6/0	31.11 (1.87; 517.39)	**0.06 (0.03; 0.08)**	18
		Arthralgia	56/56	24/271 7/272	9/3	3.44 (1.51; 7.85)	**0.06 (0.02; 0.10)**	16
		Upper respiratory tract infection	56/56	15/271 29/272	6/11	0.52 (0.28; 0.95)	**-0.05 (-0.10; -0.01)**	-20
		Insomnia	56/56	23/271 10/272	8/4	2.31 (1.12; 4.76)	**0.05 (0.01; 0.09)**	21
		Rigors	56/56	27/271 0/272	10/0	55.20 (3.38; 900.41)	**0.10 (0.06; 0.14)**	10
		Upper abdominal pain	56/56	14/271 20/272	5/7	0.70 (0.36; 1.36)	-0.02 (-0.06; 0.02)	-46
		Sore throat	56/56	21/271 19/272	8/7	1.11 (0.61; 2.02)	0.01 (-0.04; 0.05)	131
		Gingival bleeding	56/56	15/271 1/272	6/0	15.06 (2.00; 113.18)	**0.05 (0.02; 0.08)**	19
		Cough	56/56	19/271 10/272	7/4	1.91 (0.90; 4.03)	**0.03 (0.00; 0.07)**	30
		Dyspepsia	56/56	6/271 9/272	2/3	0.67 (0.24; 1.85)	-0.01 (-0.04; 0.02)	-91
		Depression	56/56	16/271 4/272	6/1	4.01 (1.36; 11.85)	**0.04 (0.01; 0.08)**	23
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Pyrexia	56/56	133/271 12/272	49/4	11.12 (6.31; 19.60)	**0.45 (0.38; 0.51)**	2
		Fatigue	56/56	108/271 37/272	40/14	2.93 (2.10; 4.09)	**0.26 (0.19; 0.33)**	4
		Headache	56/56	76/271	28/10	2.83 (1.88; 4.24)	**0.18 (0.12; 0.25)**	6

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Placebo, 48 weeks				27/272				
		Myalgia	56/56	70/271 8/272	26/3	8.78 (4.31; 17.90)	**0.23 (0.17; 0.28)**	4
		Alopecia	56/56	55/271 6/272	20/2	9.20 (4.03; 21.01)	**0.18 (0.13; 0.23)**	6
		Decreased appetite	56/56	40/271 5/272	15/2	8.03 (3.22; 20.03)	**0.13 (0.08; 0.17)**	8
		Rash	56/56	27/271 10/272	10/4	2.71 (1.34; 5.49)	**0.06 (0.02; 0.10)**	16
		Pruritus	56/56	26/271 5/272	10/2	5.22 (2.03; 13.39)	**0.08 (0.04; 0.12)**	13
		Dizziness	56/56	25/271 11/272	9/4	2.28 (1.15; 4.54)	**0.05 (0.01; 0.09)**	19
		Diarrhea	56/56	25/271 9/272	9/3	2.79 (1.33; 5.86)	**0.06 (0.02; 0.10)**	17
		Nausea	56/56	24/271 6/272	9/2	4.01 (1.67; 9.67)	**0.07 (0.03; 0.10)**	15
		Injection-site reaction	56/56	24/271 0/272	9/0	49.18 (3.01; 804.64)	**0.09 (0.05; 0.12)**	11
		Arthralgia	56/56	24/271 7/272	9/3	3.44 (1.51; 7.85)	**0.06 (0.02; 0.10)**	16
		Upper respiratory tract infection	56/56	21/271 29/272	8/11	0.73 (0.43; 1.24)	-0.03 (-0.08; 0.02)	-34
		Insomnia	56/56	20/271 10/272	7/4	2.01 (0.96; 4.21)	**0.04 (0.00; 0.08)**	27
		Rigors	56/56	19/271 0/272	7/0	39.14 (2.38; 645.05)	**0.07 (0.04; 0.10)**	14
		Upper abdominal pain	56/56	19/271 20/272	7/7	0.95 (0.52; 1.75)	0.00 (-0.05; 0.04)	-293
		Sore throat	56/56	15/271 19/272	6/7	0.79 (0.41; 1.53)	-0.01 (-0.06; 0.03)	-69
		Gingival bleeding	56/56	15/271 1/272	6/0	15.06 (2.00; 113.18)	**0.05 (0.02; 0.08)**	19

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Cough	56/56	14/271 10/272	5/4	1.41 (0.64; 3.11)	0.01 (-0.02; 0.05)	67
		Dyspepsia	56/56	14/271 9/272	5/3	1.56 (0.69; 3.55)	0.02 (-0.02; 0.05)	54
		Depression	56/56	13/271 4/272	5/1	3.26 (1.08; 9.88)	**0.03 (0.00; 0.06)**	30
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	Histological response - reduction of at least 2 points in the modified HAI score Scores for this index can range from 0 to 24, with inflammation graded from 0 (none) to 18 (severe) and fibrosis graded from 0	72/72	112/271 102/271	41/38	1.10 (0.89; 1.35)	0.04 (-0.05; 0.12)	27
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Histological response - reduction of at least 2 points in the modified HAI score. Scores for this index can range from 0 to 24, with inflammation graded from 0 (none) to 18 (severe) and	72/72	112/271 93/272	41/34	1.21 (0.97; 1.50)	0.07 (-0.01; 0.15)	14

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		fibrosis graded from 0						
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Histological response - reduction of at least 2 points in the modified HAI score Scores for this index can range from 0 to 24, with inflammation graded from 0 (none) to 18 (severe) and fibrosis graded from 0	72/72	102/271 93/272	38/34	1.10 (0.88; 1.38)	0.03 (-0.05; 0.12)	29
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	HBeAg seroconversion:	48/48	64/271 72/271	24/27	0.89 (0.66; 1.19)	-0.03 (-0.10; 0.04)	-34
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg seroconversion:	48/48	64/271 55/272	24/20	1.17 (0.85; 1.61)	0.03 (-0.04; 0.10)	29
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg seroconversion:	48/48	72/271 55/272	27/20	1.31 (0.97; 1.79)	0.06 (-0.01; 0.13)	16

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	HBeAg seroconversion	72/72	74/271 87/271	27/32	0.85 (0.66; 1.10)	-0.05 (-0.12; 0.03)	-21
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg seroconversion	72/72	74/271 52/272	27/19	1.43 (1.05; 1.95)	**0.08 (0.01; 0.15)**	12
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg seroconversion	72/72	87/271 52/272	32/19	1.68 (1.24; 2.27)	**0.13 (0.06; 0.20)**	8
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/180 mg weekly and placebo, 48 weeks	HBeAg loss	48/48	73/271 81/271	27/30	0.90 (0.69; 1.18)	-0.03 (-0.11; 0.05)	-34
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg loss	48/48	73/271 59/272	27/22	1.24 (0.92; 1.67)	0.05 (-0.02; 0.12)	19
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg loss	48/48	81/271 59/272	30/22	1.38 (1.03; 1.84)	**0.08 (0.01; 0.16)**	12

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	HBeAg loss	72/72	77/271 91/271	28/34	0.85 (0.66; 1.09)	-0.05 (-0.13; 0.03)	-19
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg loss	72/72	77/271 57/272	28/21	1.36 (1.01; 1.83)	**0.07 (0.00; 0.15)**	13
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg loss	72/72	91/271 57/272	34/21	1.60 (1.20; 2.13)	**0.13 (0.05; 0.20)**	8
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	HBV DNA <100,000 copies/m	48/48	233/271 142/271	86/52	1.64 (1.45; 1.86)	**0.34 (0.26; 0.41)**	3
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBV DNA <100,000 copies/m	48/48	233/271 169/272	86/62	1.38 (1.25; 1.54)	**0.24 (0.17; 0.31)**	4
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBV DNA <100,000 copies/m	48/48	142/271 169/272	52/62	0.84 (0.73; 0.98)	**-0.10 (-0.18; -0.01)**	-10

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Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	HBV DNA <100,000 copies/m	72/72	91/271 86/271	34/32	1.06 (0.83; 1.35)	0.02 (-0.06; 0.10)	54
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBV DNA <100,000 copies/m	72/72	91/271 60/272	34/22	1.52 (1.15; 2.01)	**0.12 (0.04; 0.19)**	9
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBV DNA <100,000 copies/m	72/72	86/271 60/272	32/22	1.44 (1.08; 1.91)	**0.10 (0.02; 0.17)**	10
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	HBV DNA <400 copies/ml	48/48	186/271 68/271	69/25	2.74 (2.19; 3.41)	**0.44 (0.36; 0.51)**	2
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBV DNA <400 copies/ml	48/48	186/271 108/272	69/40	1.73 (1.46; 2.04)	**0.29 (0.21; 0.37)**	3
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBV DNA <400 copies/ml	48/48	68/271 108/272	25/40	0.63 (0.49; 0.81)	**-0.15 (-0.22; -0.07)**	-7

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	HBV DNA <400 copies/ml	72/72	37/271 39/271	14/14	0.95 (0.63; 1.44)	-0.01 (-0.07; 0.05)	-135
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBV DNA <400 copies/ml	72/72	37/271 14/272	14/5	2.65 (1.47; 4.79)	**0.09 (0.04; 0.13)**	12
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBV DNA <400 copies/ml	72/72	39/271 14/272	14/5	2.80 (1.55; 5.03)	**0.09 (0.04; 0.14)**	11
Lau, 2005[56] Peginterferon alfa-2a (Pegasys,Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	YMDD mutations	48/48	9/271 0/271	3/0	19.00 (1.11; 324.82)	**0.03 (0.01; 0.06)**	30
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	YMDD mutations	48/48	9/271 69/272	3/25	0.13 (0.07; 0.26)	**-0.22 (-0.28; -0.16)**	-5
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	YMDD mutations	48/48	0/271 69/272	0/25	0.01 (0.00; 0.12)	**-0.25 (-0.31; -0.20)**	-4

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Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo, 48 weeks	HBeAg seroconversion	72/72	59/271 66/271	22/24	0.89 (0.66; 1.22)	-0.03 (-0.10; 0.05)	-39
	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg seroconversion	72/72	59/271 42/272	22/15	1.41 (0.99; 2.02)	**0.06 (0.00; 0.13)**	16
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26/ 180 mg weekly and placebo Placebo, 48 weeks	Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	HBeAg seroconversion	72/72	66/271 42/272	24/15	1.58 (1.11; 2.23)	**0.09 (0.02; 0.16)**	11
Bonino, 2007 [114] Peginterferon a-2a (40KD; PEGASYS, Roche, Basel, Switzerland), 26/ 180 mg once weekly Placebo, 100mg/day, 48 weeks	Lamivudine (Epivir-HBV/Zeffix, GlaxoSmithKline, Greenford, UK), 100 mg/day, 48 weeks	Sustained combined response: ALT normalization and an HBV DNA level of 20,000 copies/ml	72/72	34/177 18/181	19/10	1.93 (1.13; 3.29)	**0.09 (0.02; 0.17)**	11
Janssen, 2005[78] Peginterferon α-2b, 14/100 microg/week until week 32, then 50mg/week Lamivudine, 100mg/daily, 52 weeks	Peginterferon α-2b + Placebo, 14/ 100 microg/week, 52 weeks	ALT returned to normal	52/52	66/152 46/155	43/30	1.46 (1.08; 1.98)	**0.14 (0.03; 0.24)**	7
			78/78	46/152 44/155	30/28	1.07 (0.75; 1.51)	0.02 (-0.08; 0.12)	53
		Flu-like syndrome	78/78	96/152 84/155	63/54	1.17 (0.96; 1.41)	0.09 (-0.02; 0.20)	11
		Headache	78/78	59/152 55/155	39/35	1.09 (0.82; 1.46)	0.03 (-0.07; 0.14)	30
		Fatigue	78/78	54/152 59/155	36/38	0.93 (0.70; 1.25)	-0.03 (-0.13; 0.08)	-39

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Myalgia	78/78	42/152 41/155	28/26	1.04 (0.72; 1.51)	0.01 (-0.09; 0.11)	85
		Abdominal pain	78/78	25/152 26/155	16/17	0.98 (0.59; 1.62)	0.00 (-0.09; 0.08)	-306
		Arthralgia	78/78	20/152 22/155	13/14	0.93 (0.53; 1.63)	-0.01 (-0.09; 0.07)	-97
		Loss of >10 body weight	78/78	25/152 28/155	16/18	0.91 (0.56; 1.49)	-0.02 (-0.10; 0.07)	-62
		Anorexia	78/78	21/152 22/155	14/14	0.97 (0.56; 1.69)	0.00 (-0.08; 0.07)	-265
		Diarrhea	78/78	14/152 15/155	9/10	0.95 (0.48; 1.90)	0.00 (-0.07; 0.06)	-214
		Nausea	78/78	14/152 25/155	9/16	0.57 (0.31; 1.06)	-0.07 (-0.14; 0.00)	-14
		Local reaction	78/78	38/152 36/155	25/23	1.08 (0.72; 1.60)	0.02 (-0.08; 0.11)	56
		Alopecia	78/78	35/152 26/155	23/17	1.37 (0.87; 2.16)	0.06 (-0.03; 0.15)	16
		Pruritus	78/78	18/152 14/155	12/9	1.31 (0.68; 2.54)	0.03 (-0.04; 0.10)	36
		Depression	78/78	28/152 29/155	18/19	0.98 (0.62; 1.57)	0.00 (-0.09; 0.08)	-346
		Insomnia	78/78	20/152 11/155	13/7	1.85 (0.92; 3.74)	0.06 (-0.01; 0.13)	16
		Neutropenia (<1·5*109/L)	78/78	34/152 29/155	22/19	1.20 (0.77; 1.86)	0.04 (-0.05; 0.13)	27
		Thrombocytopenia (<75*109/L)	78/78	14/152 17/155	9/11	0.84 (0.43; 1.64)	-0.02 (-0.08; 0.05)	-57
		Improved fibrosis scores as decrease of at least 1 point for the fibrosis score	78/78	17/152 13/155	11/8	1.33 (0.67; 2.65)	0.03 (-0.04; 0.09)	36

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		(range 0–6)						
		No improvement in fibrosis scores	52/52	15/152 23/155	10/15	0.67 (0.36; 1.22)	-0.05 (-0.12; 0.02)	-20
		Worsening in fibrosis scores	52/52	20/152 22/155	13/14	0.93 (0.53; 1.63)	-0.01 (-0.09; 0.07)	-97
		Improved inflammatory changes in the liver as decrease of at least 2 points for the necroinflammatory score (range 0-18)	52/52	25/152 31/155	16/20	0.82 (0.51; 1.33)	-0.04 (-0.12; 0.05)	-28
		No Improvement in inflammatory scores	52/52	22/152 21/155	14/14	1.07 (0.61; 1.86)	0.01 (-0.07; 0.09)	108
		Worsening in inflammatory scores	52/52	5/152 6/155	3/4	0.85 (0.26; 2.73)	-0.01 (-0.05; 0.04)	-172
		HBeAg loss	52/52	57/152 40/155	38/26	1.45 (1.04; 2.03)	**0.12 (0.01; 0.22)**	9
		HBeAg seroconversion	52/52	33/152 30/155	22/19	1.12 (0.72; 1.74)	0.02 (-0.07; 0.11)	42
		HBV DNA <200 000 copies/mL	52/52	96/152 40/155	63/26	2.45 (1.83; 3.28)	**0.37 (0.27; 0.48)**	3
		HBV DNA <400 copies/mL	52/52	43/152 13/155	28/8	3.37 (1.89; 6.02)	**0.20 (0.12; 0.28)**	5
		HBsAg loss	52/52	9/152 7/155	6/5	1.31 (0.50; 3.43)	0.01 (-0.04; 0.06)	71
26 weeks followup		HBsAg seroconversion	52/52	8/152 6/155	5/4	1.36 (0.48; 3.83)	0.01 (-0.03; 0.06)	72
		HBeAg loss	78/78	46/152 49/155	30/32	0.96 (0.69; 1.34)	-0.01 (-0.12; 0.09)	-74

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		HBeAg seroconversion	78/78	38/152 39/155	25/25	0.99 (0.67; 1.46)	0.00 (-0.10; 0.10)	-620
		HBV DNA <200 000 copies/mL	78/78	41/152 37/155	27/24	1.13 (0.77; 1.66)	0.03 (-0.07; 0.13)	32
		HBV DNA <400 copies/mL	78/78	12/152 9/155	8/6	1.36 (0.59; 3.13)	0.02 (-0.04; 0.08)	48
		HBsAg loss	78/78	9/152 9/155	6/6	1.02 (0.42; 2.50)	0.00 (-0.05; 0.05)	873
		HBsAg seroconversion	78/78	9/152 7/155	6/5	1.31 (0.50; 3.43)	0.01 (-0.04; 0.06)	71
		YMDD mutant	52/52	14/152 0/155	9/0	29.57 (1.78; 491.31)	**0.09 (0.04; 0.14)**	11
Chan, 2005[59] Peginterferon alfa-2b (PegIntron; Schering-Plough Corp., Kenilworth, NJ), 14/1.5 g/kg/week for patients with body weight less than 65 kg or 100 g/week for patients with body weight >65 kg8 weeks before the commencement of lamivudine, then a combination of both treatments for 24 weeks Lamivudine (Zeffix; GlaxoSmithKline, Middlesex, UK), 100mg/day, 60 weeks	Lamivudine (Zeffix; GlaxoSmithKline, Middlesex, UK), 100 mg/day, 52 weeks	Severe relapse as ALT level >10 times ULNand HBV DNA level greater than 500,000 copies/mL	60/52	5/50 11/50	10/22	0.45 (0.17; 1.21)	-0.12 (-0.26; 0.02)	-8
		Normalization of ALT	60/52	45/50 39/50	90/78	1.15 (0.97; 1.37)	0.12 (-0.02; 0.26)	8
		Upper respiratory tract symptoms	60/52	37/50 19/50	74/38	1.95 (1.32; 2.88)	**0.36 (0.18; 0.54)**	3
		Fever	60/52	36/50 2/50	72/4	18.00 (4.58; 70.76)	**0.68 (0.54; 0.82)**	1
		Alopecia	60/52	24/50 2/50	48/4	12.00 (2.99; 48.09)	**0.44 (0.29; 0.59)**	2
		Abdominal discomfort	60/52	22/50 13/50	44/26	1.69 (0.96; 2.97)	**0.18 (0.00; 0.36)**	6
		Malaise	60/52	22/50 7/50	44/14	3.14 (1.48; 6.69)	**0.30 (0.13; 0.47)**	3
		Headache	60/52	21/50 2/50	42/4	10.50 (2.60; 42.43)	**0.38 (0.23; 0.53)**	3

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Myalgia	60/52	13/50 2/50	26/4	6.50 (1.55; 27.33)	**0.22 (0.09; 0.35)**	5
		Arthralgia	60/52	12/50 2/50	24/4	6.00 (1.41; 25.44)	**0.20 (0.07; 0.33)**	5
		Reduced appetite	60/52	12/50 0/50	24/0	25.00 (1.52; 411.09)	**0.24 (0.12; 0.36)**	4
		Local erythematous reaction	60/52	12/50 0/50	24/0	25.00 (1.52; 411.09)	**0.24 (0.12; 0.36)**	4
		Allergic rashes	60/52	9/50 1/50	18/2	9.00 (1.18; 68.42)	**0.16 (0.05; 0.27)**	6
		Dizziness	60/52	8/50 1/50	16/2	8.00 (1.04; 61.62)	**0.14 (0.03; 0.25)**	7
		Vomiting or diarrhea	60/52	7/50 3/50	14/6	2.33 (0.64; 8.51)	0.08 (-0.04; 0.20)	13
		Weight loss (>10)	60/52	7/50 1/50	14/2	7.00 (0.89; 54.83)	0**.12 (0.02; 0.22)**	8
		Increased ALT level	60/52	8/50 12/50	16/24	0.67 (0.30; 1.49)	-0.08 (-0.24; 0.08)	-13
		Decreased phosphate level	60/52	2/50 1/50	4/2	2.00 (0.19; 21.36)	0.02 (-0.05; 0.09)	50
		Decreased neutrophil count	60/52	1/50 0/50	2/0	3.00 (0.13; 71.92)	0.02 (-0.03; 0.07)	50
		Increased creatine kinase level	60/52	0/50 1/50	0/2	0.33 (0.01; 7.99)	-0.02 (-0.07; 0.03)	-50
		Increased alkaline phosphatase level	60/52	0/50 1/50	0/2	0.33 (0.01; 7.99)	-0.02 (-0.07; 0.03)	-50
		At least 2-point increase in necroinflammatory score	60/52	24/50 26/50	48/52	0.92 (0.62; 1.37)	-0.04 (-0.24; 0.16)	-25
			60/52	2/50 4/50	4/8	0.50 (0.10; 2.61)	-0.04 (-0.13; 0.05)	-25
		At least a 2-point increase in	60/52	6/50 4/50	12/8	1.50 (0.45; 4.99)	0.04 (-0.08; 0.16)	25

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		fibrosis score	60/52	4/50 2/50	8/4	2.00 (0.38; 10.43)	0.04 (-0.05; 0.13)	25
		Sustained virological response as HBeAg seroconversion and HBV DNA level < 500,000 copies/mL	60/52	30/50 14/50	60/28	2.14 (1.30; 3.53)	**0.32 (0.14; 0.50)**	3
		HBV DNA–negative by PCR	60/52	5/50 2/50	10/4	2.50 (0.51; 12.29)	0.06 (-0.04; 0.16)	17
		Sustained virological response as HBeAg seroconversion and HBV DNA level < 500,000 copies/mL	48/48	25/50 14/50	50/28	1.79 (1.06; 3.02)	**0.22 (0.03; 0.41)**	5
			24/24	18/50 7/50	36/14	2.57 (1.18; 5.61)	**0.22 (0.06; 0.38)**	5
		HBV DNA–negative by PCR	24/24	3/50 2/50	6/4	1.50 (0.26; 8.60)	0.02 (-0.07; 0.11)	50
		Virological relapse as either HBV DNA 100,000 copies at any 2 or more occasions or HBeAg reversion	60/52	12/50 7/50	24/14	1.71 (0.74; 3.99)	0.10 (-0.05; 0.25)	10
		Lamivudine-resistant mutant	60/52	10/50 19/50	20/38	0.53 (0.27; 1.02)	**-0.18 (-0.35; -0.01)**	-6
van Zonneveld, 2005[119] Peginterferon α-2b,	Peginterferon α-2b + Placebo, 14/ 100 microg/week, 52	Flares defined as an increase in serum ALT to at	52/52	34/152 37/155	22/24	0.94 (0.62; 1.41)	-0.02 (-0.11; 0.08)	-67

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
14 /100 microg/wk until week 32, then 50mg/week Lamivudine, 100mg/daily, 52 weeks	weeks	least 3 times the baseline level						
		Reduction in dose of Interferon due to adverse events	52/52	37/152 32/155	24/21	1.18 (0.78; 1.79)	0.04 (-0.06; 0.13)	27
van Zonneveld, 2005[119] Peginterferon alfa-2b (PegIntron; Schering-Plough Corp., Kenilworth, NJ), 14/ 1.5 g/kg/week for patients with body weight less than 65 kg or 100 g/week for patients with body weight > 65 kg 8 weeks before the commencement of lamivudine, then a combination of both treatments for 24 weeks Lamivudine (Zeffix; GlaxoSmithKline, Middlesex, UK), 100mg/day, 60 weeks	Lamivudine (Zeffix; GlaxoSmithKline, Middlesex, UK), 100 mg/day, 52 weeks	Biochemical relapse as ALT elevation to >2 times ULN	117/124	32/50 38/50	64/76	0.84 (0.65; 1.09)	-0.12 (-0.30; 0.06)	-8
		Decompensation as elevated serum bilirubin >50IU/L + ALT elevation >2 times ULN	117/124	2/50 4/50	4/8	0.50 (0.10; 2.61)	-0.04 (-0.13; 0.05)	-25
		Elevation of ALT >10 times ULN	60/52	9/50 15/50	18/30	0.60 (0.29; 1.24)	-0.12 (-0.29; 0.05)	-8
		Lamivudine treatment for severe post treatment biochemical relapse	84/76	7/50 14/50	14/28	0.50 (0.22; 1.13)	-0.14 (-0.30; 0.02)	-7
		Death from acute duodenal ulcer bleeding complicated by shock	116/116	1/50 0/50	2/0	3.00 (0.13; 71.92)	0.02 (-0.03; 0.07)	50
		Ascites	117/124	0/50 0/50			0.00 (-0.04; 0.04)	
		Hepatic encephalopathy	117/124	0/50 0/50			0.00 (-0.04; 0.04)	
		Lost HBeAg	60/52	30/50 13/50	60/26	2.31 (1.37; 3.88)	**0.34 (0.16; 0.52)**	3

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		HBeAg seroconversion	60/52	29/50 13/50	58/26	2.23 (1.32; 3.77)	**0.32 (0.14; 0.50)**	3
		Sustained response as sustained HBeAg loss and HBV DNA <100,000 copies/mL	117/124	14/50 4/50	28/8	3.50 (1.24; 9.90)	**0.20 (0.05; 0.35)**	5
			100/100	9/50 3/50	18/6	3.00 (0.86; 10.43)	0.12 (-0.01; 0.25)	8
			84/76	15/50 5/50	30/10	3.00 (1.18; 7.63)	**0.20 (0.05; 0.35)**	5
		Virological relapse as either HBV DNA 100,000 copies at any 2 or more occasions or HBeAg reversion	84/76	0/50 0/50			0.00 (-0.04; 0.04)	
		HBsAg clearance	52/52	1/50 0/50	2/0	3.00 (0.13; 71.92)	0.02 (-0.03; 0.07)	50
		Sustained negative HBV DNA by PCR.	117/124	0/50 0/50			0.00 (-0.04; 0.04)	
		Negative HBV DNA by PCR	117/124	6/50 2/50	12/4	3.00 (0.64; 14.16)	0.08 (-0.03; 0.19)	13
		Elevation of HBV DNA to 100,000 copies/mL	117/124	16/50 9/50	32/18	1.78 (0.87; 3.64)	0.14 (-0.03; 0.31)	7
		HBeAg seroconversion	100/100	13/50 8/50	26/16	1.63 (0.74; 3.58)	0.10 (-0.06; 0.26)	10
			148/148	13/50 15/50	26/30	0.87 (0.46; 1.63)	-0.04 (-0.22; 0.14)	-25
Flink, 2006[122] Peginterferon α-2b, 14 /100 microg/week until week 32, then	Peginterferon α-2b + Placebo, 14/ 100 microg/week, 52 weeks	HBeAg clearance	78/78	53/152 56/155	35/36	0.97 (0.71; 1.30)	-0.01 (-0.12; 0.09)	-79
				11/152 11/155	7/7	1.02 (0.46; 2.28)	0.00 (-0.06; 0.06)	714

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Intervention, Daily/Weekly Dose Length of Intervention	Control Intervention, Daily/ Weekly Dose Length of Intervention	Outcome	Time to Measure Outcomes from Randomization (weeks) After Active/Control Treatments	Cases/ Randomized	Rate of Outcomes after Active/ Control Treatment (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
50mg/week Lamivudine, 100mg/daily, 52 weeks								
Zhao, 2007[81] PegIntron; Schering Corporation, 11 /1.0 mg/kg once per week, 24 weeks	Intron A; Schering Corporation, 1 /3 MIU 3 times per week, 24 weeks	ALT level normalization	48/48	39/115 40/115	34/35	0.98 (0.68; 1.39)	-0.01 (-0.13; 0.11)	-115
		Sustained combined response: HBeAg negative, HBV DNA <5 log10 copies/mL, and normal ALT level	48/48	20/115 12/115	17/10	1.67 (0.86; 3.25)	0.07 (-0.02; 0.16)	14
		Adverse effects	48/48	86/115 86/115	75/75	1.00 (0.86; 1.16)	0.00 (-0.11; 0.11)	
		Discontinuation due to drug-related adverse effects	48/48	0/115 4/115	0/3	0.11 (0.01; 2.04)	-0.03 (-0.07; 0.00)	-29
		HBV DNA level !5 log 10 copies/mL	48/48	34/115 22/115	30/19	1.55 (0.97; 2.47)	0.10 (-0.01; 0.21)	10
		HBV DNA level 3 log copies/mL	48/48	14/115 14/115	12/12	1.00 (0.50; 2.00)	0.00 (-0.08; 0.08)	
		HBeAg loss	48/48	28/115 16/115	24/14	1.75 (1.00; 3.06)	**0.10 (0.00; 0.21)**	10
		HBeAg seroconversion	48/48	25/115 16/115	22/14	1.56 (0.88; 2.77)	0.08 (-0.02; 0.18)	13
		HBsAg seroconversion	48/48	0/115 2/115	0/2	0.20 (0.01; 4.12)	-0.02 (-0.05; 0.01)	-58

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

(B) Outcomes After Reverse Transcriptase Inhibitors

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Chan, 2007[44] Adefovir (Hepsera, Gilead Sciences, Foster City, CA), 10 mg/day, 52 weeks	Adefovir (Hepsera, Gilead Sciences, Foster City, California) for 24 weeks and then telbivudine(Idenix Pharmaceuticals, Cambridge, MA, for the remaining 28 weeks, 10 mg/day, 52 weeks	Serum ALT normalization	52/52	38/45 39/46	85/85	1.00 (0.84; 1.19)	0.00 (-0.15; 0.14)	-296
		Adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site) odds ratio of Serum ALT normalization	52/52	0/45 0/46		1.15 (0.31; 4.17)		
		Total adverse effects	52/52	27/45 31/46	61/67	0.89 (0.65; 1.22)	-0.07 (-0.27; 0.12)	-14
		Upper respiratory tract infection	52/52	5/45 6/46	11/13	0.85 (0.28; 2.59)	-0.02 (-0.15; 0.11)	-52
		Headache	52/52	3/45 6/46	7/13	0.51 (0.14; 1.92)	-0.06 (-0.19; 0.06)	-16
		Back pain	52/52	3/45 3/46	7/7	1.02 (0.22; 4.80)	0.00 (-0.10; 0.10)	690
		Diarrhea	52/52	1/45 5/46	2/11	0.20 (0.02; 1.68)	-0.09 (-0.19; 0.01)	-12
		Influenza	52/52	3/45 4/46	7/9	0.77 (0.18; 3.23)	-0.02 (-0.13; 0.09)	-49
		Upper abdominal pain	52/52	2/45 5/46	5/11	0.41 (0.08; 2.00)	-0.06 (-0.17; 0.04)	-16
		Nasopharyngitis	52/52	5/45 2/46	11/4	2.56 (0.52; 12.50)	0.07 (-0.04; 0.18)	15
		Cough	52/52	0/45 6/46	0/13	0.08 (0.00; 1.36)	**-0.13 (-0.23; -0.03)**	-8
		Arthralgia	52/52	2/45 2/46	5/4	1.02 (0.15; 6.95)	0.00 (-0.08; 0.09)	1035
		Fatigue	52/52	0/45 4/46	0/9	0.11 (0.01; 2.05)	-0.09 (-0.18; 0.00)	-12
		Dizziness	52/52	0/45	0/9	0.11 (0.01; 2.05)	-0.09 (-0.18; 0.00)	-12

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
				4/46				
		Malaise	52/52	0/45 2/46	0/4	0.20 (0.01; 4.14)	-0.04 (-0.11; 0.03)	-23
		Nausea	52/52	2/45 1/46	5/2	2.04 (0.19; 21.76)	0.02 (-0.05; 0.10)	44
		Pharyngolaryngeal pain	52/52	3/45 1/46	7/2	3.07 (0.33; 28.39)	0.04 (-0.04; 0.13)	22
		Abdominal pain	52/52	1/45 0/46	2/0	3.07 (0.13; 73.32)	0.02 (-0.04; 0.08)	45
		Epigastric discomfort	52/52	0/45 1/46	0/2	0.34 (0.01; 8.15)	-0.02 (-0.08; 0.04)	-46
		Gastritis	52/52	0/45 0/46			0.00 (-0.04; 0.04)	
		Hepatic steatosis	52/52	1/45 0/46	2/0	3.07 (0.13; 73.32)	0.02 (-0.04; 0.08)	45
		Mouth ulceration	52/52	2/45 1/46	5/2	2.04 (0.19; 21.76)	0.02 (-0.05; 0.10)	44
		Myalgia	52/52	0/45 2/46	0/4	0.20 (0.01; 4.14)	-0.04 (-0.11; 0.03)	-23
		Toothache	52/52	1/45 0/46	2/0	3.07 (0.13; 73.32)	0.02 (-0.04; 0.08)	45
		Hepatitis B	52/52	2/45 0/46	5/0	5.11 (0.25; 103.54)	0.04 (-0.03; 0.12)	23
		Hordeolum	52/52	0/45 0/46			0.00 (-0.04; 0.04)	
		Allergic rhinitis	52/52	2/45 0/46	5/0	5.11 (0.25; 103.54)	0.04 (-0.03; 0.12)	23
		HBV DNA PCR-negative	52/52	18/45 25/46	40/54	0.74 (0.47; 1.15)	-0.14 (-0.35; 0.06)	-7
		HBeAg loss	52/52	9/45 12/46	21/26	0.77 (0.36; 1.64)	-0.06 (-0.23; 0.11)	-16
		HBeAg seroconversion	52/52	9/45 11/46	19/24	0.84 (0.38; 1.82)	-0.04 (-0.21; 0.13)	-26
		Primary treatment	52/52	13/45	29/11	2.66 (1.03; 6.84)	0.18 (0.02; 0.34)	6

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		failure		5/46				
		Adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site) odds ratio of HBV DNA PCR-negative	52/52	0/45 0/46		0.84 (0.31; 2.27)		
		Adjusted odds ratio of HBeAg loss	52/52	0/45 0/46		1.19 (0.39; 3.70)		
		Adjusted odds ratio of HBeAg seroconversion	52/52	0/45 0/46		1.12 (0.35; 3.57)		
		Adjusted odds ratio of primary treatment failure	52/52	0/45 0/46		2.50 (0.60; 10.00)		
Hadziyannis 2003[41] Adefovir dipivoxil, 10 mg daily , 48 weeks	Placebo, 48 weeks	ALT normalization	48/48	84/123 17/61	68/28	2.45 (1.61; 3.73)	**0.40 (0.26; 0.54)**	2
		At least one adverse event	48/48	94/123 45/61	76/74	1.04 (0.87; 1.24)	0.03 (-0.11; 0.16)	38
		Severe (grade 3 or 4) adverse events	48/48	7/123 6/61	6/10	0.58 (0.20; 1.65)	-0.04 (-0.13; 0.04)	-24
		Serious adverse events not related to treatment	48/48	4/123 4/61	3/7	0.50 (0.13; 1.92)	-0.03 (-0.10; 0.04)	-30
		Any adverse event	48/48	94/123 45/61	76/74	1.04 (0.87; 1.24)	0.03 (-0.11; 0.16)	38
		Headache	48/48	29/123 10/61	24/16	1.44 (0.75; 2.75)	0.07 (-0.05; 0.19)	14
		Pharyngitis	48/48	23/123 14/61	19/23	0.81 (0.45; 1.47)	-0.04 (-0.17; 0.08)	-24
		Abdominal pain	48/48	18/123 3/61	15/5	2.98 (0.91; 9.71)	0.10 (0.01; 0.18)	10

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Asthenia	48/48	16/123 10/61	13/16	0.79 (0.38; 1.64)	-0.03 (-0.14; 0.08)	-30
		Influenza-like syndrome	48/48	13/123 13/61	11/21	0.50 (0.25; 1.00)	-0.11 (-0.22; 0.01)	-9
		Back pain	48/48	12/123 4/61	10/7	1.49 (0.50; 4.42)	0.03 (-0.05; 0.11)	31
		Pain	48/48	10/123 6/61	8/10	0.83 (0.32; 2.17)	-0.02 (-0.11; 0.07)	-59
		Increased cough	48/48	10/123 4/61	8/7	1.24 (0.41; 3.79)	0.02 (-0.06; 0.09)	64
		Insomnia	48/48	6/123 4/61	5/7	0.74 (0.22; 2.54)	-0.02 (-0.09; 0.06)	-60
		Dyspepsia	48/48	6/123 2/61	5/3	1.49 (0.31; 7.16)	0.02 (-0.04; 0.07)	63
		Rhinitis	48/48	6/123 1/61	5/2	2.98 (0.37; 24.17)	0.03 (-0.02; 0.08)	31
		Histological improvement = reduction of at least 2 points in the Knodell necroinflammatory score, with no worsening of fibrosis	48/48	77/123 19/61	63/31	2.01 (1.35; 2.99)	**0.31 (0.17; 0.46)**	3
		Improved necroinflammatory activity	48/48	98/123 26/61	80/42	1.87 (1.38; 2.53)	**0.37 (0.23; 0.51)**	3
		Unchanged necroinflammatory activity	48/48	21/123 4/61	17/7	2.60 (0.93; 7.25)	**0.11 (0.01; 0.20)**	10
		Worse necroinflammatory activity	48/48	4/123 31/61	3/51	0.06 (0.02; 0.17)	**-0.48 (-0.60; -0.35)**	-2

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Improved fibrosis	48/48	59/123 15/61	48/25	1.95 (1.21; 3.14)	**0.23 (0.09; 0.37)**	4
		Unchanged fibrosis	48/48	58/123 22/61	47/36	1.31 (0.89; 1.92)	0.11 (-0.04; 0.26)	9
		Worse fibrosis	48/48	5/123 23/61	4/38	0.11 (0.04; 0.27)	**-0.34 (-0.46; -0.21)**	-3
		Undetectable HBV DNA	48/48	63/123 0/61	51/0	63.50 (4.00; 1009.28)	**0.51 (0.42; 0.60)**	2
		HBV polymerase gene mutations	48/48	0/123 3/61	0/5	0.07 (0.00; 1.36)	-0.05 (-0.11; 0.01)	-20
Marcellin, 2003[126] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	Normalization of ALT	48/48	81/171 93/173	47/54	0.88 (0.71; 1.09)	-0.06 (-0.17; 0.04)	-16
Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Normalization of ALT	48/48	81/171 26/167	47/16	3.04 (2.07; 4.48)	**0.32 (0.23; 0.41)**	3
	Placebo, 48 weeks	Normalization of ALT	48/48	93/173 26/167	54/16	3.45 (2.36; 5.05)	**0.38 (0.29; 0.47)**	3
	Adefovir dipivoxil, 30 mg/day, 48 weeks	Increases in ALT to >10 times ULN	48/48	17/171 14/173	10/8	1.23 (0.63; 2.41)	0.02 (-0.04; 0.08)	54
	Placebo, 48 weeks	Increases in ALT to >10 times ULN	48/48	17/171 32/167	10/19	0.52 (0.30; 0.90)	**-0.09 (-0.17; -0.02)**	-11
Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Increases in ALT >10 times ULN	48/48	14/173 32/167	8/19	0.42 (0.23; 0.76)	**-0.11 (-0.18; -0.04)**	-9
Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	Discontinuation	48/48	12/171 14/173	7/8	0.87 (0.41; 1.82)	-0.01 (-0.07; 0.05)	-93
Adefovir dipivoxil, 10 mg/day, 48 weeks	Placebo, 48 weeks	Discontinuation	48/48	12/171 13/167	7/8	0.90 (0.42; 1.92)	-0.01 (-0.06; 0.05)	-130
Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Discontinuation	48/48	14/173 13/167	8/8	1.04 (0.50; 2.15)	0.00 (-0.05; 0.06)	325
Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	Severe (grade 3 or 4) clinical adverse events	48/48	17/171 16/173	10/9	1.07 (0.56; 2.06)	0.01 (-0.06; 0.07)	144

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Adefovir dipivoxil, 10 mg/day, 48 weeks	Placebo, 48 weeks	Severe (grade 3 or 4) clinical adverse events	48/48	17/171 13/167	10/8	1.28 (0.64; 2.55)	0.02 (-0.04; 0.08)	46
Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Severe (grade 3 or 4) clinical adverse events	48/48	16/173 13/167	9/8	1.19 (0.59; 2.39)	0.01 (-0.04; 0.07)	68
Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	Discontinuation due to adverse events	48/48	3/171 5/173	2/3	0.61 (0.15; 2.50)	-0.01 (-0.04; 0.02)	-88
Adefovir dipivoxil, 10 mg/day, 48 weeks	Placebo, 48 weeks	Discontinuation due to adverse events	48/48	3/171 2/167	2/1	1.46 (0.25; 8.66)	0.01 (-0.02; 0.03)	180
Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Discontinuation due to adverse events	48/48	5/173 2/167	3/1	2.41 (0.47; 12.27)	0.02 (-0.01; 0.05)	59
Marcellin, 2003[126] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	Increases from baseline of 0.5mg per deciliter (44 µmol per liter) or greater in the serum creatinine level	48/48	0/171 14/173	0/8	0.03 (0.00; 0.58)	-0.08 (-0.12; -0.04)	-12
		Headache	48/48	43/171 45/173	25/26	0.97 (0.67; 1.39)	-0.01 (-0.10; 0.08)	-116
		Asthenia	48/48	42/171 45/173	25/26	0.94 (0.66; 1.36)	-0.01 (-0.11; 0.08)	-69
		Abdominal pain	48/48	31/171 38/173	18/22	0.83 (0.54; 1.26)	-0.04 (-0.12; 0.05)	-26
		Flu-like syndrome	48/48	28/171 32/173	16/18	0.89 (0.56; 1.40)	-0.02 (-0.10; 0.06)	-47
		Pain	48/48	19/171 13/173	11/8	1.48 (0.75; 2.90)	0.04 (-0.03; 0.10)	28
		Back pain	48/48	11/171 17/173	6/10	0.65 (0.32; 1.36)	-0.03 (-0.09; 0.02)	-29

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Nausea	48/48	17/171 31/173	10/18	0.55 (0.32; 0.96)	**-0.08 (-0.15; -0.01)**	-13
		Diarrhea	48/48	23/171 25/173	13/14	0.93 (0.55; 1.57)	-0.01 (-0.08; 0.06)	-100
		Dyspepsia	48/48	15/171 19/173	9/11	0.80 (0.42; 1.52)	-0.02 (-0.09; 0.04)	-45
		Flatulence	48/48	13/171 18/173	8/10	0.73 (0.37; 1.44)	-0.03 (-0.09; 0.03)	-36
		Anorexia	48/48	6/171 18/173	4/10	0.34 (0.14; 0.83)	-**0.07 (-0.12; -0.02)**	-15
		Dizziness	48/48	9/171 18/173	5/10	0.51 (0.23; 1.09)	-0.05 (-0.11; 0.01)	-19
		Pharyngitis	48/48	44/171 70/173	26/40	0.64 (0.47; 0.87)	**-0.15 (-0.25; -0.05)**	-7
		Increased cough	48/48	11/171 19/173	6/11	0.59 (0.29; 1.19)	-0.05 (-0.10; 0.01)	-22
	Placebo, 48 weeks	Headache	48/48	43/171 37/167	25/22	1.13 (0.77; 1.67)	0.03 (-0.06; 0.12)	33
		Asthenia	48/48	42/171 32/167	25/19	1.28 (0.85; 1.93)	0.05 (-0.03; 0.14)	19
		Abdominal pain	48/48	31/171 32/167	18/19	0.95 (0.61; 1.48)	-0.01 (-0.09; 0.07)	-97
		Flu-like syndrome	48/48	28/171 31/167	16/19	0.88 (0.55; 1.40)	-0.02 (-0.10; 0.06)	-46
		Pain	48/48	19/171 21/167	11/13	0.88 (0.49; 1.58)	-0.01 (-0.08; 0.05)	-68
		Back pain	48/48	11/171 11/167	6/7	0.98 (0.44; 2.19)	0.00 (-0.05; 0.05)	-649
		Nausea	48/48	17/171 23/167	10/14	0.72 (0.40; 1.30)	-0.04 (-0.11; 0.03)	-26
		Diarrhea	48/48	23/171 13/167	13/8	1.73 (0.91; 3.30)	0.06 (-0.01; 0.12)	18
		Dyspepsia	48/48	15/171 14/167	9/8	1.05 (0.52; 2.10)	0.00 (-0.06; 0.06)	257

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Flatulence	48/48	13/171 10/167	8/6	1.27 (0.57; 2.82)	0.02 (-0.04; 0.07)	62
		Anorexia	48/48	6/171 9/167	4/5	0.65 (0.24; 1.79)	-0.02 (-0.06; 0.03)	-53
		Dizziness	48/48	9/171 13/167	5/8	0.68 (0.30; 1.54)	-0.03 (-0.08; 0.03)	-40
		Pharyngitis	48/48	44/171 54/167	26/32	0.80 (0.57; 1.11)	-0.07 (-0.16; 0.03)	-15
		Increased cough	48/48	11/171 21/167	6/13	0.51 (0.25; 1.03)	-0.06 (-0.12; 0.00)	-16
Marcellin, 2003[126] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Headache	48/48	45/173 37/167	26/22	1.17 (0.80; 1.72)	0.04 (-0.05; 0.13)	26
		Asthenia	48/48	45/173 32/167	26/19	1.36 (0.91; 2.03)	0.07 (-0.02; 0.16)	15
		Abdominal pain	48/48	38/173 32/167	22/19	1.15 (0.75; 1.74)	0.03 (-0.06; 0.11)	36
		Flu-like syndrome	48/48	32/173 31/167	18/19	1.00 (0.64; 1.56)	0.00 (-0.08; 0.08)	-1521
		Pain	48/48	13/173 21/167	8/13	0.60 (0.31; 1.15)	-0.05 (-0.11; 0.01)	-20
		Back pain	48/48	17/173 11/167	10/7	1.49 (0.72; 3.09)	0.03 (-0.03; 0.09)	31
		Nausea	48/48	31/173 23/167	18/14	1.30 (0.79; 2.14)	0.04 (-0.04; 0.12)	24
		Diarrhea	48/48	25/173 13/167	14/8	1.86 (0.98; 3.51)	**0.07 (0.00; 0.13)**	15
		Dyspepsia	48/48	19/173 14/167	11/8	1.31 (0.68; 2.53)	0.03 (-0.04; 0.09)	38
		Flatulence	48/48	18/173 10/167	10/6	1.74 (0.83; 3.65)	0.04 (-0.01; 0.10)	23
		Anorexia	48/48	18/173 9/167	10/5	1.93 (0.89; 4.18)	0.05 (-0.01; 0.11)	20
		Dizziness	48/48	18/173 13/167	10/8	1.34 (0.68; 2.64)	0.03 (-0.03; 0.09)	38

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Pharyngitis	48/48	70/173 54/167	40/32	1.25 (0.94; 1.66)	0.08 (-0.02; 0.18)	12
		Increased cough	48/48	19/173 21/167	11/13	0.87 (0.49; 1.56)	-0.02 (-0.08; 0.05)	-63
Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	Histological improvement was defined as a decrease of at least 2 points in the Knodell necroinflammatory score from baseline to week 48, with no concurrent worsening of the Knodell fibrosis score	48/48	89/171 98/173	52/57	0.92 (0.76; 1.12)	-0.05 (-0.15; 0.06)	-22
Adefovir dipivoxil, 10 mg/day, 48 weeks	Placebo, 48 weeks		48/48	89/171 41/167	52/25	2.12 (1.57; 2.87)	**0.27 (0.18; 0.37)**	4
Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks		48/48	96/173 41/167	55/25	2.26 (1.68; 3.04)	**0.31 (0.21; 0.41)**	3
Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	No histological improvement	48/48	61/171 47/173	36/27	1.31 (0.96; 1.80)	**0.09 (-0.01; 0.18)**	12
Adefovir dipivoxil, 10 mg/day, 48 weeks	Placebo, 48 weeks	No histological improvement	48/48	61/171 105/167	36/63	0.57 (0.45; 0.72)	**-0.27 (-0.37; -0.17)**	-4
Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	No histological improvement	48/48	47/173 105/167	27/63	0.43 (0.33; 0.57)	**-0.36 (-0.46; -0.26)**	-3
Adefovir dipivoxil, 10 mg/day, 48 weeks	Placebo, 48 weeks	Relative risk of histological improvement defined as a decrease of at least 2 points in the Knodell necroinflammatory score from baseline to week 48, with no concurrent	48/48	0/171 0/167		**2.10 (1.60; 2.80)**		
Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks		48/48	0/173 0/167		**2.30 (1.70; 3.10)**		

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		worsening of the Knodell fibrosis score adjusted for 7 locations (countries)						
Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	Change in Knodell necroinflammatory activity scores	48/48	107/171 112/173	63/65	0.97 (0.82; 1.13)	-0.02 (-0.12; 0.08)	-46
		No change in Knodell necroinflammatory activity scores	48/48	23/171 18/173	13/10	1.29 (0.72; 2.31)	0.03 (-0.04; 0.10)	33
		Worse Knodell necroinflammatory activity scores	48/48	20/171 15/173	12/9	1.35 (0.71; 2.55)	0.03 (-0.03; 0.09)	33
	Placebo, 48 weeks	Change in Knodell necroinflammatory activity scores	48/48	107/171 59/167	63/35	1.77 (1.40; 2.24)	**0.27 (0.17; 0.37)**	4
		No change in Knodell necroinflammatory activity scores	48/48	23/171 37/167	13/22	0.61 (0.38; 0.98)	**-0.09 (-0.17; -0.01)**	-11
		Worse Knodell necroinflammatory activity scores	48/48	20/171 49/167	12/29	0.40 (0.25; 0.64)	**-0.18 (-0.26; -0.09)**	-6
Marcellin, 2003[42] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Change in Knodell necroinflammatory activity scores	48/48	112/173 59/167	65/35	1.83 (1.45; 2.31)	**0.29 (0.19; 0.40)**	3
		No change in Knodell necroinflammatory activity scores	48/48	18/173 37/167	10/22	0.47 (0.28; 0.79)	**-0.12 (-0.20; -0.04)**	-9
		Worse Knodell necroinflammatory activity scores	48/48	15/173 49/167	9/29	0.30 (0.17; 0.51)	**-0.21 (-0.29; -0.13)**	-5

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Marcellin, 2003[42] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	Change in Knodell fibrosis scores	48/48	62/171 78/173	36/45	0.80 (0.62; 1.04)	-0.09 (-0.19; 0.02)	-11
		No change in Knodell fibrosis scores	48/48	67/171 53/173	39/31	1.28 (0.96; 1.71)	0.09 (-0.01; 0.19)	12
		Worse Knodell fibrosis scores	48/48	21/171 14/173	12/8	1.52 (0.80; 2.88)	0.04 (-0.02; 0.11)	24
	Placebo, 48 weeks	Change in Knodell fibrosis scores	48/48	62/171 35/167	36/21	1.73 (1.21; 2.47)	**0.15 (0.06; 0.25)**	7
		No change in Knodell fibrosis scores	48/48	67/171 72/167	39/43	0.91 (0.70; 1.17)	-0.04 (-0.14; 0.07)	-25
		Worse Knodell fibrosis scores	48/48	21/171 38/167	12/23	0.54 (0.33; 0.88)	**-0.10 (-0.19; -0.02)**	-10
Marcellin, 2003[42] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Change in Knodell fibrosis scores	48/48	78/173 35/167	45/21	2.15 (1.54; 3.01)	**0.24 (0.14; 0.34)**	4
		No change in Knodell fibrosis scores	48/48	53/173 72/167	31/43	0.71 (0.53; 0.94)	**-0.12 (-0.23; -0.02)**	-8
		Worse Knodell Fibrosis scores	48/48	14/173 38/167	8/23	0.36 (0.20; 0.63)	**-0.15 (-0.22; -0.07)**	-7
Marcellin, 2003[42] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	HBV DNA <400 copies/ml	48/48	36/171 67/173	21/39	0.54 (0.38; 0.77)	**-0.18 (-0.27; -0.08)**	-6
	Placebo, 48 weeks	HBV DNA <400 copies/ml	48/48	36/171 0/167	21/0	71.30 (4.41; 1152.34)	**0.21 (0.15; 0.27)**	5
Marcellin, 2003[42] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	HBV DNA <400 copies/ml	48/48	67/173 0/167	39/0	130.34 (8.14; 2088.39)	**0.39 (0.31; 0.46)**	3
Marcellin, 2003[42] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	HBeAg seroconversion	48/48	20/171 23/173	12/13	0.88 (0.50; 1.54)	-0.02 (-0.09; 0.05)	-63
	Placebo, 48 weeks	HBeAg seroconversion	48/48	20/171 9/167	12/5	2.17 (1.02; 4.63)	**0.06 (0.00; 0.12)**	16

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Marcellin, 2003[42] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	HBeAg seroconversion	48/48	23/173 9/167	13/5	2.47 (1.18; 5.17)	**0.08 (0.02; 0.14)**	13
Marcellin, 2003[42] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	HBeAg loss	48/48	41/171 44/173	24/25	0.94 (0.65; 1.36)	-0.01 (-0.11; 0.08)	-69
	Placebo, 48 weeks	HBeAg loss	48/48	41/171 17/167	24/10	2.36 (1.40; 3.98)	**0.14 (0.06; 0.22)**	7
Marcellin, 2003[42] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	HBeAg loss	48/48	44/173 17/167	25/10	2.50 (1.49; 4.19)	**0.15 (0.07; 0.23)**	7
Westland, 2003[100] Adefovir dipivoxil, 20 mg/day (10 or 30 mg), 48 weeks	Placebo, 48 weeks	Emerging amino acid substitutions in the HBV-RT domain	48/48	130/467 137/228	28/60	0.46 (0.39; 0.55)	**-0.32 (-0.40; -0.25)**	-3
		Amino acid substitutions rt221Y	48/48	1/467 7/228	0/3	0.07 (0.01; 0.56)	**-0.03 (-0.05; -0.01)**	-35
		Amino acid substitutions rt134D	48/48	4/467 2/228	1/1	0.98 (0.18; 5.29)	0.00 (-0.01; 0.01)	-4840
		Amino acid substitutions rt219A	48/48	3/467 3/228	1/1	0.49 (0.10; 2.40)	-0.01 (-0.02; 0.01)	-149
		Amino acid substitutions rt91I	48/48	1/467 4/228	0/2	0.12 (0.01; 1.09)	-0.02 (-0.03; 0.00)	-65
		Amino acid substitutions rt134N	48/48	1/467 4/228	0/2	0.12 (0.01; 1.09)	-0.02 (-0.03; 0.00)	-65
		Amino acid substitutions rt54H	48/48	3/467 1/228	1/0	1.46 (0.15; 14.00)	0.00 (-0.01; 0.01)	491
		Amino acid substitutions rt145M	48/48	0/467 4/228	0/2	0.05 (0.00; 1.01)	-0.02 (-0.04; 0.00)	-57
		Substitutions emerged at conserved sites in the HBV polymerase/RT	48/48	4/467 6/228	1/3	0.33 (0.09; 1.14)	-0.02 (-0.04; 0.00)	-56

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Unconfirmed (i.e., occurring at one visit only) 1.0 log10 or greater increase in serum HBV-DNA level	48/48	24/467 63/228	5/28	0.19 (0.12; 0.29)	**-0.22 (-0.29; -0.16)**	-4
Perrillo, 2004[58] Adefovir dipivoxil, 10 mg/day for 52 weeks Lamivudine, 100mg/day for at least 6 months, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	Normalization ALT	52/52	14/46 3/49	30/6	4.97 (1.53; 16.18)	**0.24 (0.09; 0.39)**	4
	Lamivudine, 100 mg/day, 52 weeks	At least 1 adverse event	52/52	36/46 40/49	78/82	0.96 (0.78; 1.17)	-0.03 (-0.19; 0.13)	-30
	Lamivudine, 100 mg/day, 52 weeks	HBV DNA level <10 in 5 degree copies/ mL or a 2 log10 copies/mL reduction from baseline HBV DNA	52/52	39/46 5/49	85/10	8.31 (3.59; 19.24)	**0.75 (0.61; 0.88)**	1
		HBV DNA negative by polymerase chain reaction (200 copies/ml)	52/52	9/46 0/49	20/0	20.21 (1.21; 337.68)	**0.20 (0.08; 0.31)**	5
		HBeAg loss	52/52	6/46 1/49	13/2	6.39 (0.80; 51.08)	**0.11 (0.00; 0.22)**	9
		Detectable YMDD mutant	52/52	26/46 44/49	57/90	0.63 (0.48; 0.82)	**-0.33 (-0.50; -0.17)**	-3
		HBV DNA negative (<500 copies/ml)	52/52	14/46 2/49	30/4	7.46 (1.79; 31.03)	**0.26 (0.12; 0.41)**	4
		Wild type mutation	52/52	2/46 0/49	4/0	5.32 (0.26; 107.93)	0.04 (-0.03; 0.11)	23
		HBeAg seroconversion	52/52	3/46 1/49	7/2	3.20 (0.34; 29.63)	0.04 (-0.04; 0.13)	22
Peters, 2004[43] Adefovir dipivoxil, 10 mg/day Lamivudine, 100mg/day for 48 weeks	Lamivudine, 100 mg/day, 48 weeks	Normalization ALT	48/48	10/20 1/19	50/5	9.50 (1.34; 67.27)	**0.45 (0.21; 0.69)**	2
	Adefovir dipivoxil, 10 mg/day, 48 weeks	Normalization ALT	48/48	10/20 9/19	50/47	1.06 (0.55; 2.01)	0.03 (-0.29; 0.34)	38

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	Lamivudine, 100 mg/day, 48 weeks	Any adverse event	48/48	18/20 19/19	90/100	0.90 (0.76; 1.07)	-0.10 (-0.25; 0.05)	-10
		Asthenia	48/48	10/20 6/19	50/32	1.58 (0.72; 3.50)	0.18 (-0.12; 0.49)	5
		Headache	48/48	6/20 5/19	30/26	1.14 (0.42; 3.12)	0.04 (-0.25; 0.32)	27
		Pharyngitis	48/48	1/20 6/19	5/32	0.16 (0.02; 1.20)	**-0.27 (-0.50; -0.04)**	-4
		Abdominal pain	48/48	6/20 5/19	30/26	1.14 (0.42; 3.12)	0.04 (-0.25; 0.32)	27
		Insomnia	48/48	0/20 2/19	0/11	0.19 (0.01; 3.73)	-0.11 (-0.26; 0.05)	-9
		Rash	48/48	0/20 4/19	0/21	0.11 (0.01; 1.84)	**-0.21 (-0.40; -0.02)**	-5
		Fever	48/48	0/20 1/19	0/5	0.32 (0.01; 7.35)	-0.05 (-0.19; 0.08)	-19
		Sinusitis	48/48	1/20 5/19	5/26	0.19 (0.02; 1.48)	-0.21 (-0.43; 0.01)	-5
		Arthralgia	48/48	1/20 3/19	5/16	0.32 (0.04; 2.79)	-0.11 (-0.30; 0.08)	-9
		Back pain	48/48	3/20 3/19	15/16	0.95 (0.22; 4.14)	-0.01 (-0.23; 0.22)	-127
		Increased cough	48/48	0/20 3/19	0/16	0.14 (0.01; 2.47)	-0.16 (-0.34; 0.02)	-6
		Nausea	48/48	4/20 1/19	20/5	3.80 (0.47; 31.01)	0.15 (-0.05; 0.35)	7
		Pain	48/48	4/20 4/19	20/21	0.95 (0.28; 3.27)	-0.01 (-0.26; 0.24)	-95
		Diarrhea	48/48	2/20 6/19	10/32	0.32 (0.07; 1.38)	-0.22 (-0.46; 0.03)	-5
		Gastroenteritis	48/48	0/20 3/19	0/16	0.14 (0.01; 2.47)	-0.16 (-0.34; 0.02)	-6
		Infection	48/48	3/20 1/19	15/5	2.85 (0.32; 25.07)	0.10 (-0.09; 0.28)	10

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Rhinitis	48/48	2/20 5/19	10/26	0.38 (0.08; 1.73)	-0.16 (-0.40; 0.07)	-6
		Bacterial infection	48/48	3/20 0/19	15/0	6.67 (0.37; 121.07)	0.15 (-0.02; 0.32)	7
	Adefovir dipivoxil, 10 mg/day, 48 weeks	Any adverse event	48/48	18/20 18/19	90/95	0.95 (0.79; 1.14)	-0.05 (-0.21; 0.12)	-21
		Asthenia	48/48	10/20 9/19	50/47	1.06 (0.55; 2.01)	0.03 (-0.29; 0.34)	38
		Headache	48/48	6/20 5/19	30/26	1.14 (0.42; 3.12)	0.04 (-0.25; 0.32)	27
		Pharyngitis	48/48	1/20 5/19	5/26	0.19 (0.02; 1.48)	-0.21 (-0.43; 0.01)	-5
		Abdominal pain	48/48	6/20 4/19	30/21	1.43 (0.48; 4.27)	0.09 (-0.18; 0.36)	11
		Insomnia	48/48	0/20 4/19	0/21	0.11 (0.01; 1.84)	**-0.21 (-0.40; -0.02)**	-5
		Rash	48/48	0/20 4/19	0/21	0.11 (0.01; 1.84)	**-0.21 (-0.40; -0.02)**	-5
		Fever	48/48	0/20 3/19	0/16	0.14 (0.01; 2.47)	-0.16 (-0.34; 0.02)	-6
		Sinusitis	48/48	1/20 3/19	5/16	0.32 (0.04; 2.79)	-0.11 (-0.30; 0.08)	-9
		Arthralgia	48/48	1/20 2/19	5/11	0.48 (0.05; 4.82)	-0.06 (-0.22; 0.11)	-18
		Back pain	48/48	3/20 2/19	15/11	1.43 (0.27; 7.61)	0.04 (-0.16; 0.25)	22
		Increased cough	48/48	0/20 2/19	0/11	0.19 (0.01; 3.73)	-0.11 (-0.26; 0.05)	-9
		Nausea	48/48	4/20 2/19	20/11	1.90 (0.39; 9.20)	0.09 (-0.13; 0.32)	11
		Pain	48/48	4/20 2/19	20/11	1.90 (0.39; 9.20)	0.09 (-0.13; 0.32)	11
		Diarrhea	48/48	2/20 1/19	10/5	1.90 (0.19; 19.27)	0.05 (-0.12; 0.21)	21

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Gastroenteritis	48/48	0/20 1/19	0/5	0.32 (0.01; 7.35)	-0.05 (-0.19; 0.08)	-19
		Infection	48/48	3/20 1/19	15/5	2.85 (0.32; 25.07)	0.10 (-0.09; 0.28)	10
		Rhinitis	48/48	2/20 1/19	10/5	1.90 (0.19; 19.27)	0.05 (-0.12; 0.21)	21
		Bacterial infection	48/48	3/20 0/19	15/0	6.67 (0.37; 121.07)	0.15 (-0.02; 0.32)	7
	Lamivudine, 100 mg/day, 48 weeks	ALT Grade 3 (>5-10 times the ULN)	48/48	1/20 0/19	5/0	2.86 (0.12; 66.11)	0.05 (-0.08; 0.18)	20
		ALT Grade 4 >10 times the ULN)	48/48	1/20 3/19	5/16	0.32 (0.04; 2.79)	-0.11 (-0.30; 0.08)	-9
		AST Grade3 (>5-10 times the ULN)	48/48	0/20 1/19	0/5	0.32 (0.01; 7.35)	-0.05 (-0.19; 0.08)	-19
		Grade4 (>10 times the ULN)	48/48	0/20 2/19	0/11	0.19 (0.01; 3.73)	-0.11 (-0.26; 0.05)	-9
		Amylase Grade3 (>2-5 times the ULN)	48/48	2/20 3/19	10/16	0.63 (0.12; 3.38)	-0.06 (-0.27; 0.15)	-17
		Grade4 (5 times the ULN)	48/48	0/20 0/19			0.00 (-0.09; 0.09)	
		Serum glucose Grade3 (30-39 mg/dL; 251-500 mg/dL)	48/48	1/20 3/19	5/16	0.32 (0.04; 2.79)	-0.11 (-0.30; 0.08)	-9
		Grade4 (>30 mg/dL; <500 mg/dL)	48/48	0/20 0/19			0.00 (-0.09; 0.09)	
		Urine Glucose Grade3 (3+)	48/48	1/20 4/19	5/21	0.24 (0.03; 1.94)	-0.16 (-0.37; 0.05)	-6
		Grade4 (4+)	48/48	0/20 0/19			**0.00 (-0.09; 0.09)**	
	Adefovir dipivoxil, 10 mg/day, 48	ALT Grade 3 (>5-10 times the ULN)	48/48	1/20 7/19	5/37	0.14 (0.02; 1.00)	**-0.32 (-0.56; -0.08)**	-3

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	weeks	ALT Grade 4 >10 times the ULN)	48/48	1/20 0/19	5/0	2.86 (0.12; 66.11)	0.05 (-0.08; 0.18)	20
		AST Grade 3 (>5-10 times the ULN)	48/48	0/20 1/19	0/5	0.32 (0.01; 7.35)	-0.05 (-0.19; 0.08)	-19
		Grade 4 (>10 times the ULN)	48/48	0/20 0/19			0.00 (-0.09; 0.09)	
		Amylase Grade 3 (>2-5 times the ULN)	48/48	2/20 0/19	10/0	4.76 (0.24; 93.19)	0.10 (-0.05; 0.25)	10
		Grade 4 (5 times the ULN)	48/48	0/20 0/19			0.00 (-0.09; 0.09)	
		Serum Glucose Grade 3 (30-39mg/dL; 251-500 mg/dL)	48/48	1/20 2/19	5/11	0.48 (0.05; 4.82)	-0.06 (-0.22; 0.11)	-18
		Grade 4 (>30mg/dL; <500 mg/dL)	48/48	0/20 0/19			0.00 (-0.09; 0.09)	
		Urine Glucose Grade3 (3+)	48/48	1/20 2/19	5/11	0.48 (0.05; 4.82)	-0.06 (-0.22; 0.11)	-18
		Grade4 (4+)	48/48	0/20 0/19			0.00 (-0.09; 0.09)	
	Lamivudine, 100 mg/day, 48 weeks	HBV DNA undetectable	48/48	7/20 0/19	35/0	14.29 (0.87; 234.09)	**0.35 (0.13; 0.57)**	3
	Adefovir dipivoxil, 10 mg/day, 48 weeks	HBV DNA undetectable	48/48	7/20 5/19	35/26	1.33 (0.51; 3.48)	0.09 (-0.20; 0.37)	12
	Lamivudine, 100 mg/day, 48 weeks	HBeAg loss	48/48	3/20 0/19	15/0	6.67 (0.37; 121.07)	0.15 (-0.02; 0.32)	7
	Adefovir dipivoxil, 10 mg/day, 48 weeks	HBeAg loss	48/48	3/20 3/19	15/16	0.95 (0.22; 4.14)	-0.01 (-0.23; 0.22)	-127
	Lamivudine, 100 mg/day, 48 weeks	HBeAg seroconversion	48/48	1/20 0/19	5/0	2.86 (0.12; 66.11)	0.05 (-0.08; 0.18)	20

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	Adefovir dipivoxil, 10 mg/day, 48 weeks	HBeAg seroconversion	48/48	1/20 2/19	5/11	0.48 (0.05; 4.82)	-0.06 (-0.22; 0.11)	-18
	Lamivudine, 100 mg/day, 48 weeks	HBsAg negative	48/48	1/20 0/19	5/0	2.86 (0.12; 66.11)	0.05 (-0.08; 0.18)	20
	Adefovir dipivoxil, 10 mg/day, 48 weeks	HBsAg negative	48/48	1/20 0/19	5/0	2.86 (0.12; 66.11)	0.05 (-0.08; 0.18)	20
Izzedine, 2004[99] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	Hypophosphatemia mg/dL (2.0-2.2)	48/48	6/171 15/173	4/9	0.40 (0.16; 1.02)	-0.05 (-0.10; 0.00)	-19
		Hypophosphatemia mg/dL (1.5-<2.0)	48/48	4/171 21/173	2/12	0.19 (0.07; 0.55)	**-0.10 (-0.15; -0.04)**	-10
		Hypophosphatemia mg/dL (1.0-1.5)	48/48	1/171 5/173	1/3	0.20 (0.02; 1.71)	-0.02 (-0.05; 0.00)	-43
		Hypophosphatemia mg/dL (<1.0)	48/48	0/171 1/173	0/1	0.34 (0.01; 8.22)	-0.01 (-0.02; 0.01)	-173
	Placebo, 48 weeks	Hypophosphatemia mg/dL (2.0-2.2)	48/48	6/171 8/167	4/5	0.73 (0.26; 2.07)	-0.01 (-0.06; 0.03)	-78
		Hypophosphatemia mg/dL (1.5-<2.0)	48/48	4/171 9/167	2/5	0.43 (0.14; 1.38)	-0.03 (-0.07; 0.01)	-33
		Hypophosphatemia mg/dL (1.0-1.5)	48/48	1/171 0/167	1/0	2.93 (0.12; 71.42)	0.01 (-0.01; 0.02)	171
		Hypophosphatemia mg/dL (<1.0)	48/48	0/171 0/167			0.00 (-0.01; 0.01)	
Izzedine, 2004[99] Adefovir dipivoxil, 30 mg/day, 48 weeks	placebo, 48 weeks	Hypophosphatemia mg/dL (2.0-2.2)	48/48	15/173 8/167	9/5	1.81 (0.79; 4.16)	0.04 (-0.01; 0.09)	26
		Hypophosphatemia mg/dL (1.5-<2.0)	48/48	21/173 9/167	12/5	2.25 (1.06; 4.77)	**0.07 (0.01; 0.13)**	15
		Hypophosphatemia mg/dL (1.0-1.5)	48/48	5/173 0/167	3/0	10.62 (0.59; 190.58)	**0.03 (0.00; 0.06)**	35
		Hypophosphatemia mg/dL (<1.0)	48/48	1/173 0/167	1/0	2.90 (0.12; 70.60)	0.01 (-0.01; 0.02)	173
Izzedine, 2004[99] Adefovir dipivoxil, 10	Adefovir dipivoxil, 30 mg/day, 48	Creatinine mg/dL (1.5-2.0)	48/48	2/171 17/173	1/10	0.12 (0.03; 0.51)	-**0.09 (-0.13; -0.04)**	-12

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
mg/day, 48 weeks	weeks	Creatinine mg/dL (>2.0-3.0)	48/48	0/171 0/173			0.00 (-0.01; 0.01)	
		Creatinine mg/dL (>3.0-6.0)	48/48	0/171 0/173			0.00 (-0.01; 0.01)	
		Creatinine mg/dL (>6.0)-	48/48	0/171 0/173			0.00 (-0.01; 0.01)	
	Placebo, 48 weeks	Creatinine mg/dL (1.5-2.0)	48/48	2/171 0/167	1/0	4.88 (0.24; 100.97)	0.01 (-0.01; 0.03)	86
		Creatinine mg/dL (>2.0-3.0)	48/48	0/171 0/167			0.00 (-0.01; 0.01)	
		Creatinine mg/dL (>3.0-6.0)	48/48	0/171 0/167			0.00 (-0.01; 0.01)	
		Creatinine mg/dL (>6.0)-	48/48	0/171 0/167			0.00 (-0.01; 0.01)	
Izzedine, 2004[99] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo,48 weeks	Creatinine mg/dL (1.5-2.0)	48/48	17/173 0/167	10/0	33.79 (2.05; 557.45)	**0.10 (0.05; 0.14)**	10
		Creatinine mg/dL (>2.0-3.0)	48/48	0/173 0/167			0.00 (-0.01; 0.01)	
		Creatinine mg/dL (>3.0-6.0)	48/48	0/173 0/167			0.00 (-0.01; 0.01)	
		Creatinine mg/dL (>6.0)-	48/48	0/173 0/167			0.00 (-0.01; 0.01)	
Izzedine, 2004[99] Adefovir dipivoxil, 10 mg/day, 48 weeks	Placebo, 48 weeks	Hypophosphatemia mg/dL (2.0-2.2)	48/48	6/171 1/167	4/1	5.86 (0.71; 48.15)	**0.03 (0.00; 0.06)**	34
		Hypophosphatemia mg/dL (1.5-<2.0)	48/48	4/171 1/167	2/1	3.91 (0.44; 34.59)	0.02 (-0.01; 0.04)	57
		Hypophosphatemia mg/dL (1.0-1.5)	48/48	0/171 0/167			0.00 (-0.01; 0.01)	
		Hypophosphatemia mg/dL (<1.0)	48/48	0/171 0/167			0.00 (-0.01; 0.01)	
		Creatinine mg/dL (1.5-2.0)	48/48	1/171 0/167	1/0	2.93 (0.12; 71.42)	0.01 (-0.01; 0.02)	171
		Creatinine mg/dL (>2.0-3.0)	48/48	0/171 0/167			0.00 (-0.01; 0.01)	

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Creatinine mg/dL (>3.0-6.0)	48/48	0/171 0/167			0.00 (-0.01; 0.01)	
		Creatinine mg/dL (>6.0)-	48/48	0/171 0/167			0.00 (-0.01; 0.01)	
	Adefovir dipivoxil, 30 mg/day, 48 weeks	Dose reduced due to an adverse event or abnormal laboratory result	48/48	5/171 42/173	3/24	0.12 (0.05; 0.30)	**-0.21 (-0.28; -0.14)**	-5
	Placebo, 48 weeks	Dose reduced due to an adverse event or abnormal laboratory result	48/48	5/171 2/167	3/1	2.44 (0.48; 12.41)	0.02 (-0.01; 0.05)	58
Izzedine, 2004[99] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Dose reduced due to an adverse event or abnormal laboratory result	48/48	42/173 2/167	24/1	20.27 (4.99; 82.41)	**0.23 (0.16; 0.30)**	4
Izzedine, 2004[99] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	Hematuria <10 RBCs	48/48	11/171 21/173	6/12	0.53 (0.26; 1.07)	-0.06 (-0.12; 0.00)	-18
		Hematuria 10-100 RBCs	48/48	18/171 29/173	11/17	0.63 (0.36; 1.09)	-0.06 (-0.13; 0.01)	-16
		Hematuria >100 RBCs	48/48	21/171 23/173	12/13	0.92 (0.53; 1.61)	-0.01 (-0.08; 0.06)	-99
		Hematuria obstructive or Rx required	48/48	0/171 0/173			0.00 (-0.01; 0.01)	
	Placebo, 48 weeks	Hematuria <10 RBCs	48/48	11/171 11/167	6/7	0.98 (0.44; 2.19)	0.00 (-0.05; 0.05)	-649
		Hematuria 10-100 RBCs	48/48	18/171 17/167	11/10	1.03 (0.55; 1.94)	0.00 (-0.06; 0.07)	288
		Hematuria >100 RBCs	48/48	21/171 21/167	12/13	0.98 (0.55; 1.72)	0.00 (-0.07; 0.07)	-340
		Hematuria obstructive or Rx required	48/48	0/171 0/167			0.00 (-0.01; 0.01)	

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Izzedine, 2004[99] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Hematuria <10 RBCs	48/48	21/173 11/167	12/7	1.84 (0.92; 3.70)	0.06 (-0.01; 0.12)	18
		Hematuria 10-100 RBCs	48/48	29/173 17/167	17/10	1.65 (0.94; 2.88)	0.07 (-0.01; 0.14)	15
		Hematuria >100 RBCs	48/48	23/173 21/167	13/13	1.06 (0.61; 1.84)	0.01 (-0.06; 0.08)	139
		Hematuria obstruc-tive or Rx required	48/48	0/173 0/167			0.00 (-0.01; 0.01)	
Izzedine, 2004[99] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	Glycosuria (+1)	48/48	1/171 3/173	½	0.34 (0.04; 3.21)	-0.01 (-0.03; 0.01)	-87
		Glycosuria (+2)	48/48	1/171 3/173	1/2	0.34 (0.04; 3.21)	-0.01 (-0.03; 0.01)	-87
		Glycosuria (+3)	48/48	1/171 2/173	1/1	0.51 (0.05; 5.53)	-0.01 (-0.03; 0.01)	-175
		Glycosuria (+4)	48/48	0/171 0/173			0.00 (-0.01; 0.01)	
	Placebo, 48 weeks	Glycosuria (+1)	48/48	1/171 5/167	1/3	0.20 (0.02; 1.65)	-0.02 (-0.05; 0.00)	-42
		Glycosuria (+2)	48/48	1/171 3/167	1/2	0.33 (0.03; 3.10)	-0.01 (-0.04; 0.01)	-83
		Glycosuria (+3)	48/48	1/171 5/167	1/3	0.20 (0.02; 1.65)	-0.02 (-0.05; 0.00)	-42
		Glycosuria (+4)	48/48	0/171 0/167			0.00 (-0.01; 0.01)	
Izzedine, 2004[99] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Glycosuria (+1)	48/48	3/173 5/167	2/3	0.58 (0.14; 2.39)	-0.01 (-0.04; 0.02)	-79
		Glycosuria (+2)	48/48	3/173 3/167	2/2	0.97 (0.20; 4.72)	0.00 (-0.03; 0.03)	-1605
		Glycosuria (+3)	48/48	2/173 5/167	1/3	0.39 (0.08; 1.96)	-0.02 (-0.05; 0.01)	-54
		Glycosuria (+4)	48/48	0/173 0/167			0.00 (-0.01; 0.01)	
Izzedine, 2004[99] Adefovir dipivoxil, 10	Adefovir dipivoxil, 30 mg/day, 48	Proteinuria mg/dL (<100)	48/48	24/171 38/173	14/22	0.64 (0.40; 1.02)	-0.08 (-0.16; 0.00)	-13

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
mg/day, 48 weeks	weeks	Proteinuria mg/dL (100–1000)	48/48	10/171 23/173	6/13	0.44 (0.22; 0.90)	**-0.07 (-0.14; -0.01)**	-13
		Proteinuria mg/dL (>1000)	48/48	0/171 0/173			0.00 (-0.01; 0.01)	
		Proteinuria mg/dL (nephrotic syndrome)	48/48	0/171 0/173			0.00 (-0.01; 0.01)	
	Placebo, 48 weeks	Proteinuria mg/dL (<100)	48/48	24/171 17/167	14/10	1.38 (0.77; 2.47)	0.04 (-0.03; 0.11)	26
		Proteinuria mg/dL (100–1000)	48/48	10/171 11/167	6/7	0.89 (0.39; 2.03)	-0.01 (-0.06; 0.04)	-135
		Proteinuria mg/dL (>1000)	48/48	0/171 0/167			0.00 (-0.01; 0.01)	
		Proteinuria mg/dL (nephrotic syndrome)	48/48	0/171 0/167			0.00 (-0.01; 0.01)	
Izzedine, 2004[99] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	Proteinuria mg/dL (<100)	48/48	38/173 17/167	22/10	2.16 (1.27; 3.67)	**0.12 (0.04; 0.19)**	8
		Proteinuria mg/dL (100–1000)	48/48	23/173 11/167	13/7	2.02 (1.02; 4.01)	**0.07 (0.00; 0.13)**	15
		Proteinuria mg/dL (>1000)	48/48	0/173 0/167			0.00 (-0.01; 0.01)	
		Proteinuria mg/dL (nephrotic syndrome	48/48	0/173 0/167			0.00 (-0.01; 0.01)	
Hadziyannis, 2005[98] Adefovir dipivoxil, 10mg daily ,continued adefovir therapy of the previous treatment for 48 weeks, total 96 weeks	Placebo after 48 weeks of adefovir therapy, 96 weeks	Normalization of ALT	96/96	47/80 12/40	59/30	1.96 (1.18; 3.25)	**0.29 (0.11; 0.47)**	3
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Normalization of ALT	96/96	47/80 40/60	59/67	0.88 (0.68; 1.14)	-0.08 (-0.24; 0.08)	-13
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Normalization of ALT	114/96	43/80 12/40	54/30	1.79 (1.07; 3.00)	**0.24 (0.06; 0.42)**	4

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	Adefovir dipivoxil, 10 mg daily after 48 weeks of placebo therapy , 96 weeks	Normalization of ALT	114/96	43/80 40/60	54/67	0.81 (0.61; 1.06)	-0.13 (-0.29; 0.03)	-8
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Any adverse events	96/96	58/80 32/40	72/80	0.91 (0.74; 1.11)	-0.08 (-0.23; 0.08)	-13
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Any adverse events	96/96	58/80 41/60	72/68	1.06 (0.85; 1.32)	0.04 (-0.11; 0.19)	24
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Any adverse events	114/96	60/80 32/40	75/80	0.94 (0.77; 1.15)	-0.05 (-0.21; 0.11)	-20
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Any adverse events	114/96	60/80 41/60	75/68	1.10 (0.89; 1.36)	0.07 (-0.08; 0.22)	15
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Headache	96/96	12/80 4/40	15/10	1.50 (0.52; 4.36)	0.05 (-0.07; 0.17)	20
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Abdominal pain	96/96	16/80 7/40	20/18	1.14 (0.51; 2.55)	0.03 (-0.12; 0.17)	40
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Asthenia	96/96	8/80 6/40	10/15	0.67 (0.25; 1.79)	-0.05 (-0.18; 0.08)	-20
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Flu-like syndrome	96/96	6/80 4/40	8/10	0.75 (0.22; 2.51)	-0.03 (-0.13; 0.08)	-40
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Back pain	96/96	4/80 5/40	5/12	0.40 (0.11; 1.41)	-0.08 (-0.19; 0.04)	-13

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Pain	96/96	4/80 2/40	5/5	1.00 (0.19; 5.23)	0.00 (-0.08; 0.08)	
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Accidental injury	96/96	4/80 2/40	5/5	1.00 (0.19; 5.23)	0.00 (-0.08; 0.08)	
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Headache	96/96	12/80 5/60	15/8	1.80 (0.67; 4.84)	0.07 (-0.04; 0.17)	15
		Abdominal pain	96/96	16/80 5/60	20/8	2.40 (0.93; 6.19)	**0.12 (0.00; 0.23)**	9
		Asthenia	96/96	8/80 3/60	10/5	2.00 (0.55; 7.22)	0.05 (-0.04; 0.14)	20
		Flu-like syndrome	96/96	6/80 5/60	8/8	0.90 (0.29; 2.81)	-0.01 (-0.10; 0.08)	-120
		Back pain	96/96	4/80 3/60	5/5	1.00 (0.23; 4.30)	0.00 (-0.07; 0.07)	
		Pain	96/96	4/80 4/60	5/7	0.75 (0.20; 2.88)	-0.02 (-0.10; 0.06)	-60
		Accidental injury	96/96	4/80 2/60	5/3	1.50 (0.28; 7.92)	0.02 (-0.05; 0.08)	60
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Headache	114/96	19/80 4/40	24/10	2.38 (0.87; 6.52)	**0.14 (0.01; 0.27)**	7
		Abdominal pain	114/96	20/80 7/40	25/18	1.43 (0.66; 3.09)	0.08 (-0.08; 0.23)	13
		Asthenia	114/96	15/80 6/40	19/15	1.25 (0.53; 2.98)	0.04 (-0.10; 0.18)	27
		Flu-like syndrome	114/96	14/80 4/40	18/10	1.75 (0.62; 4.97)	0.08 (-0.05; 0.20)	13
		Back pain	114/96	9/80 5/40	11/12	0.90 (0.32; 2.51)	-0.01 (-0.14; 0.11)	-80
		Pain	114/96	12/80 2/40	15/5	3.00 (0.71; 12.76)	**0.10 (0.00; 0.20)**	10
		Accidental injury	114/96	8/80 2/40	10/5	2.00 (0.45; 8.98)	0.05 (-0.04; 0.14)	20

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Headache	114/96	19/80 5/60	24/8	2.85 (1.13; 7.20)	**0.15 (0.04; 0.27)**	6
		Abdominal pain	114/96	20/80 5/60	25/8	3.00 (1.19; 7.54)	**0.17 (0.05; 0.28)**	6
		Asthenia	114/96	15/80 3/60	19/5	3.75 (1.14; 12.37)	**0.14 (0.04; 0.24)**	7
		Flu-like syndrome	114/96	14/80 5/60	18/8	2.10 (0.80; 5.51)	0.09 (-0.02; 0.20)	11
		Back pain	114/96	9/80 3/60	11/5	2.25 (0.64; 7.96)	0.06 (-0.03; 0.15)	16
		Pain	114/96	12/80 4/60	15/7	2.25 (0.76; 6.63)	0.08 (-0.02; 0.18)	12
		Accidental injury	114/96	8/80 2/60	10/3	3.00 (0.66; 13.62)	0.07 (-0.01; 0.15)	15
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Diarrhea	96/96	6/80 4/40	8/10	0.75 (0.22; 2.51)	-0.03 (-0.13; 0.08)	-40
		Dyspepsia	96/96	4/80 5/40	5/12	0.40 (0.11; 1.41)	-0.08 (-0.19; 0.04)	-13
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Diarrhea	96/96	6/80 1/60	8/2	4.50 (0.56; 36.40)	0.06 (-0.01; 0.12)	17
		Dyspepsia	96/96	4/80 1/60	5/2	3.00 (0.34; 26.16)	0.03 (-0.02; 0.09)	30
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Diarrhea	114/96	6/80 4/40	8/10	0.75 (0.22; 2.51)	-0.03 (-0.13; 0.08)	-40
		Dyspepsia	114/96	7/80 5/40	9/12	0.70 (0.24; 2.07)	-0.04 (-0.16; 0.08)	-27
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy , 96 weeks	Diarrhea	114/96	6/80 1/60	8/2	4.50 (0.56; 36.40)	0.06 (-0.01; 0.12)	17
		Dyspepsia	114/96	7/80 1/60	9/2	5.25 (0.66; 41.54)	**0.07 (0.00; 0.14)**	14
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Pharyngitis	96/96	14/80 8/40	18/20	0.88 (0.40; 1.91)	-0.03 (-0.17; 0.12)	-40
		Increased cough	96/96	3/80 4/40	4/10	0.38 (0.09; 1.60)	-0.06 (-0.16; 0.04)	-16

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Bronchitis	96/96	2/80 1/40	2/2	1.00 (0.09; 10.70)	0.00 (-0.06; 0.06)	
		Increased Alanine aminotransferase levels	96/96	2/80 6/40	2/15	0.17 (0.04; 0.79)	**-0.13 (-0.24; -0.01)**	-8
		Arthralgia	96/96	6/80 5/40	8/12	0.60 (0.19; 1.85)	-0.05 (-0.17; 0.07)	-20
		Increased creatinine levels	96/96	2/80 0/40	2/0	2.53 (0.12; 51.50)	0.03 (-0.03; 0.08)	40
		Hematuria	96/96	1/80 0/40	1/0	1.52 (0.06; 36.46)	0.01 (-0.03; 0.06)	80
		Kidney calculus	96/96	0/80 0/40			0.00 (-0.04; 0.04)	
		Kidney pain	96/96	0/80 0/40			0.00 (-0.04; 0.04)	
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Pharyngitis	96/96	14/80 8/60	18/13	1.31 (0.59; 2.93)	0.04 (-0.08; 0.16)	24
		Increased cough	96/96	3/80 2/60	4/3	1.13 (0.19; 6.52)	0.00 (-0.06; 0.07)	240
		Bronchitis	96/96	2/80 1/60	2/2	1.50 (0.14; 16.16)	0.01 (-0.04; 0.06)	120
		Increased Alanine aminotransferase levels	96/96	2/80 1/60	2/2	1.50 (0.14; 16.16)	0.01 (-0.04; 0.06)	120
		Arthralgia	96/96	6/80 1/60	8/2	4.50 (0.56; 36.40)	0.06 (-0.01; 0.12)	17
		Increased creatinine levels	96/96	2/80 0/60	2/0	3.77 (0.18; 77.01)	0.03 (-0.02; 0.07)	40
		Hematuria	96/96	1/801/60	1/2	0.75 (0.05; 11.75)	0.00 (-0.04; 0.04)	-240
		Kidney calculus	96/96	0/80 1/60	0/2	0.25 (0.01; 6.06)	-0.02 (-0.06; 0.03)	-60
		Kidney pain	96/96	0/80 1/60	0/2	0.25 (0.01; 6.06)	-0.02 (-0.06; 0.03)	-60
	Placebo after 48	Pharyngitis	114/96	25/80	31/20	1.56 (0.78; 3.15)	0.11 (-0.05; 0.27)	9

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	weeks of adefovir therapy, 96 weeks			8/40				
		Increased cough	114/96	7/80 4/40	9/10	0.88 (0.27; 2.81)	-0.01 (-0.12; 0.10)	-80
		Bronchitis	114/96	9/80 1/40	11/2	4.50 (0.59; 34.29)	**0.09 (0.00; 0.17)**	11
		Increased alanine aminotransferase levels	114/96	3/80 6/40	4/15	0.25 (0.07; 0.95)	-0.11 (-0.23; 0.01)	-9
		Arthralgia	114/96	6/80 5/40	8/12	0.60 (0.19; 1.85)	-0.05 (-0.17; 0.07)	-20
		Increased creatinine levels	114/96	3/80 0/40	4/0	3.54 (0.19; 66.97)	0.04 (-0.02; 0.09)	27
		Hematuria	114/96	2/80 0/40	2/0	2.53 (0.12; 51.50)	0.03 (-0.03; 0.08)	40
		Kidney calculus	114/96	1/80 0/40	1/0	1.52 (0.06; 36.46)	0.01 (-0.03; 0.06)	80
		Kidney pain	114/96	4/80 0/40	5/0	4.56 (0.25; 82.59)	0.05 (-0.01; 0.11)	20
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Pharyngitis	114/96	25/80 8/60	31/13	2.34 (1.14; 4.83)	**0.18 (0.05; 0.31)**	6
		Increased cough	114/96	7/80 2/60	9/3	2.63 (0.57; 12.19)	0.05 (-0.02; 0.13)	18
		Bronchitis	114/96	9/80 1/60	11/2	6.75 (0.88; 51.84)	**0.10 (0.02; 0.17)**	10
		Increased ALT levels	114/96	3/80 1/60	4/2	2.25 (0.24; 21.10)	0.02 (-0.03; 0.07)	48
		Arthralgia	114/96	6/80 1/60	8/2	4.50 (0.56; 36.40)	0.06 (-0.01; 0.12)	17
		Increased creatinine levels	114/96	3/80 0/60	4/0	5.27 (0.28; 100.17)	0.04 (-0.01; 0.09)	27
		Hematuria	114/96	2/80 1/60	2/2	1.50 (0.14; 16.16)	0.01 (-0.04; 0.06)	120
		Kidney calculus	114/96	1/80 1/60	1/2	0.75 (0.05; 11.75)	0.00 (-0.04; 0.04)	-240

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Kidney pain	114/96	4/80 1/60	5/2	3.00 (0.34; 26.16)	0.03 (-0.02; 0.09)	30
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Improvement in histological scores	96/96	17/80 4/40	21/10	2.13 (0.77; 5.90)	0.11 (-0.02; 0.24)	9
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Improvement in histological scores	96/96	17/80 14/60	21/23	0.91 (0.49; 1.70)	-0.02 (-0.16; 0.12)	-48
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Serum HBV DNA level <1000 log copies/ml	96/96	50/80 3/40	62/8	8.33 (2.77; 25.07)	**0.55 (0.42; 0.68)**	2
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Serum HBV DNA level <1000 log copies/ml	96/96	50/80 37/60	62/62	1.01 (0.78; 1.32)	0.01 (-0.15; 0.17)	120
	Placebo after 48 weeks of adefovir therapy, 96 weeks	Serum HBV DNA level <1000 log copies/ml	114/96	53/80 3/40	66/8	8.83 (2.94; 26.52)	**0.59 (0.46; 0.72)**	2
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Serum HBV DNA level <1000 log copies/ml	114/96	53/80 37/60	66/62	1.07 (0.83; 1.38)	0.05 (-0.12; 0.21)	22
	Placebo after 48 weeks of adefovir therapy, 96 weeks	HBsAg seroconversion	96/96	1/80 0/40	1/0	1.52 (0.06; 36.46)	0.01 (-0.03; 0.06)	80
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	HBsAg seroconversion	96/96	1/80 1/60	1/2	0.75 (0.05; 11.75)	0.00 (-0.04; 0.04)	-240
	Placebo after 48 weeks of adefovir therapy, 96 weeks	conserved site mutation (rtN236T)	114/96	4/80 0/40	5/0	4.56 (0.25; 82.59)	0.05 (-0.01; 0.11)	20

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	Conserved site mutation (rtN236T)	114/96	4/80 0/60	5/0	6.78 (0.37; 123.52)	**0.05 (0.00; 0.10)**	20
	Placebo after 48 weeks of adefovir therapy, 96 weeks	conserved site substitution mutation (rtA181V) in the B domain of HBV polymerase	114/96	3/80 0/40	4/0	3.54 (0.19; 66.97)	0.04 (-0.02; 0.09)	27
	Adefovir dipivoxil, 10mg daily after 48 weeks of placebo therapy, 96 weeks	conserved site substitution mutation (rtA181V) in the B domain of HBV polymerase	114/96	3/80 0/60	4/0	5.27 (0.28; 100.17)	0.04 (-0.01; 0.09)	27
Zeng, 2006[40] Adefovir dipivoxil, 10 mg/day, 12 weeks Adefovir dipivoxil, 10 mg/day then placebo	placebo for 12 weeks followed by Adefovir dipivoxil for 40 weeks	ALT normalization	39794	92/240 15/120	38/12	3.07 (1.86; 5.06)	**0.26 (0.17; 0.34)**	4
	Placebo, 12 weeks	ALT normalization	39794	48/120 15/120	40/12	3.20 (1.90; 5.39)	**0.28 (0.17; 0.38)**	4
Zeng, 2006[40] Adefovir dipivoxil, 10 mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Placebo, placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, 52 weeks	ALT normalization	52/52	74/120 23/120	62/19	3.22 (2.17; 4.77)	**0.43 (0.31; 0.54)**	2
Zeng, 2006[40] Adefovir dipivoxil, 10 mg/day , total duration of Adefovir dipivoxil 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, 52 weeks	ALT normalization	52/52	176/240 23/120	73/19	3.83 (2.63; 5.57)	**0.54 (0.45; 0.63)**	2
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of	Adefovir dipivoxil, 10 mg/day , total duration of Adefovir dipivoxil 52 weeks	ALT normalization	52/52	74/120 176/240	62/73	0.84 (0.72; 0.99)	**-0.12 (-0.22; -0.01)**	-9

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Adefovir dipivoxil 40 weeks, total 52 weeks								
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day, 12 weeks	Placebo, 12 weeks followed by adefovir	ALT increase to >5 ULN and 2 baseline (for first 12 weeks) or 2 nadir (for subsequent intervals)	12/12	1/240 5/120	0/4	0.10 (0.01; 0.85)	-0.04 (-0.07; 0.00)	-27
	Placebo, 12 weeks		12/12	1/120 5/120	1/4	0.20 (0.02; 1.69)	-0.03 (-0.07; 0.01)	-30
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	ALT increase to >5 ULN and 2 baseline (for first 12 weeks) or 2 nadir (for subsequent intervals).	52/52	0/120 34/120	0/28	0.01 (0.00; 0.23)	**-0.28 (-0.36; -0.20)**	-4
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day, 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks		52/52	1/240 34/120	0/28	0.01 (0.00; 0.11)	**-0.28 (-0.36; -0.20)**	-4
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Adefovir dipivoxil, 10 mg/day, 52 weeks	ALT increase to > 5 ULN and 2 baseline (for first 12 weeks) or 2 nadir (for subsequent intervals)	52/52	0/120 1/240		0.66 (0.03; 16.18)	0.00 (-0.02; 0.01)	-240
Zeng, 2006[40] Adefovir dipivoxil, 10 mg/day, 12 weeks	Placebo, 12 weeks	ALT normalization	52/52	140/360 15/120	39/12	3.11 (1.90; 5.08)	**0.26 (0.19; 0.34)**	4
		Discontinuation due to adverse effects	39794	2/240 0/120	1/0	2.51 (0.12; 51.88)	0.01 (-0.01; 0.03)	120
		Discontinuation due to adverse effects	39794	1/120 0/120	1/0	3.00 (0.12; 72.91)	0.01 (-0.01; 0.03)	120

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	Reactivation of hepatitis B	52/52	1/120 11/120	1/9	0.09 (0.01; 0.69)	**-0.08 (-0.14; -0.03)**	-12
		Upper respiratory tract infection	52/52	10/120 9/120	8/8	1.11 (0.47; 2.64)	0.01 (-0.06; 0.08)	120
		Fatigue	52/52	7/120 8/120	6/7	0.88 (0.33; 2.34)	-0.01 (-0.07; 0.05)	-120
		Nasopharyngitis	52/52	6/120 2/120	5/2	3.00 (0.62; 14.57)	0.03 (-0.01; 0.08)	30
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day, 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	Reactivation of hepatitis B	52/52	1/240 11/120	0/9	0.05 (0.01; 0.35)	**-0.09 (-0.14; -0.04)**	-11
		Upper respiratory tract infection	52/52	20/240 9/120	8/8	1.11 (0.52; 2.37)	0.01 (-0.05; 0.07)	120
		Fatigue	52/52	6/240 8/120	2/7	0.38 (0.13; 1.06)	-0.04 (-0.09; 0.01)	-24
		Nasopharyngitis	52/52	11/240 2/120	5/2	2.75 (0.62; 12.21)	0.03 (-0.01; 0.06)	34
Zeng, 2006[40] Adefovir dipivoxil, 10 mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Adefovir dipivoxil, 10mg/day , 52 weeks	Reactivation of Hepatitis B	52/52	1/120 1/240	1/0	2.00 (0.13; 31.70)	0.00 (-0.01; 0.02)	240
		Upper respiratory tract infection	52/52	10/120 20/240	8/8	1.00 (0.48; 2.07)	0.00 (-0.06; 0.06)	
		Fatigue	52/52	7/120 6/240	6/2	2.33 (0.80; 6.79)	0.03 (-0.01; 0.08)	30
		Nasopharyngitis	52/52	6/120 11/240	5/5	1.09 (0.41; 2.88)	0.00 (-0.04; 0.05)	240
	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	Incidence of elevation of serum ALT to >5 times the ULN	52/52	46/120 66/120	38/55	0.70 (0.53; 0.92)	**-0.17 (-0.29; -0.04)**	-6
Zeng, 2006[40] Adefovir dipivoxil, 10 mg/day, 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	Incidence of elevation of serum ALT to >5 times the ULN	52/52	51/240 66/120	21/55	0.39 (0.29; 0.52)	**-0.34 (-0.44; -0.23)**	-3

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Zeng, 2006[40] Adefovir dipivoxil, 10 mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Adefovir dipivoxil, 10 mg/day, 52 weeks	Incidence of elevation of serum ALT >5 times the ULN	52/52	46/120 51/240	38/21	1.80 (1.29; 2.52)	**0.17 (0.07; 0.27)**	6
Zeng, 2006[40] Adefovir dipivoxil, 10 mg/day, 12 weeks	placebo for 12 weeks	HBV DNA <105 copies/mL	39794	113/240 4/120	47/3	14.13 (5.34; 37.37)	**0.44 (0.37; 0.51)**	2
		HBV DNA < 300 copies/mL	39794	11/240 0/120	5/0	11.55 (0.69; 194.31)	**0.05 (0.02; 0.08)**	22
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	HBV DNA <105 copies/mL	52/52	81/120 13/120	68/11	6.23 (3.67; 10.57)	**0.57 (0.47; 0.67)**	2
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day, 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	HBV DNA <105 copies/mL	52/52	155/240 13/120	65/11	5.96 (3.54; 10.05)	**0.54 (0.46; 0.62)**	2
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Adefovir dipivoxil, 10 mg/day , 52 weeks	HBV DNA <105 copies/mL	52/52	81/120 155/240	68/65	1.05 (0.89; 1.22)	0.03 (-0.07; 0.13)	34
	Placebo for 12 weeks after adefovir dipivoxil for 40 weeks, total 52 weeks	HBV DNA <300 copies/mL	52/52	36/120 1/120	30/1	36.00 (5.02; 258.36)	**0.29 (0.21; 0.38)**	3
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day, 52 weeks	Placebo for 12 weeks after adefovir dipivoxil for 40 weeks, total 52 weeks	HBV DNA <300 copies/mL	52/52	67/240 1/120	28/1	33.50 (4.71; 238.38)	**0.27 (0.21; 0.33)**	4

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Adefovir dipivoxil, 10 mg/day , 52 weeks	HBV DNA <300 copies/mL.	52/52	36/120 67/240	30/28	1.07 (0.76; 1.51)	0.02 (-0.08; 0.12)	48
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day, 12 weeks	Placebo, 12 weeks	HBeAg loss	12/12	14/240 6/120	6/5	1.17 (0.46; 2.96)	0.01 (-0.04; 0.06)	120
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	HBeAg loss	52/52	24/120 10/120	20/8	2.40 (1.20; 4.80)	**0.12 (0.03; 0.20)**	9
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day, 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	HBeAg loss	52/52	30/240 10/120	12/8	1.50 (0.76; 2.96)	0.04 (-0.02; 0.11)	24
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Adefovir dipivoxil, 10mg/day,52 weeks	HBeAg loss	52/52	24/120 30/240	20/12	1.60 (0.98; 2.61)	0.08 (-0.01; 0.16)	13
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day, 12 weeks	Placebo, 12 weeks	HBeAg seroconversion	39794	14/240 6/120	6/5	1.17 (0.46; 2.96)	0.01 (-0.04; 0.06)	120
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	HBeAg seroconversion	52/52	21/120 8/120	18/7	2.63 (1.21; 5.69)	**0.11 (0.03; 0.19)**	9

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day, 52 weeks	Placebo for 12 weeks after Adefovir for 40 weeks, total 52 weeks	HBeAg seroconversion	52/52	19/240 8/120	8/7	1.19 (0.54; 2.63)	0.01 (-0.04; 0.07)	80
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Adefovir dipivoxil, 10mg/day, 52 weeks	HBeAg seroconversion	52/52	21/120 19/240	18/8	2.21 (1.24; 3.95)	**0.10 (0.02; 0.17)**	10
	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	Increase in HBV DNA of at least 1 log 10 copies/ml	52/52	11/120 6/120	9/5	1.83 (0.70; 4.80)	0.04 (-0.02; 0.11)	24
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day, 52 weeks	Placebo for 12 weeks after Adefovir dipivoxil for 40 weeks, total 52 weeks	Increase in HBV DNA of at least 1 log 10 copies/ml	52/52	28/240 6/120	12/5	2.33 (0.99; 5.48)	**0.07 (0.01; 0.12)**	15
Zeng, 2006[40] Adefovir dipivoxil, 10mg/day after placebo for 12 weeks, duration of Adefovir dipivoxil 40 weeks, total 52 weeks	Adefovir dipivoxil, 10 mg/day , 52 weeks	Increase in HBV DNA of at least 1 log 10 copies/ml	52/52	11/120 28/240	9/12	0.79 (0.41; 1.52)	-0.03 (-0.09; 0.04)	-40
Hadziyannis, 2006[97] Adefovir dipivoxil, 10mg daily, 240 weeks	Adefovir dipivoxil, 10 mg daily, 114 weeks	ALT normalization	240/114	86/125 89/125	69/71	0.97 (0.82; 1.14)	-0.02 (-0.14; 0.09)	-42
		Death not related to treatment (car accident)	240/114	0/125 1/125	0/1	0.33 (0.01; 8.10)	-0.01 (-0.03; 0.01)	-125
		Treatment failure: hepatocellular carcinoma or harbored HBV with an adefovir resis-tance mutation and either termination	240/114	23/125 3/125	18/2	7.67 (2.36; 24.89)	**0.16 (0.09; 0.23)**	6

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		the study or adding lamivudine						
		Hepatocellular carcinoma	240/114	5/125 1/125	4/1	5.00 (0.59; 42.19)	0.03 (-0.01; 0.07)	31
		Adefovir-resistance mutations with virologic resistance and ALT elevations, virologic resistance, and ALT elevation (clinical resistance)	240/114	14/125 8/125	11/6	1.75 (0.76; 4.02)	0.05 (-0.02; 0.12)	21
		Any adverse events	240/114	117/125 60/125	94/48	1.95 (1.62; 2.35)	**0.46 (0.36; 0.55)**	2
		Abdominal pain	240/114	30/125 20/125	24/16	1.50 (0.90; 2.49)	0.08 (-0.02; 0.18)	12
		Headache	240/114	29/125 19/125	23/15	1.53 (0.91; 2.57)	0.08 (-0.02; 0.18)	12
		Flu-like syndrome	240/114	27/125 14/125	22/11	1.93 (1.06; 3.50)	**0.10 (0.01; 0.19)**	10
		Asthenia	240/114	20/125 15/125	16/12	1.33 (0.72; 2.48)	0.04 (-0.05; 0.13)	25
		Infection	240/114	20/125 0/125	16/0	41.00 (2.51; 670.54)	**0.16 (0.09; 0.23)**	6
		Back pain	240/114	19/125 9/125	15/7	2.11 (0.99; 4.48)	**0.08 (0.00; 0.16)**	12
		Pain	240/114	19/125 12/125	15/10	1.58 (0.80; 3.12)	0.06 (-0.03; 0.14)	18
		Accidental injury	240/114	15/125 8/125	12/6	1.88 (0.82; 4.26)	0.06 (-0.02; 0.13)	18
		Dyspepsia	240/114	12/125 7/125	10/6	1.71 (0.70; 4.21)	0.04 (-0.03; 0.11)	25
		Pharyngitis	240/114	34/125 25/125	27/20	1.36 (0.86; 2.14)	0.07 (-0.03; 0.18)	14
		Bronchitis	240/114	19/125	15/7	2.11 (0.99; 4.48)	**0.08 (0.00; 0.16)**	12

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
				9/125				
		Cough increased	240/114	14/125 7/125	11/6	2.00 (0.84; 4.79)	0.06 (-0.01; 0.12)	18
		Rhinitis	240/114	13/125 0/125	10/0	27.00 (1.62; 449.30)	**0.10 (0.05; 0.16)**	10
		At least a 1-point improvement in Ishak fibrosis score	240/192	69/125 89/125	55/71	0.78 (0.64; 0.94)	**-0.16 (-0.28; -0.04)**	-6
		HBV DNA <1000 copies /ml	240/114	84/125 96/125	67/77	0.88 (0.75; 1.02)	-0.10 (-0.21; 0.01)	-10
		HBV DNA 1000 to 10,000 copies/mL	240/114	9/125 14/125	7/11	0.64 (0.29; 1.43)	-0.04 (-0.11; 0.03)	-25
		HBV DNA 10,000 to 100,000 copies/mL	240/114	6/125 3/125	5/2	2.02 (0.52; 7.88)	0.02 (-0.02; 0.07)	41
		HBV DNA >100,000 copies/mL	240/114	3/125 10/125	2/8	0.30 (0.08; 1.06)	-0.06 (-0.11; 0.00)	-18
		HBsAg loss	240/114	0/125 6/125	0/5	0.08 (0.00; 1.35)	**-0.05 (-0.09; -0.01)**	-21
		HBsAg seroconversion	240/114	0/125 5/125	0/4	0.09 (0.01; 1.63)	-0.04 (-0.08; 0.00)	-25
		Adefovir-resistance mutations (N236T or A181V)	240/114	36/125 14/125	29/11	2.57 (1.46; 4.53)	**0.18 (0.08; 0.27)**	6
		Mutation and virologic resistance: adefovir-resistance mutations with HBV DNA increased from nadir by at least 1-log 10 copies/ml or never suppressed to less than 3-log 10 copies /ml	240/114	25/125 10/125	20/8	2.50 (1.25; 4.99)	**0.12 (0.04; 0.20)**	8

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Akyildiz, 2007[45] Adefovir dipivoxil, 10mg/dayLamivudine, 100mg/day for 3 months48 weeks	Adefovir dipivoxil, 10 mg/day, 48 weeks	ALT flare (>5 times ULN (Grade 3 toxicity)) without any clinical decompensation	48/48	0/29 2/25	0/8	0.17 (0.01; 3.45)	-0.08 (-0.20; 0.04)	-12
		Mild ALT elevation according to baseline levels	48/48	8/29 4/25	28/16	1.72 (0.59; 5.05)	0.12 (-0.10; 0.33)	9
		HBV DNA <2000 copies/ml	24/24	12/29 9/25	41/34	1.20 (0.60; 2.37)	0.07 (-0.19; 0.32)	15
		HBV DNA <2000 copies/ml	48/48	17/29 14/25	57/56	1.05 (0.66; 1.66)	0.03 (-0.24; 0.29)	38
Lai, 2002[77] Entecavir, 0.01mg/day, 24 weeks	Entecavir, 0.1 mg/day, 24 weeks	Normalization of ALT levels when elevated at baseline	24/24	15/52 15/34	29/44	0.65 (0.37; 1.16)	-0.15 (-0.36; 0.05)	-7
		ALT >2 X baseline levels	24/24	6/52 6/34	12/18	0.65 (0.23; 1.86)	-0.06 (-0.22; 0.09)	-16
		ALT >3 X baseline levels	24/24	2/52 2/34	4/6	0.65 (0.10; 4.42)	-0.02 (-0.12; 0.07)	-49
		ALT >2 X baseline levels and also >10X ULN	24/24	1/52 0/34	2/0	1.98 (0.08; 47.26)	0.02 (-0.04; 0.08)	52
	Entecavir, 0.5 mg/day, 24 weeks	Normalization of ALT levels when elevated at baseline	24/24	15/52 20/43	29/47	0.62 (0.36; 1.06)	-0.18 (-0.37; 0.02)	-6
		ALT >2 X baseline levels	24/24	6/52 5/43	12/12	0.99 (0.33; 3.03)	0.00 (-0.13; 0.13)	-1118
		ALT >3 X baseline levels	24/24	2/52 1/43	4/2	1.65 (0.16; 17.63)	0.02 (-0.05; 0.08)	66
		ALT >2 X baseline levels and also >10X ULN	24/24	1/52 0/43	2/0	2.49 (0.10; 59.62)	0.02 (-0.04; 0.07)	52

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	Lamivudine, 100 mg/day, 24 weeks	Normalization of ALT levels when elevated at baseline	24/24	15/52 13/40	29/32	0.89 (0.48; 1.65)	-0.04 (-0.23; 0.15)	-27
		ALT >2 X baseline levels	24/24	6/52 2/40	12/5	2.31 (0.49; 10.83)	0.07 (-0.04; 0.18)	15
		ALT >3 X baseline levels	24/24	2/52 0/40	4/0	3.87 (0.19; 78.38)	0.04 (-0.03; 0.10)	26
		ALT >2 X baseline levels and also >10X ULN	24/24	1/52 0/40	2/0	2.32 (0.10; 55.50)	0.02 (-0.04; 0.08)	52
Lai, 2002[77] Entecavir, 0.1 mg/day, 24 weeks	Entecavir, 0.5 mg/day, 24 weeks	Normalization of ALT levels when elevated at baseline	24/24	15/34 20/43	44/47	0.95 (0.58; 1.56)	-0.02 (-0.25; 0.20)	-42
		ALT >2 X baseline levels	24/24	6/34 5/43	18/12	1.52 (0.51; 4.55)	0.06 (-0.10; 0.22)	17
		ALT >3 X baseline levels	24/24	2/34 1/43	6/2	2.53 (0.24; 26.73)	0.04 (-0.06; 0.13)	28
		ALT >2 X baseline levels and also >10X ULN	24/24	0/34 0/43			0.00 (-0.05; 0.05)	
	Lamivudine, 100 mg/day, 24 weeks	Normalization of ALT levels when elevated at baseline	24/24	15/34 13/40	44/32	1.36 (0.76; 2.44)	0.12 (-0.11; 0.34)	9
		ALT >2 X baseline levels	24/24	6/34 2/40	18/5	3.53 (0.76; 16.36)	0.13 (-0.02; 0.27)	8
		ALT >3 X baseline levels	24/24	2/34 0/40	6/0	5.86 (0.29; 117.96)	0.06 (-0.03; 0.15)	17
		ALT >2 X baseline levels and also >10X ULN	24/24	0/34 0/40			0.00 (-0.05; 0.05)	

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lai, 2002[77] Entecavir, 0.5 mg/day, 24 weeks	Lamivudine, 100 mg/day, 24 weeks	Normalization of ALT levels when elevated at baseline	24/24	20/43 13/40	47/32	1.43 (0.83; 2.48)	0.14 (-0.07; 0.35)	7
		ALT >2 X baseline levels	24/24	5/43 2/40	12/5	2.33 (0.48; 11.32)	0.07 (-0.05; 0.18)	15
		ALT >3 X baseline levels	24/24	1/43 0/40	2/0	2.80 (0.12; 66.70)	0.02 (-0.04; 0.09)	43
		ALT >2 X baseline levels and also >10X ULN	24/24	0/43 0/40			0.00 (-0.05; 0.05)	
Lai, 2002[77] Entecavir, 0.01 mg/day, 24 weeks	Entecavir, 0.1 mg/day, 24 weeks	HBV-DNA loss by branched-chain assay + HBeAg loss + normal ALT for HBeAg+ at baseline and HBV-DNA loss + normal ALT for HBeAg- at baseline	24/24	12/52 21/34	23/62	0.37 (0.21; 0.66)	-**0.39 (-0.59; -0.19)**	-3
	Entecavir, 0.1 mg/day, 24 weeks	HBV-DNA loss by branched-chain assay + HBeAg loss + normal ALT for HBeAg+ at baseline and HBV-DNA loss by branched-chain assay + normal ALT for HBeAg- at baseline	24/24	3/52 8/34	6/24	0.25 (0.07; 0.86)	**-0.18 (-0.33; -0.02)**	-6
	Entecavir, 0.1 mg/day, 24 weeks	HBV-DNA loss by branched-chain assay + present HBeAg or elevated	24/24	9/52 13/34	17/38	0.45 (0.22; 0.94)	**-0.21 (-0.40; -0.02)**	-5

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		ALT for HBeAg+ at baseline or HBV-DNA loss+ elevated ALT for HBeAg- at baseline						
	Entecavir, 0.5 mg/day, 24 weeks	Complete or partial response (see above)	24/24	12/52 36/43	23/84	0.28 (0.16; 0.46)	**-0.61 (-0.77; -0.45)**	-2
	Entecavir, 0.5 mg/day, 24 weeks	Complete response	24/24	3/52 7/43	6/16	0.35 (0.10; 1.29)	-0.11 (-0.23; 0.02)	-10
	Entecavir, 0.5 mg/day, 24 weeks	Partial response	24/24	9/52 29/43	17/67	0.26 (0.14; 0.48)	**-0.50 (-0.68; -0.33)**	-2
	Lamivudine, 100 mg/day, 24 weeks	Complete or partial response (see above)	24/24	12/52 23/40	23/57	0.40 (0.23; 0.70)	**-0.34 (-0.54; -0.15)**	-3
	Lamivudine, 100 mg/day, 24 weeks	Complete response	24/24	3/52 6/40	6/15	0.38 (0.10; 1.44)	-0.09 (-0.22; 0.04)	-11
	Lamivudine, 100 mg/day, 24 weeks	Partial response	24/24	9/52 17/40	17/42	0.41 (0.20; 0.82)	-**0.25 (-0.44; -0.07)**	-4
Lai, 2002[77] Entecavir, 0.1mg/day, 24 weeks	Entecavir, 0.5 mg/day, 24 weeks	Complete or partial response (see above)	24/24	21/34 36/43	62/84	0.74 (0.55; 0.99)	**-0.22 (-0.42; -0.02)**	-5
	Entecavir, 0.5 mg/day, 24 weeks	Complete response	24/24	8/34 7/43	24/16	1.45 (0.58; 3.59)	0.07 (-0.11; 0.25)	14
	Entecavir, 0.5 mg/day, 24 weeks	Partial response	24/24	13/34 29/43	38/67	0.57 (0.35; 0.91)	**-0.29 (-0.51; -0.08)**	-3
	Lamivudine, 100 mg/day, 24 weeks	Complete or partial response (see above)	24/24	21/34 23/40	62/57	1.07 (0.74; 1.56)	0.04 (-0.18; 0.27)	23
	Lamivudine, 100 mg/day, 24 weeks	Complete response	24/24	8/34 6/40	24/15	1.57 (0.60; 4.08)	0.09 (-0.10; 0.27)	12
	Lamivudine, 100 mg/day, 24 weeks	Partial response	24/24	13/34 17/40	38/42	0.90 (0.51; 1.57)	-0.04 (-0.27; 0.18)	-23

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lai, 2002[77] Entecavir, 0.5mg/day, 24 weeks	Lamivudine, 100 mg/day, 24 weeks	Complete or partial response (see above)	24/24	36/43 23/40	84/57	1.46 (1.08; 1.96)	**0.26 (0.07; 0.45)**	4
	Lamivudine, 100 mg/day, 24 weeks	Complete response	24/24	7/43 6/40	16/15	1.09 (0.40; 2.96)	0.01 (-0.14; 0.17)	78
	Lamivudine, 100 mg/day, 24 weeks	Partial response	24/24	29/43 17/40	67/42	1.59 (1.05; 2.41)	**0.25 (0.04; 0.46)**	4
Lai, 2002[77] Entecavir, 0.01mg/day, 24 weeks	Entecavir, 0.1 mg/day, 24 weeks	Bilirubin >2X baseline levels	24/24	4/52 2/34	8/6	1.31 (0.25; 6.75)	0.02 (-0.09; 0.13)	55
		Bilirubin >3X baseline levels	24/24	1/52 0/34	2/0	1.98 (0.08; 47.26)	0.02 (-0.04; 0.08)	52
		Bilirubin >2X baseline levels and also 5X ULN	24/24	1/52 0/34	2/0	1.98 (0.08; 47.26)	0.02 (-0.04; 0.08)	52
		ALT ≥2 baseline levels and bilirubin ≥2 baseline levels with bilirubin 2X ULN	24/24	0/52 0/34			0.00 (-0.05; 0.05)	
	Entecavir, 0.5 mg/day, 24 weeks	Bilirubin >2X baseline levels	24/24	4/52 4/43	8/9	0.83 (0.22; 3.11)	-0.02 (-0.13; 0.10)	-62
		Bilirubin >3X baseline levels	24/24	1/52 1/43	2/2	0.83 (0.05; 12.83)	0.00 (-0.06; 0.05)	-248
		Bilirubin >2X baseline levels and also 5X ULN	24/24	1/52 0/43	2/0	2.49 (0.10; 59.62)	0.02 (-0.04; 0.07)	52
		ALT ≥2 baseline levels and bilirubin ≥2 baseline levels with bilirubin 2 X ULN	24/24	0/52 0/43			0.00 (-0.04; 0.04)	
	Lamivudine, 100 mg/day, 24 weeks	Bilirubin >2X baseline levels	24/24	4/52 2/40	8/5	1.54 (0.30; 7.98)	0.03 (-0.07; 0.13)	37
		Bilirubin >3X baseline levels	24/24	1/52 1/40	2/2	0.77 (0.05; 11.92)	-0.01 (-0.07; 0.06)	-173

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Bilirubin >2X baseline levels and also 5X ULN	24/24	1/52 0/40	2/0	2.32 (0.10; 55.50)	0.02 (-0.04; 0.08)	52
		ALT ≥2 baseline levels and bilirubin ≥2 baseline levels with bilirubin 2 X ULN	24/24	0/52 0/40			0.00 (-0.04; 0.04)	
Lai, 2002[77] Entecavir, 0.1 mg/day, 24 weeks	Entecavir, 0.5 mg/day, 24 weeks	Bilirubin >2X baseline levels	24/24	2/34 4/43	6/9	0.63 (0.12; 3.25)	-0.03 (-0.15; 0.08)	-29
		Bilirubin >3X baseline levels	24/24	0/34 1/43	0/2	0.42 (0.02; 9.97)	-0.02 (-0.09; 0.04)	-43
		Bilirubin >2X baseline levels and also 5X ULN	24/24	0/34 0/43			0.00 (-0.05; 0.05)	
		ALT >2 baseline levels and bilirubin >2 baseline levels with bilirubin 2 X ULN	24/24	0/34 0/43			0.00 (-0.05; 0.05)	
	Lamivudine, 100 mg/day, 24 weeks	Bilirubin >2X baseline levels	24/24	2/34 2/40	6/5	1.18 (0.17; 7.91)	0.01 (-0.10; 0.11)	113
		Bilirubin >3X baseline levels	24/24	0/34 1/40	0/2	0.39 (0.02; 9.28)	-0.03 (-0.09; 0.04)	-40
		Bilirubin >2X baseline levels and also 5X ULN	24/24	0/34 0/40			0.00 (-0.05; 0.05)	
		ALT >2 baseline levels and bilirubin >2 baseline levels with bilirubin 2 X ULN	24/24	0/34 0/40			0.00 (-0.05; 0.05)	

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lai, 2002[77] Entecavir, 0.5 mg/day, 24 weeks	Lamivudine, 100 mg/day, 24 weeks	Bilirubin >2X baseline levels	24/24	4/43 2/40	9/5	1.86 (0.36; 9.61)	0.04 (-0.07; 0.15)	23
		Bilirubin >3X baseline levels	24/24	1/43 1/40	2/2	0.93 (0.06; 14.38)	0.00 (-0.07; 0.06)	-573
		Bilirubin >2X baseline levels and also 5X ULN	24/24	0/43 0/40			0.00 (-0.05; 0.05)	
		ALT >2 baseline levels and bilirubin >2 baseline levels with bilirubin 2 X ULN	24/24	0/43 0/40			0.00 (-0.05; 0.05)	
Lai, 2002[77] Entecavir, 0.01 mg/day, 24 weeks	Entecavir, 0.1 mg/day, 24 weeks	Any adverse event	24/24	38/52 25/34	73/74	0.99 (0.77; 1.29)	0.00 (-0.20; 0.19)	-221
		Headache	24/24	11/52 12/34	21/35	0.60 (0.30; 1.20)	-0.14 (-0.34; 0.05)	-7
		Abdominal pain	24/24	12/52 11/34	23/32	0.71 (0.36; 1.43)	-0.09 (-0.29; 0.10)	-11
		Rhinitis	24/24	9/52 8/34	17/24	0.74 (0.31; 1.72)	-0.06 (-0.24; 0.11)	-16
		Fatigue	24/24	6/52 6/34	12/18	0.65 (0.23; 1.86)	-0.06 (-0.22; 0.09)	-16
		Fever	24/24	5/52 5/34	10/15	0.65 (0.20; 2.09)	-0.05 (-0.19; 0.09)	-20
		Diarrhea	24/24	3/52 4/34	6/12	0.49 (0.12; 2.06)	-0.06 (-0.19; 0.07)	-17
		Nausea	24/24	3/52 2/34	6/6	0.98 (0.17; 5.57)	0.00 (-0.10; 0.10)	-884
		Dizziness	24/24	3/52 1/34	6/3	1.96 (0.21; 18.09)	0.03 (-0.06; 0.11)	35
		Cough	24/24	2/52 5/34	4/15	0.26 (0.05; 1.27)	-0.11 (-0.24; 0.02)	-9
		Myalgia	24/24	2/52 2/34	4/6	0.65 (0.10; 4.42)	-0.02 (-0.12; 0.07)	-49

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	Entecavir, 0.5 mg/day, 24 weeks	Any adverse event	24/24	38/52 30/43	73/70	1.05 (0.81; 1.35)	0.03 (-0.15; 0.22)	30
		Headache	24/24	11/52 14/43	21/33	0.65 (0.33; 1.28)	-0.11 (-0.29; 0.06)	-9
		Abdominal pain	24/24	12/52 12/43	23/28	0.83 (0.41; 1.65)	-0.05 (-0.22; 0.13)	-21
		Rhinitis	24/24	9/52 5/43	17/12	1.49 (0.54; 4.11)	0.06 (-0.08; 0.20)	18
		Fatigue	24/24	6/52 8/43	12/19	0.62 (0.23; 1.65)	-0.07 (-0.22; 0.07)	-14
		Fever	24/24	5/52 2/43	10/5	2.07 (0.42; 10.13)	0.05 (-0.05; 0.15)	20
		Diarrhea	24/24	3/52 5/43	6/12	0.50 (0.13; 1.96)	-0.06 (-0.17; 0.06)	-17
		Nausea	24/24	3/52 5/43	6/12	0.50 (0.13; 1.96)	-0.06 (-0.17; 0.06)	-17
		Dizziness	24/24	3/52 5/43	6/12	0.50 (0.13; 1.96)	-0.06 (-0.17; 0.06)	-17
		Cough	24/24	2/52 2/43	4/5	0.83 (0.12; 5.63)	-0.01 (-0.09; 0.07)	-124
		Myalgia	24/24	2/52 0/43	4/0	4.15 (0.20; 84.21)	0.04 (-0.03; 0.10)	26
	Lamivudine, 100 mg/day, 24 weeks	Any adverse event	24/24	38/52 30/40	73/75	0.97 (0.76; 1.24)	-0.02 (-0.20; 0.16)	-52
		Headache	24/24	11/52 8/40	21/20	1.06 (0.47; 2.38)	0.01 (-0.15; 0.18)	87
		Abdominal pain	24/24	12/52 7/40	23/18	1.32 (0.57; 3.04)	0.06 (-0.11; 0.22)	18
		Rhinitis	24/24	9/52 8/40	17/20	0.87 (0.37; 2.04)	-0.03 (-0.19; 0.13)	-37
		Fatigue	24/24	6/52 7/40	12/18	0.66 (0.24; 1.81)	-0.06 (-0.21; 0.09)	-17
		Fever	24/24	5/52 6/40	10/15	0.64 (0.21; 1.95)	-0.05 (-0.19; 0.08)	-19

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Diarrhea	24/24	3/52 4/40	6/10	0.58 (0.14; 2.43)	-0.04 (-0.15; 0.07)	-24
		Nausea	24/24	3/52 3/40	6/8	0.77 (0.16; 3.61)	-0.02 (-0.12; 0.09)	-58
		Dizziness	24/24	3/52 2/40	6/5	1.15 (0.20; 6.58)	0.01 (-0.08; 0.10)	130
		Cough	24/24	2/52 2/40	4/5	0.77 (0.11; 5.23)	-0.01 (-0.10; 0.07)	-87
		Myalgia	24/24	2/52 4/40	4/10	0.38 (0.07; 2.00)	-0.06 (-0.17; 0.05)	-16
Lai, 2002[77] Entecavir, 0.1 mg/day, 24 weeks	Entecavir, 0.5 mg/day, 24 weeks	Any adverse event	24/24	25/34 30/43	74/70	1.05 (0.80; 1.40)	0.04 (-0.16; 0.24)	27
		Headache	24/24	12/34 14/43	35/33	1.08 (0.58; 2.03)	0.03 (-0.19; 0.24)	37
		Abdominal pain	24/24	11/34 12/43	32/28	1.16 (0.59; 2.30)	0.04 (-0.16; 0.25)	22
		Rhinitis	24/24	8/34 5/43	24/12	2.02 (0.73; 5.63)	0.12 (-0.05; 0.29)	8
		Fatigue	24/24	6/34 8/43	18/19	0.95 (0.36; 2.47)	-0.01 (-0.18; 0.16)	-104
		Fever	24/24	5/34 2/43	15/5	3.16 (0.65; 15.30)	0.10 (-0.03; 0.24)	10
		Diarrhea	24/24	4/34 5/43	12/12	1.01 (0.29; 3.48)	0.00 (-0.14; 0.15)	731
		Nausea	24/24	2/34 5/43	6/12	0.51 (0.10; 2.45)	-0.06 (-0.18; 0.07)	-17
		Dizziness	24/24	1/34 5/43	3/12	0.25 (0.03; 2.06)	-0.09 (-0.20; 0.02)	-12
		Cough	24/24	5/34 2/43	15/5	3.16 (0.65; 15.30)	0.10 (-0.03; 0.24)	10
		Myalgia	24/24	2/34 0/43	6/0	6.29 (0.31; 126.72)	0.06 (-0.03; 0.15)	17
	Lamivudine, 100 mg/day, 24 weeks	Any adverse event	24/24	25/34 30/40	74/75	0.98 (0.75; 1.28)	-0.01 (-0.21; 0.19)	-68

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Headache	24/24	12/34 8/40	35/20	1.76 (0.82; 3.81)	0.15 (-0.05; 0.36)	7
		Abdominal pain	24/24	11/34 7/40	32/18	1.85 (0.81; 4.24)	0.15 (-0.05; 0.34)	7
		Rhinitis	24/24	8/34 8/40	24/20	1.18 (0.49; 2.80)	0.04 (-0.15; 0.22)	28
		Fatigue	24/24	6/34 7/40	18/18	1.01 (0.37; 2.71)	0.00 (-0.17; 0.18)	680
		Fever	24/24	5/34 6/40	15/15	0.98 (0.33; 2.93)	0.00 (-0.17; 0.16)	-340
		Diarrhea	24/24	4/34 4/40	12/10	1.18 (0.32; 4.35)	0.02 (-0.13; 0.16)	57
		Nausea	24/24	2/34 3/40	6/8	0.78 (0.14; 4.42)	-0.02 (-0.13; 0.10)	-62
		Dizziness	24/24	1/34 2/40	3/5	0.59 (0.06; 6.21)	-0.02 (-0.11; 0.07)	-49
		Cough	24/24	5/34 2/40	15/5	2.94 (0.61; 14.21)	0.10 (-0.04; 0.23)	10
		Myalgia	24/24	2/34 4/40	6/10	0.59 (0.11; 3.02)	-0.04 (-0.16; 0.08)	-24
Lai, 2002[77] Entecavir, 0.5 mg/day, 24 weeks	Lamivudine, 100 mg/day, 24 weeks	Any adverse event	24/24	30/43 30/40	70/75	0.93 (0.71; 1.21)	-0.05 (-0.24; 0.14)	-19
		Headache	24/24	14/43 8/40	33/20	1.63 (0.77; 3.46)	0.13 (-0.06; 0.31)	8
		Abdominal pain	24/24	12/43 7/40	28/18	1.59 (0.70; 3.65)	0.10 (-0.07; 0.28)	10
		Rhinitis	24/24	5/43 8/40	12/20	0.58 (0.21; 1.63)	-0.08 (-0.24; 0.07)	-12
		Fatigue	24/24	8/43 7/40	19/18	1.06 (0.42; 2.66)	0.01 (-0.15; 0.18)	91
		Fever	24/24	2/43 6/40	5/15	0.31 (0.07; 1.45)	-0.10 (-0.23; 0.02)	-10
		Diarrhea	24/24	5/43 4/40	12/10	1.16 (0.34; 4.03)	0.02 (-0.12; 0.15)	61

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Nausea	24/24	5/43 3/40	12/8	1.55 (0.40; 6.07)	0.04 (-0.08; 0.17)	24
		Dizziness	24/24	5/43 2/40	12/5	2.33 (0.48; 11.32)	0.07 (-0.05; 0.18)	15
		Cough	24/24	2/43 2/40	5/5	0.93 (0.14; 6.30)	0.00 (-0.10; 0.09)	-287
		Myalgia	24/24	0/43 4/40	0/10	0.10 (0.01; 1.86)	-0.10 (-0.20; 0.00)	-10
Lai, 2002[77] Entecavir, 0.01 mg/day, 24 weeks	Entecavir, 0.1 mg/day, 24 weeks	Undetectable HBV DNA using Amplicor PCR assay	24/24	1/52 9/34	2/26	0.07 (0.01; 0.55)	**-0.25 (-0.40; -0.09)**	-4
	Entecavir, 0.5 mg/day, 24 weeks	Undetectable HBV DNA using Amplicor PCR assay	24/24	1/52 11/43	2/26	0.08 (0.01; 0.56)	**-0.24 (-0.37; -0.10)**	-4
	Lamivudine, 100 mg/day, 24 weeks	Undetectable HBV DNA using Amplicor PCR assay	24/24	1/52 7/40	2/18	0.11 (0.01; 0.86)	**-0.16 (-0.28; -0.03)**	-6
Lai, 2002[77] Entecavir, 0.1 mg/day, 24 weeks	Entecavir, 0.5 mg/day, 24 weeks	Undetectable HBV DNA using Amplicor PCR assay	24/24	9/34 11/43	26/26	1.03 (0.49; 2.21)	0.01 (-0.19; 0.21)	112
	Lamivudine, 100 mg/day, 24 weeks	Undetectable HBV DNA using Amplicor PCR assay	24/24	9/34 7/40	26/18	1.51 (0.63; 3.63)	0.09 (-0.10; 0.28)	11
Lai, 2002[77] Entecavir, 0.5 mg/day, 24 weeks	Lamivudine, 100 mg/day, 24 weeks	Undetectable HBV DNA using Amplicor PCR assay	24/24	11/43 7/40	26/18	1.46 (0.63; 3.40)	0.08 (-0.09; 0.26)	12
Lai, 2002[77] Entecavir, 0.01 mg/day,	Entecavir, 0.1 mg/day, 24 weeks	Undetectable HBV DNA using	24/24	12/52 21/34	23/62	0.37 (0.21; 0.66)	**-0.39 (-0.59; -0.19)**	-3

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
24 weeks		Quantiplex bDNA assay						
	Entecavir, 0.5 mg/day, 24 weeks	Undetectable HBV DNA using Quantiplex bDNA assay	24/24	12/52 36/43	23/84	0.28 (0.16; 0.46)	**-0.61 (-0.77; -0.45)**	-2
	Lamivudine, 100 mg/day, 24 weeks	Undetectable HBV DNA using Quantiplex bDNA assay	24/24	12/52 23/40	23/57	0.40 (0.23; 0.70)	**-0.34 (-0.54; -0.15)**	-3
Lai, 2002[77] Entecavir, 0.1 mg/day, 24 weeks	Entecavir, 0.5 mg/day, 24 weeks	Undetectable HBV DNA using Quantiplex bDNA assay	24/24	21/34 36/43	62/84	0.74 (0.55; 0.99)	**-0.22 (-0.42; -0.02)**	-5
	Lamivudine, 100 mg/day, 24 weeks	Undetectable HBV DNA using Quantiplex bDNA assay	24/24	21/34 23/40	62/57	1.07 (0.74; 1.56)	0.04 (-0.18; 0.27)	23
Lai, 2002[77] Entecavir, 0.5 mg/day, 24 weeks	Lamivudine, 100 mg/day, 24 weeks	Undetectable HBV DNA using Quantiplex bDNA assay	24/24	36/43 23/40	84/57	1.46 (1.08; 1.96)	**0.26 (0.07; 0.45)**	4
Lai, 2002[77] Entecavir, 0.01 mg/day, 24 weeks	Entecavir, 0.1 mg/day, 24 weeks	HBV-DNA levels still detectable by branched-chain assay	24/24	40/52 13/34	77/38	2.01 (1.28; 3.16)	**0.39 (0.19; 0.59)**	3
	Entecavir, 0.5 mg/day, 24 weeks	HBV-DNA levels still detectable by branched-chain assay	24/24	40/52 7/43	77/16	4.73 (2.36; 9.46)	**0.61 (0.45; 0.77)**	2
	Lamivudine, 100 mg/day, 24 weeks	HBV-DNA levels still detectable by branched-chain assay	24/24	40/52 16/40	77/40	1.92 (1.28; 2.89)	**0.37 (0.18; 0.56)**	3

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lai, 2002[77] Entecavir, 0.1 mg/day, 24 weeks	Entecavir, 0.5 mg/day, 24 weeks	HBV-DNA levels still detectable by branched-chain assay	24/24	13/34 7/43	38/16	2.35 (1.05; 5.23)	**0.22 (0.02; 0.42)**	5
	Lamivudine, 100 mg/day, 24 weeks	HBV-DNA levels still detectable by branched-chain assay	24/24	13/34 16/40	38/40	0.96 (0.54; 1.69)	-0.02 (-0.24; 0.21)	-57
Lai, 2002[77] Entecavir, 0.5 mg/day, 24 weeks	Lamivudine, 100 mg/day, 24 weeks	HBV-DNA levels still detectable by branched-chain assay	24/24	7/43 16/40	16/40	0.41 (0.19; 0.89)	**-0.24 (-0.42; -0.05**)	-4
Lai, 2002[77] Entecavir, 0.01 mg/day, 24 weeks	Entecavir, 0.1 mg/day, 24 weeks	HBeAg loss	24/24	0/52 4/34	0/13	0.07 (0.00; 1.32)	-0.12 (-0.23; 0.00)	-8
	Entecavir, 0.5 mg/day, 24 weeks	HBeAg loss	24/24	0/52 0/43			0.00 (-0.04; 0.04)	
	Lamivudine, 100 mg/day, 24 weeks	HBeAg loss	24/24	0/52 2/40	0/6	0.15 (0.01; 3.14)	-0.05 (-0.13; 0.03)	-20
Lai, 2002[77] Entecavir, 0.1 mg/day, 24 weeks	Entecavir, 0.5 mg/day, 24 weeks	HBeAg loss	24/24	4/34 0/43	13/0	11.31 (0.63; 203.14)	**0.12 (0.00; 0.23)**	8
	Lamivudine, 100 mg/day, 24 weeks	HBeAg loss	24/24	4/34 2/40	13/6	2.35 (0.46; 12.07)	0.07 (-0.06; 0.20)	15
Lai, 2002[77] Entecavir, 0.5 mg/day, 24 weeks	Lamivudine, 100 mg/day, 24 weeks	HBeAg loss	24/24	0/43 2/40	0/6	0.19 (0.01; 3.77)	-0.05 (-0.13; 0.03)	-20
Lai, 2002[77] Entecavir, 0.01 mg/day, 24 weeks	Entecavir, 0.1 mg/day, 24 weeks	HBeAg seroconversion	24/24	0/52 2/34	0/7	0.13 (0.01; 2.67)	-0.06 (-0.15; 0.03)	-17
	Entecavir, 0.5 mg/day, 24 weeks	HBeAg seroconversion	24/24	0/52 0/43			0.00 (-0.04; 0.04)	
	Lamivudine, 100 mg/day, 24 weeks	HBeAg seroconversion	24/24	0/52 1/40	0/3	0.26 (0.01; 6.17)	-0.03 (-0.09; 0.04)	-40
Lai, 2002[77] Entecavir, 0.1 mg/day, 24 weeks	Entecavir, 0.5 mg/day, 24 weeks	HBeAg seroconversion	24/24	2/34 0/43	7/0	6.29 (0.31; 126.72)	0.06 (-0.03; 0.15)	17

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	Lamivudine, 100 mg/day, 24 weeks	HBeAg seroconversion	24/24	2/34 1/40	7/3	2.35 (0.22; 24.83)	0.03 (-0.06; 0.13)	30
Lai, 2002[77] Entecavir, 0.5 mg/day, 24 weeks	Lamivudine, 100 mg/day, 24 weeks	HBeAg seroconversion	24/24	0/43 1/40	0/3	0.31 (0.01; 7.41)	-0.03 (-0.09; 0.04)	-40
Chang, 2005[76] Entecavir, 1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Normalization of ALT levels	24/24	11/42 17/47	26/36	0.72 (0.38; 1.37)	-0.10 (-0.29; 0.09)	-10
	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Normalization of ALT levels	24/24	11/42 12/47	26/26	1.03 (0.51; 2.07)	0.01 (-0.18; 0.19)	152
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Normalization of ALT levels	24/24	11/42 7/45	26/16	1.68 (0.72; 3.94)	0.11 (-0.06; 0.28)	9
Chang, 2005[76] Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Normalization of ALT levels	24/24	17/47 12/47	36/26	1.42 (0.76; 2.63)	0.11 (-0.08; 0.29)	9
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Normalization of ALT levels	24/24	17/47 7/45	36/16	2.33 (1.07; 5.07)	**0.21 (0.03; 0.38)**	5
Chang, 2005[76] Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Normalization of ALT levels	24/24	12/47 7/45	26/16	1.64 (0.71; 3.79)	0.10 (-0.06; 0.26)	10

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Chang, 2005[76] Entecavir, 1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Normalization of ALT levels	48/48	19/42 17/47	45/36	1.25 (0.75; 2.07)	0.09 (-0.11; 0.29)	11
	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Normalization of ALT levels	48/48	19/42 14/47	45/30	1.52 (0.88; 2.63)	0.15 (-0.04; 0.35)	6
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, 48 weeks	Normalization of ALT levels	48/48	19/42 2/45	45/4	10.18 (2.52; 41.07)	**0.41 (0.25; 0.57)**	2
Chang, 2005[76] Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Normalization of ALT levels	48/48	17/47 14/47	36/30	1.21 (0.68; 2.17)	0.06 (-0.13; 0.25)	16
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Normalization of ALT levels	48/48	17/47 2/45	36/4	8.14 (1.99; 33.23)	**0.32 (0.17; 0.47)**	3
Chang, 2005[76] Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Normalization of ALT levels	48/48	14/47 2/45	30/4	6.70 (1.61; 27.84)	**0.25 (0.11; 0.40)**	4
Chang, 2005[76] Entecavir, 1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	ALT levels >2 that at baseline and 10 times the ULN	48/48	3/42 1/47	7/2	3.36 (0.36; 31.05)	0.05 (-0.04; 0.14)	20

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	ALT levels >2 that at baseline and 10 times the ULN	48/48	3/42 2/47	7/4	1.68 (0.29; 9.56)	0.03 (-0.07; 0.13)	35
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	ALT levels >2 that at baseline and 10 times the ULN	48/48	3/42 5/45	7/11	0.64 (0.16; 2.53)	-0.04 (-0.16; 0.08)	-25
Chang, 2005[76] Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	ALT levels >2 that at baseline and 10 times the ULN	48/48	1/47 2/47	2/4	0.50 (0.05; 5.33)	-0.02 (-0.09; 0.05)	-47
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	ALT levels >2 that at baseline and 10 times the ULN	48/48	1/47 5/45	2/11	0.19 (0.02; 1.58)	-0.09 (-0.19; 0.01)	-11
Chang, 2005[76] Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	ALT levels >2 that at baseline and 10 times the ULN	48/48	2/47 5/45	4/11	0.38 (0.08; 1.87)	-0.07 (-0.18; 0.04)	-15
Chang, 2005[76] Entecavir, 1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Death	48/48	0/42 1/47	0/2	0.37 (0.02; 8.89)	-0.02 (-0.08; 0.04)	-47
	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Death	48/48	0/42 1/47	0/2	0.37 (0.02; 8.89)	-0.02 (-0.08; 0.04)	-47

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Death	48/48	0/42 0/45			0.00 (-0.04; 0.04)	
Chang, 2005[76] Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Death	48/48	1/47 1/47	2/2	1.00 (0.06; 15.52)	0.00 (-0.06; 0.06)	
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Death	48/48	1/47 0/45	2/0	2.88 (0.12; 68.79)	0.02 (-0.04; 0.08)	47
Chang, 2005[76] Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total48 weeks	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total48 weeks	Death	48/48	1/47 0/45	2/0	2.88 (0.12; 68.79)	0.02 (-0.04; 0.08)	47
Chang, 2005[76] Entecavir, 1 mg/day after at least 24 weeks of lamivudine, total48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total48 weeks	Death	76/76	0/42 0/47			0.00 (-0.04; 0.04)	
	Entecavir, 0.1 mg/ day after at least 24 weeks of lamivudine, total48 weeks	Death	76/76	0/42 0/47			0.00 (-0.04; 0.04)	
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total48 weeks	Death	76/76	0/42 0/45			0.00 (-0.04; 0.04)	

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Chang, 2005[76] Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Death	76/76	0/47 0/47			0.00 (-0.04; 0.04)	
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Death	76/76	0/47 0/45			0.00 (-0.04; 0.04)	
Chang, 2005[76] Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Death	76/76	0/47 0/45			0.00 (-0.04; 0.04)	
Chang, 2005[76] Entecavir, 1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Any adverse event	48/48	36/42 34/47	86/72	1.18 (0.96; 1.47)	0.13 (-0.03; 0.30)	7
		Headache	48/48	10/42 12/47	24/26	0.93 (0.45; 1.93)	-0.02 (-0.20; 0.16)	-58
		Fatigue	48/48	7/42 7/47	17/15	1.12 (0.43; 2.93)	0.02 (-0.13; 0.17)	56
		Pyrexia	48/48	6/42 4/47	14/9	1.68 (0.51; 5.54)	0.06 (-0.07; 0.19)	17
		Bronchitis not otherwise specified	48/48	5/42 1/47	12/2	5.60 (0.68; 45.98)	0.10 (-0.01; 0.20)	10
		Upper respiratory tract infection not otherwise specified	48/48	4/42 4/47	10/9	1.12 (0.30; 4.20)	0.01 (-0.11; 0.13)	99
		Diarrhea not otherwise specified	48/48	3/42 6/47	7/13	0.56 (0.15; 2.10)	-0.06 (-0.18; 0.07)	-18
		Upper abdominal pain	48/48	3/42 2/47	7/4	1.68 (0.29; 9.56)	0.03 (-0.07; 0.13)	35
		Back pain	48/48	2/42 9/47	5/19	0.25 (0.06; 1.09)	**-0.14 (-0.27; -0.01)**	-7

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Arthralgia	48/48	2/42 7/47	5/15	0.32 (0.07; 1.46)	-0.10 (-0.22; 0.02)	-10
		Nasopharyngitis	48/48	1/42 5/47	2/11	0.22 (0.03; 1.84)	-0.08 (-0.18; 0.02)	-12
		Any severe (grade 3–4) adverse event	48/48	11/42 10/47	26/21	1.23 (0.58; 2.60)	0.05 (-0.13; 0.23)	20
		Any serious adverse event	48/48	5/42 2/47	12/4	2.80 (0.57; 13.67)	0.08 (-0.04; 0.19)	13
		Discontinuations due to adverse events	48/48	3/42 3/47	7/6	1.12 (0.24; 5.25)	0.01 (-0.10; 0.11)	132
		Increase in ALT>2 X baseline	48/48	7/42 7/47	17/15	1.12 (0.43; 2.93)	0.02 (-0.13; 0.17)	56
		Increase in ALT>3 X baseline	48/48	3/42 2/47	7/4	1.68 (0.29; 9.56)	0.03 (-0.07; 0.13)	35
	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Any adverse event	48/48	36/42 35/47	86/74	1.15 (0.93; 1.42)	0.11 (-0.05; 0.28)	9
		Headache	48/48	10/42 13/47	24/28	0.86 (0.42; 1.75)	-0.04 (-0.22; 0.14)	-26
		Fatigue	48/48	7/42 9/47	17/19	0.87 (0.36; 2.13)	-0.02 (-0.18; 0.13)	-40
		Pyrexia	48/48	6/42 5/47	14/11	1.34 (0.44; 4.08)	0.04 (-0.10; 0.17)	27
		Bronchitis not otherwise specified	48/48	5/42 0/47	12/0	12.28 (0.70; 215.63)	**0.12 (0.02; 0.22)**	8
		Upper respiratory tract infection not otherwise specified	48/48	4/42 2/47	10/4	2.24 (0.43; 11.60)	0.05 (-0.05; 0.16)	19
		Diarrhea not otherwise specified	48/48	3/42 5/47	7/11	0.67 (0.17; 2.64)	-0.03 (-0.15; 0.08)	-29
		Upper abdominal pain	48/48	3/42 3/47	7/6	1.12 (0.24; 5.25)	0.01 (-0.10; 0.11)	132
		Back pain	48/48	2/42 2/47	5/4	1.12 (0.16; 7.60)	0.01 (-0.08; 0.09)	197

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Arthralgia	48/48	2/42 3/47	5/6	0.75 (0.13; 4.25)	-0.02 (-0.11; 0.08)	-62
		Nasopharyngitis	48/48	1/42 5/47	2/11	0.22 (0.03; 1.84)	-0.08 (-0.18; 0.02)	-12
		Any severe (grade 3–4) adverse event	48/48	11/42 11/47	26/23	1.12 (0.54; 2.31)	0.03 (-0.15; 0.21)	36
		Any serious adverse event	48/48	5/42 1/47	12/2	5.60 (0.68; 45.98)	0.10 (-0.01; 0.20)	10
		Discontinuations due to adverse events	48/48	3/42 3/47	7/6	1.12 (0.24; 5.25)	0.01 (-0.10; 0.11)	132
		Increase in ALT >2 X baseline	48/48	7/42 11/47	17/23	0.71 (0.30; 1.67)	-0.07 (-0.23; 0.10)	-15
		Increase in ALT >3 X baseline	48/48	3/42 4/47	7/9	0.84 (0.20; 3.54)	-0.01 (-0.13; 0.10)	-73
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Any adverse event	48/48	36/42 38/45	86/84	1.02 (0.85; 1.21)	0.01 (-0.14; 0.16)	79
		Headache	48/48	10/42 10/45	24/22	1.07 (0.50; 2.31)	0.02 (-0.16; 0.19)	63
		Fatigue	48/48	7/42 6/45	17/13	1.25 (0.46; 3.42)	0.03 (-0.12; 0.18)	30
		Pyrexia	48/48	6/42 3/45	14/7	2.14 (0.57; 8.03)	0.08 (-0.05; 0.20)	13
		Bronchitis not otherwise specified	48/48	5/42 2/45	12/4	2.68 (0.55; 13.07)	0.07 (-0.04; 0.19)	13
		Upper respiratory tract infection not otherwise specified	48/48	4/42 6/45	10/13	0.71 (0.22; 2.36)	-0.04 (-0.17; 0.10)	-26
		Diarrhea not otherwise specified	48/48	3/42 3/45	7/7	1.07 (0.23; 5.02)	0.00 (-0.10; 0.11)	210
		Upper abdominal pain	48/48	3/42 5/45	7/11	0.64 (0.16; 2.53)	-0.04 (-0.16; 0.08)	-25
		Back pain	48/48	2/42 3/45	5/7	0.71 (0.13; 4.07)	-0.02 (-0.12; 0.08)	-53

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Arthralgia	48/48	2/42 2/45	5/4	1.07 (0.16; 7.27)	0.00 (-0.08; 0.09)	315
		Nasopharyngitis	48/48	1/42 5/45	2/11	0.21 (0.03; 1.76)	-0.09 (-0.19; 0.02)	-11
		Any severe (grade 3–4) adverse event	48/48	11/42 9/45	26/20	1.31 (0.60; 2.84)	0.06 (-0.12; 0.24)	16
		Any serious adverse event	48/48	5/42 3/45	12/7	1.79 (0.45; 7.01)	0.05 (-0.07; 0.17)	19
		Discontinuations due to adverse events	48/48	3/42 4/45	7/9	0.80 (0.19; 3.38)	-0.02 (-0.13; 0.10)	-57
		Increase in ALT>2 X baseline	48/48	7/42 15/45	17/33	0.50 (0.23; 1.10)	-0.17 (-0.34; 0.01)	-6
		Increase in ALT>3 X baseline	48/48	3/42 6/45	7/13	0.54 (0.14; 2.01)	-0.06 (-0.19; 0.06)	-16
Chang, 2005[76] Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Any adverse event	48/48	34/47 35/47	72/74	0.97 (0.76; 1.24)	-0.02 (-0.20; 0.16)	-47
		Headache	48/48	12/47 13/47	26/28	0.92 (0.47; 1.81)	-0.02 (-0.20; 0.16)	-47
		Fatigue	48/48	7/47 9/47	15/19	0.78 (0.32; 1.92)	-0.04 (-0.19; 0.11)	-23
		Pyrexia	48/48	4/47 5/47	9/11	0.80 (0.23; 2.80)	-0.02 (-0.14; 0.10)	-47
		Bronchitis not otherwise specified	48/48	1/47 0/47	2/0	3.00 (0.13; 71.82)	0.02 (-0.04; 0.08)	47
		Upper respiratory tract infection not otherwise specified	48/48	4/47 2/47	9/4	2.00 (0.38; 10.40)	0.04 (-0.06; 0.14)	23
		Diarrhea not otherwise specified	48/48	6/47 5/47	13/11	1.20 (0.39; 3.66)	0.02 (-0.11; 0.15)	47
		Upper abdominal pain	48/48	2/47 3/47	4/6	0.67 (0.12; 3.81)	-0.02 (-0.11; 0.07)	-47
		Back pain	48/48	9/47 2/47	19/4	4.50 (1.03; 19.73)	**0.15 (0.02; 0.28)**	7

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Arthralgia	48/48	7/47 3/47	15/6	2.33 (0.64; 8.48)	0.09 (-0.04; 0.21)	12
		Nasopharyngitis	48/48	5/47 5/47	11/11	1.00 (0.31; 3.23)	0.00 (-0.12; 0.12)	
		Any severe (grade 3–4) adverse event	48/48	10/47 11/47	21/23	0.91 (0.43; 1.93)	-0.02 (-0.19; 0.15)	-47
		Any serious adverse event	48/48	2/47 1/47	4/2	2.00 (0.19; 21.31)	0.02 (-0.05; 0.09)	47
		Discontinuations due to adverse events	48/48	3/47 3/47	6/6	1.00 (0.21; 4.70)	0.00 (-0.10; 0.10)	
		Increase in ALT >2 X baseline	48/48	7/47 11/47	15/23	0.64 (0.27; 1.50)	-0.09 (-0.24; 0.07)	-12
		Increase in ALT >3 X baseline	48/48	2/47 4/47	4/9	0.50 (0.10; 2.60)	-0.04 (-0.14; 0.06)	-23
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Any adverse event	48/48	34/47 38/45	72/84	0.86 (0.69; 1.06)	-0.12 (-0.29; 0.04)	-8
		Headache	48/48	12/47 10/45	26/22	1.15 (0.55; 2.39)	0.03 (-0.14; 0.21)	30
		Fatigue	48/48	7/47 6/45	15/13	1.12 (0.41; 3.07)	0.02 (-0.13; 0.16)	64
		Pyrexia	48/48	4/47 3/45	9/7	1.28 (0.30; 5.39)	0.02 (-0.09; 0.13)	54
		Bronchitis not otherwise specified	48/48	1/47 2/45	2/4	0.48 (0.04; 5.10)	-0.02 (-0.10; 0.05)	-43
		Upper respiratory tract infection not otherwise specified	48/48	4/47 6/45	9/13	0.64 (0.19; 2.11)	-0.05 (-0.18; 0.08)	-21
		Diarrhea not otherwise specified	48/48	6/47 3/45	13/7	1.91 (0.51; 7.20)	0.06 (-0.06; 0.18)	16
		Upper abdominal pain	48/48	2/47 5/45	4/11	0.38 (0.08; 1.87)	-0.07 (-0.18; 0.04)	-15
		Back pain	48/48	9/47 3/45	19/7	2.87 (0.83; 9.94)	0.12 (-0.01; 0.26)	8

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Arthralgia	48/48	7/47 2/45	15/4	3.35 (0.73; 15.28)	0.10 (-0.01; 0.22)	10
		Nasopharyngitis	48/48	5/47 5/45	11/11	0.96 (0.30; 3.09)	0.00 (-0.13; 0.12)	-212
		Any severe (grade 3–4) adverse event	48/48	10/47 9/45	21/20	1.06 (0.48; 2.37)	0.01 (-0.15; 0.18)	78
		Any serious adverse event	48/48	2/47 3/45	4/7	0.64 (0.11; 3.64)	-0.02 (-0.12; 0.07)	-41
		Discontinuations due to adverse events	48/48	3/47 4/45	6/9	0.72 (0.17; 3.03)	-0.03 (-0.13; 0.08)	-40
		Increase in ALT >2 X baseline	48/48	7/47 15/45	15/33	0.45 (0.20; 0.99)	-0.18 (-0.36; -0.01)	-5
		Increase in ALT >3 X baseline	48/48	2/47 6/45	4/13	0.32 (0.07; 1.50)	-0.09 (-0.21; 0.02)	-11
Chang, 2005[76] Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Any adverse event	48/48	35/47 38/45	74/84	0.88 (0.72; 1.09)	-0.10 (-0.26; 0.06)	-10
		Headache	48/48	13/47 10/45	28/22	1.24 (0.61; 2.55)	0.05 (-0.12; 0.23)	18
		Fatigue	48/48	9/47 6/45	19/13	1.44 (0.56; 3.71)	0.06 (-0.09; 0.21)	17
		Pyrexia	48/48	5/47 3/45	11/7	1.60 (0.40; 6.29)	0.04 (-0.07; 0.15)	25
		Bronchitis not otherwise specified	48/48	0/47 2/45	0/4	0.19 (0.01; 3.89)	-0.04 (-0.12; 0.03)	-23
		Upper respiratory tract infection not otherwise specified	48/48	2/47 6/45	4/13	0.32 (0.07; 1.50)	-0.09 (-0.21; 0.02)	-11
		Diarrhea not otherwise specified	48/48	5/47 3/45	11/7	1.60 (0.40; 6.29)	0.04 (-0.07; 0.15)	25
		Upper abdominal pain	48/48	3/47 5/45	6/11	0.57 (0.15; 2.26)	-0.05 (-0.16; 0.07)	-21
		Back pain	48/48	2/47 3/45	4/7	0.64 (0.11; 3.64)	-0.02 (-0.12; 0.07)	-41

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Arthralgia	48/48	3/47 2/45	6/4	1.44 (0.25; 8.20)	0.02 (-0.07; 0.11)	52
		Nasopharyngitis	48/48	5/47 5/45	11/11	0.96 (0.30; 3.09)	0.00 (-0.13; 0.12)	-212
		Any severe (grade 3-4) adverse event	48/48	11/47 9/45	23/20	1.17 (0.54; 2.55)	0.03 (-0.13; 0.20)	29
		Any serious adverse event	48/48	1/47 3/45	2/7	0.32 (0.03; 2.96)	-0.05 (-0.13; 0.04)	-22
		Discontinuations due to adverse events	48/48	3/47 4/45	6/9	0.72 (0.17; 3.03)	-0.03 (-0.13; 0.08)	-40
		Increase in ALT >2 X baseline	48/48	11/47 15/45	23/33	0.70 (0.36; 1.36)	-0.10 (-0.28; 0.08)	-10
		Increase in ALT >3 X baseline	48/48	4/47 6/45	9/13	0.64 (0.19; 2.11)	-0.05 (-0.18; 0.08)	-21
Chang, 2005[76] Entecavir, 1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Any adverse event	76/76	8/42 9/47	19/19	0.99 (0.42; 2.34)	0.00 (-0.16; 0.16)	-987
		Any severe (grade 3–4) adverse event	76/76	2/42 1/47	5/2	2.24 (0.21; 23.80)	0.03 (-0.05; 0.10)	38
		Any serious adverse event	76/76	0/42 0/47			0.00 (-0.04; 0.04)	
		Increase in ALT >2 X baseline	76/76	7/42 8/47	17/17	0.98 (0.39; 2.47)	0.00 (-0.16; 0.15)	-282
		Increase in ALT>3 X baseline	76/76	6/42 4/47	14/9	1.68 (0.51; 5.54)	0.06 (-0.07; 0.19)	17
	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Any adverse event	76/76	8/42 5/47	19/11	1.79 (0.63; 5.05)	0.08 (-0.06; 0.23)	12
		Any severe (grade 3-4) adverse event	76/76	2/42 2/47	5/4	1.12 (0.16; 7.60)	0.01 (-0.08; 0.09)	197
		Any serious adverse event	76/76	0/42 1/47	0/2	0.37 (0.02; 8.89)	-0.02 (-0.08; 0.04)	-47
		Increase in ALT >2 X baseline	76/76	7/42 9/47	17/19	0.87 (0.36; 2.13)	-0.02 (-0.18; 0.13)	-40

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Increase in ALT >3 X baseline	76/76	6/42 6/47	14/13	1.12 (0.39; 3.21)	0.02 (-0.13; 0.16)	66
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Any adverse event	76/76	8/42 5/45	19/11	1.71 (0.61; 4.83)	0.08 (-0.07; 0.23)	13
		Any severe (grade 3-4) adverse event	76/76	2/42 1/45	5/2	2.14 (0.20; 22.77)	0.03 (-0.05; 0.10)	39
		Any serious adverse event	76/76	0/42 2/45	0/4	0.21 (0.01; 4.33)	-0.04 (-0.12; 0.03)	-23
		Increase in ALT >2 X baseline	76/76	7/42 3/45	17/7	2.50 (0.69; 9.04)	0.10 (-0.03; 0.23)	10
		Increase in ALT >3 X baseline	76/76	6/42 2/45	14/4	3.21 (0.69; 15.05)	0.10 (-0.02; 0.22)	10
Chang, 2005[76] Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Any adverse event	76/76	9/47 5/47	19/11	1.80 (0.65; 4.97)	0.09 (-0.06; 0.23)	12
		Any severe (grade 3-4) adverse event	76/76	1/47 2/47	2/4	0.50 (0.05; 5.33)	-0.02 (-0.09; 0.05)	-47
		Any serious adverse event	76/76	0/47 1/47	0/2	0.33 (0.01; 7.98)	-0.02 (-0.08; 0.04)	-47
		Increase in ALT >2 X baseline	76/76	8/47 9/47	17/19	0.89 (0.38; 2.11)	-0.02 (-0.18; 0.13)	-47
		Increase in ALT >3 X baseline	76/76	4/47 6/47	9/13	0.67 (0.20; 2.21)	-0.04 (-0.17; 0.08)	-23
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Any adverse event	76/76	9/47 5/45	19/11	1.72 (0.63; 4.75)	0.08 (-0.06; 0.23)	12
		Any severe (grade 3-4) adverse event	76/76	1/47 1/45	2/2	0.96 (0.06; 14.85)	0.00 (-0.06; 0.06)	-1058
		Any serious adverse event	76/76	0/47 2/45	0/4	0.19 (0.01; 3.89)	-0.04 (-0.12; 0.03)	-23
		Increase in ALT >2 X baseline	76/76	8/47 3/45	17/7	2.55 (0.72; 9.02)	0.10 (-0.03; 0.23)	10
		Increase in ALT >3 X baseline	76/76	4/47 2/45	9/4	1.91 (0.37; 9.95)	0.04 (-0.06; 0.14)	25
Chang, 2005[76] Entecavir, 0.1 mg/day	Lamivudine, 100 mg/day after at	Any adverse event	76/76	5/47 5/45	11/11	0.96 (0.30; 3.09)	0.00 (-0.13; 0.12)	-212

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
after at least 24 weeks of lamivudine, total 48 weeks	least 24 weeks of lamivudine, total 48 weeks	Any severe (grade 3-4) adverse event	76/76	2/47 1/45	4/2	1.91 (0.18; 20.39)	0.02 (-0.05; 0.09)	49
		Any serious adverse event	76/76	1/47 2/45	2/4	0.48 (0.04; 5.10)	-0.02 (-0.10; 0.05)	-43
		Increase in ALT >2 X baseline	76/76	9/47 3/45	19/7	2.87 (0.83; 9.94)	0.12 (-0.01; 0.26)	8
		Increase in ALT >3 X baseline	76/76	6/47 2/45	13/4	2.87 (0.61; 13.50)	0.08 (-0.03; 0.20)	12
Chang, 2005[76] Entecavir, 1 mg/day after at least 24 weeks of lamivudine, total48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA loss by bDNA assay	24/24	33/42 24/47	79/51	1.54 (1.12; 2.12)	**0.28 (0.09; 0.46)**	4
	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA loss by bDNA assay	24/24	33/42 9/47	79/19	4.10 (2.23; 7.54)	**0.59 (0.43; 0.76)**	2
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA loss by bDNA assay	24/24	33/42 6/45	79/13	5.89 (2.75; 12.62)	**0.65 (0.49; 0.81)**	2
Chang, 2005[76] Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, 48 weeks	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA loss by bDNA assay	24/24	24/47 9/47	51/19	2.67 (1.39; 5.11)	**0.32 (0.14; 0.50)**	3
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, 48 weeks	HBV DNA by bDNA assay	24/24	24/47 6/45	51/13	3.83 (1.73; 8.49)	**0.38 (0.20; 0.55)**	3

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Chang, 2005[76] Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA by bDNA assay	24/24	9/47 6/45	19/13	1.44 (0.56; 3.71)	0.06 (-0.09; 0.21)	17
Chang, 2005[76] Entecavir, 1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	24/24	7/42 4/47	17/9	1.96 (0.62; 6.22)	0.08 (-0.06; 0.22)	12
	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	24/24	7/42 0/47	17/0	16.74 (0.99; 284.58)	**0.17 (0.05; 0.28)**	6
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	24/24	7/42 1/45	17/2	7.50 (0.96; 58.41)	**0.14 (0.02; 0.27)**	7
Chang, 2005[76] Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	24/24	4/47 0/47	9/0	9.00 (0.50; 162.62)	**0.09 (0.00; 0.17)**	12
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	24/24	4/47 1/45	9/2	3.83 (0.44; 32.97)	0.06 (-0.03; 0.15)	16
Chang, 2005[76] Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	24/24	0/47 1/45	0/2	0.32 (0.01; 7.64)	-0.02 (-0.08; 0.04)	-45

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Chang, 2005[76] entecavir, 1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	48/48	11/42 12/47	26/26	1.03 (0.51; 2.07)	0.01 (-0.18; 0.19)	152
	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	48/48	11/42 2/47	26/4	6.15 (1.45; 26.19)	**0.22 (0.07; 0.36)**	5
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	48/48	11/42 2/45	26/4	5.89 (1.39; 25.04)	**0.22 (0.07; 0.36)**	5
Chang, 2005[76] entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.1 mg/ day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	48/48	12/47 2/47	26/4	6.00 (1.42; 25.36)	**0.21 (0.08; 0.35)**	5
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	48/48	12/47 2/45	26/4	5.74 (1.36; 24.25)	**0.21 (0.07; 0.35)**	5
Chang, 2005[76] entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, total 48 weeks	HBV DNA <400 copies/mL	48/48	2/47 2/45	4/4	0.96 (0.14; 6.51)	0.00 (-0.09; 0.08)	-529
Sherman, 2006[75] Entecavir, 1 mg/day, 63 weeks	Lamivudine, 100 , 52 weeks	ALT normalization (<1.0 X ULN)	63/52	86/141 22/145	61/15	4.02 (2.68; 6.04)	**0.46 (0.36; 0.56)**	2
		ALT flares	63/52	1/141 16/145	1/11	0.06 (0.01; 0.48)	**-0.10 (-0.16; -0.05)**	-10
		Death	48/48	0/141 1/145	0/1	0.34 (0.01; 8.34)	-0.01 (-0.03; 0.01)	-145

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Deaths	63/52	1/141 2/145	1/1	0.51 (0.05; 5.61)	-0.01 (-0.03; 0.02)	-149
		Treatment failure as no response. Response was defined as histological improvement, (>2-point decrease in the Knodell necroinflammatory score and no worsening of the Knodell fibrosis score); serum HBV DNA <0.7 MEq/mL by bDNA assay and ALT <1.25 ULN	48/48	0/141 2/145	0/1	0.21 (0.01; 4.25)	-0.01 (-0.04; 0.01)	-73
		HBV DNA <0.7 MEq/mL by bDNA and ALT <1.25 X ULN	63/52	77/141 6/145	55/4	13.20 (5.94; 29.31)	**0.50 (0.42; 0.59)**	2
		Adverse events	48/48	1/141 8/145	1/6	0.13 (0.02; 1.01)	**-0.05 (-0.09; -0.01)**	-21
		Any adverse event	63/52	120/141 117/145	85/81	1.05 (0.95; 1.17)	0.04 (-0.04; 0.13)	23
		Serious adverse events	63/52	14/141 11/145	10/8	1.31 (0.62; 2.78)	0.02 (-0.04; 0.09)	43
		Discontinuations because of adverse events	63/52	2/141 10/145	1/7	0.21 (0.05; 0.92)	**-0.05 (-0.10; -0.01)**	-18
		Improvement of 2 points in the necroinflammatory component of the	63/52	68/141 32/145	48/22	2.19 (1.54; 3.10)	**0.26 (0.16; 0.37)**	4

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Knodell score with no worsening in the fibrosis component of the score						
		No histological improvement	63/52	42/141 66/145	30/46	0.65 (0.48; 0.89)	**-0.16 (-0.27; -0.05)**	-6
		Improvement in Ishak fibrosis	63/52	42/141 19/145	30/13	2.27 (1.39; 3.71)	**0.17 (0.07; 0.26)**	6
		No change in Ishak fibrosis	63/52	54/141 49/145	38/34	1.13 (0.83; 1.54)	0.05 (-0.07; 0.16)	22
		Worsening in Ishak fibrosis	63/52	14/141 30/145	10/21	0.48 (0.27; 0.87)	**-0.11 (-0.19; -0.03)**	-9
		HBV DNA <300 copies/mL by PCR	63/52	27/141 2/145	19/1	13.88 (3.36; 57.29)	**0.18 (0.11; 0.25)**	6
		Loss of HBeAg	63/52	14/141 5/145	10/3	2.88 (1.07; 7.78)	**0.06 (0.01; 0.12)**	15
		HBeAg seroconversion	63/52	11/141 4/145	8/3	2.83 (0.92; 8.67)	**0.05 (0.00; 0.10)**	20
		HBV DNA <0.7 MEq/mL without HBeAg loss	63/52	80/141 7/145	57/5	11.75 (5.62; 24.56)	**0.52 (0.43; 0.61)**	2
		No response (HBV DNA >0.7 MEq/mL)	63/52	40/141 121/145	28/83	0.34 (0.26; 0.45)	**-0.55 (-0.65; -0.45)**	-2
		HBV DNA <0.7 MEq/mL and HBeAg loss	87/76	5/141 1/145	4/1	5.14 (0.61; 43.46)	**0.03 (0.00; 0.06)**	35
Gish, 2007[101] entecavir, 0.5 mg/day, 96 weeks	Lamivudine , 100 mg/day, 96 weeks	ALT normalization (<1 ULN)	48/48	161/243 116/165	66/70	0.94 (0.82; 1.08)	-0.04 (-0.13; 0.05)	-25
		ALT normalization (<1 ULN)	96/96	193/243 112/165	79/68	1.17 (1.03; 1.32)	**0.12 (0.03; 0.20)**	9
		ALT normalization (<1 ULN)	96/96	307/354 280/355	87/79	1.10 (1.03; 1.18)	**0.08 (0.02; 0.13)**	13

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		ALT levels >2 baseline and 10 X the ULN)	96/96	11/354 25/355	3/7	0.44 (0.22; 0.88)	**-0.04 (-0.07; -0.01)**	-25
		Liver decompensation	96/96	0/354 1/355		0.33 (0.01; 8.18)	0.00 (-0.01; 0.00)	-355
		Death	120/120	2/354 4/355	1/1	0.50 (0.09; 2.72)	-0.01 (-0.02; 0.01)	-178
		Death	96/96	0/354 2/355	0/1	0.20 (0.01; 4.16)	-0.01 (-0.02; 0.00)	-178
		Discontinuation due to adverse effect	96/96	1/243 9/165	0/5	0.08 (0.01; 0.59)	**-0.05 (-0.09; -0.01)**	-20
		Serious adverse events	96/96	28/354 28/355	8/8	1.00 (0.61; 1.66)	0.00 (-0.04; 0.04)	4488
		Any adverse effect	96/96	308/354 298/355	87/84	1.04 (0.98; 1.10)	0.03 (-0.02; 0.08)	33
		Any adverse effect	120/120	92/243 85/165	38/52	0.73 (0.59; 0.91)	**-0.14 (-0.23; -0.04)**	-7
		Serious adverse events	144/144	9/243 11/165	4/7	0.56 (0.24; 1.31)	-0.03 (-0.07; 0.02)	-34
		HBV DNA level <300 copies/mL (57 IU/mL by PCR assay	48/48	156/243 66/165	64/40	1.60 (1.30; 1.98)	**0.24 (0.15; 0.34)**	4
		HBV DNA level <300 copies/mL (57 IU/mL by PCR assay	96/96	180/243 60/165	74/36	2.04 (1.64; 2.53)	**0.38 (0.29; 0.47)**	3
		HBeAg seroconversion	96/96	26/243 20/165	11/12	0.88 (0.51; 1.53)	-0.01 (-0.08; 0.05)	-70
		HBV DNA levels <0.7 MEq/mL and loss of HBeAg	96/96	111/354 93/355	31/26	1.20 (0.95; 1.51)	0.05 (-0.01; 0.12)	19
		HBV DNA levels <0.7 MEq/mL but HBeAg+	96/96	202/354 86/355	57/24	2.36 (1.92; 2.89)	**0.33 (0.26; 0.40)**	3

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		HBV DNA levels >105 copies/mL	96/96	5/243 43/165	2/26	0.08 (0.03; 0.20)	**-0.24 (-0.31; -0.17)**	-4
		HBV DNA level <300 copies/mL (57 IU/mL) by PCR	96/96	284/354 137/355	80/39	2.08 (1.81; 2.39)	**0.42 (0.35; 0.48)**	2
		HBeAg seroconversion	96/96	110/243 92/165	45/56	0.81 (0.67; 0.99)	**-0.10 (-0.20; -0.01)**	-10
		HBsAg loss	96/96	18/243 10/165	7/6	1.22 (0.58; 2.58)	0.01 (-0.04; 0.06)	74
		HBsAg seroconversion	96/96	6/243 8/165	2/5	0.51 (0.18; 1.44)	-0.02 (-0.06; 0.01)	-42
		Virologic break through (1 log10 increase in HBV DNA level above nadir by PCR, as determined by 2 sequential measure-ments or last on-treatment measurement)	96/96	13/354 0/355	4/0	27.08 (1.62; 453.72)	**0.04 (0.02; 0.06)**	27
Chang, 2006[73] Entecavir (Baraclude, Bristol-Myers Squibb), 0.5 mg/day, 52 weeks	Lamivudine (Epivir-HBV, GlaxoSmithKline), 100 mg/day, 52 weeks	ALT normalization (≤1× ULN)	52/52	242/354 213/355	68/60	1.14 (1.02; 1.27)	**0.08 (0.01; 0.15)**	12
		ALT >2× baseline and >10 × ULN	52/52	12/354 23/355	3/6	0.52 (0.26; 1.04)	-0.03 (-0.06; 0.00)	-32
		ALT >2 × reference value and >10 x ULN	76/76	2/354 9/355	1/3	0.22 (0.05; 1.02)	-0.02 (-0.04; 0.00)	-51
		Death	52/52	0/354 2/355	0/1	0.20 (0.01; 4.16)	-0.01 (-0.02; 0.00)	-178
		Hepatic decompensation	76/76	0/354 1/355		0.33 (0.01; 8.18)	0.00 (-0.01; 0.00)	-355
		Undetectable HBV DNA by PCR and normal ALT	76/76	51/354 40/355	14/11	1.28 (0.87; 1.88)	0.03 (-0.02; 0.08)	32

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Discontinuation due to adverse events	52/52	1/354 9/355	0/3	0.11 (0.01; 0.87)	**-0.02 (-0.04; -0.01)**	-44
		Any adverse event	52/52	306/354 297/355	86/84	1.03 (0.97; 1.10)	0.03 (-0.02; 0.08)	36
		Serious adverse event	52/52	27/354 30/355	8/8	0.90 (0.55; 1.49)	-0.01 (-0.05; 0.03)	-121
		Discontinuation due to adverse event	52/52	1/354 9/355	0/3	0.11 (0.01; 0.87)	**-0.02 (-0.04; -0.01)**	-44
		ALT >2 X baseline and >5× ULN	52/52	37/354 59/355	10/17	0.63 (0.43; 0.92)	**-0.06 (-0.11; -0.01)**	-16
		ALT > 2 X reference value and >5× ULN	76/76	3/354 16/355	1/5	0.19 (0.06; 0.64)	**-0.04 (-0.06; -0.01)**	-27
		Histological improvement-improvement by at least 2 points in the Knodell necroinflammatory score, with no worsening in the Knodell fibrosis score	52/52	226/354 195/355	64/55	1.16 (1.03; 1.31)	**0.09 (0.02; 0.16)**	11
		No improvement in Knodell necroinflammatory score	52/52	66/354 74/355	19/21	0.89 (0.66; 1.20)	-0.02 (-0.08; 0.04)	-45
		Improved Ishak fibrosis scores	52/52	138/354 124/355	39/35	1.12 (0.92; 1.35)	0.04 (-0.03; 0.11)	25
		Worsened Ishak fibrosis scores	52/52	28/354 36/355	8/10	0.78 (0.49; 1.25)	-0.02 (-0.06; 0.02)	-45
		HBV DNA <300	52/52	236/354	67/36	1.83 (1.57; 2.14)	**0.30 (0.23; 0.37)**	3

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		copies/ml by PCR assay		129/355				
		HBV DNA <0.7 MEq/ml by branched-chain DNA assay	52/52	322/354 232/355	91/65	1.39 (1.28; 1.51)	**0.26 (0.20; 0.31)**	4
		Loss of HBeAg	52/52	78/354 70/355	22/20	1.12 (0.84; 1.49)	0.02 (-0.04; 0.08)	43
		HBeAg seroconversion	52/52	74/354 64/355	21/18	1.16 (0.86; 1.57)	0.03 (-0.03; 0.09)	35
		HBsAg loss	52/52	6/354 4/355	2/1	1.50 (0.43; 5.28)	0.01 (-0.01; 0.02)	176
		HBV DNA level, ≥0.7 MEq per milliliter	52/52	19/354 94/355	5/26	0.20 (0.13; 0.32)	-**0.21 (-0.26; -0.16)**	-5
		HBV DNA <0.7 MEq /ml and HBeAg loss	52/52	74/354 67/355	21/19	1.11 (0.82; 1.49)	0.02 (-0.04; 0.08)	49
		HBV DNA level of < 0.7 MEq /ml, without HBeAg loss	52/52	247/354 165/355	70/46	1.50 (1.32; 1.71)	**0.23 (0.16; 0.30)**	4
		HBV DNA < 0.7 MEq /ml and HBeAg loss	76/76	61/354 49/355	17/14	1.25 (0.88; 1.76)	0.03 (-0.02; 0.09)	29
		Undetectable HBV DNA by PCR	76/76	25/354 20/355	7/6	1.25 (0.71; 2.21)	0.01 (-0.02; 0.05)	70
		Virological rebound confirmed increase in the HBV DNA level by at least 1 log [on a base-10 scale] copy/ml from the nadir value	76/76	6/354 63/355	2/18	0.10 (0.04; 0.22)	**-0.16 (-0.20; -0.12)**	-6

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		ALT normalization (≤1.0 X ULN)	52/52	253/325 222/313	78/71	1.10 (1.00; 1.20)	**0.07 (0.00; 0.14)**	14
		ALT >2 X baseline and >10× ULN	52/52	3/325 5/313	1/2	0.58 (0.14; 2.40)	-0.01 (-0.02; 0.01)	-148
		ALT >2 X baseline and >10× ULN	76/76	23/325 29/313	7/9	0.76 (0.45; 1.29)	-0.02 (-0.06; 0.02)	-46
		Death	52/52	2/325 0/313	1/0	4.82 (0.23; 99.92)	**0.01 (0.00; 0.02)**	163
		Any adverse event	52/52	246/325 248/313	76/79	0.96 (0.88; 1.04)	-0.04 (-0.10; 0.03)	-28
		Serious adverse event	52/52	21/325 24/313	6/8	0.84 (0.48; 1.48)	-0.01 (-0.05; 0.03)	-83
		Discontinuation due to adverse event	52/52	6/325 9/313	2/3	0.64 (0.23; 1.78)	-0.01 (-0.03; 0.01)	-97
		ALT >2 X baseline and >5× ULN	52/52	6/325 10/313	2/3	0.58 (0.21; 1.57)	-0.01 (-0.04; 0.01)	-74
		ALT >2 X baseline and >5 X ULN	76/76	36/325 77/313	11/25	0.45 (0.31; 0.65)	**-0.14 (-0.19; -0.08)**	-7
		Histological improvement-improvement by at least 2 points in the Knodell necro-inflammatory score, with no worsening in the Knodell fibrosis score	52/52	208/325 174/313	64/56	1.15 (1.01; 1.31)	**0.08 (0.01; 0.16)**	12
		No improvement in Knodell necro-inflammatory score	52/52	57/325 76/313	18/24	0.72 (0.53; 0.98)	-0.07 (-0.13; 0.00)	-15
		HBV DNA <300 copies/ml by PCR assay	52/52	293/325 225/313	90/72	1.25 (1.16; 1.36)	**0.18 (0.12; 0.24)**	5

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Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		HBV DNA <0.7 MEq/ml by branched-chain DNA assay	52/52	309/325 279/313	95/89	1.07 (1.02; 1.12)	**0.06 (0.02; 0.10)**	17
		Virological rebound confirmed increase in the HBV DNA level by at least 1 log [on a base-10 scale] copy/ml from the nadir value	52/52	5/325 25/313	2/8	0.19 (0.07; 0.50)	**-0.06 (-0.10; -0.03)**	-16
Schiff, 2003[47] Lamivudine, 100 mg/daily, 52 weeks	Placebo, , 52 weeks	Normal ALT	52/52	51/119 8/56	43/14	3.00 (1.53; 5.89)	**0.29 (0.16; 0.41)**	3
		Discontinuation due to adverse effects	52/52	3/119 5/56	3/9	0.28 (0.07; 1.14)	-0.06 (-0.14; 0.02)	-16
		Malaise/fatigue	52/52	32/119 18/56	27/32	0.84 (0.52; 1.36)	-0.05 (-0.20; 0.09)	-19
		Fever	52/52	9/119 0/56	8/0	9.03 (0.53; 152.37)	**0.08 (0.02; 0.13)**	13
		Headache	52/52	18/119 13/56	15/23	0.65 (0.34; 1.23)	-0.08 (-0.21; 0.05)	-12
		Nausea/vomiting	52/52	20/119 11/56	17/20	0.86 (0.44; 1.66)	-0.03 (-0.15; 0.10)	-35
		Hair loss/alopecia	52/52	2/119 2/56	2/4	0.47 (0.07; 3.26)	-0.02 (-0.07; 0.03)	-53
		Muscle pain	52/52	22/119 5/56	18/9	2.07 (0.83; 5.18)	0.10 (-0.01; 0.20)	10
		Viral respiratory infections	52/52	3/119 0/56	3/0	3.33 (0.17; 63.30)	0.03 (-0.01; 0.06)	40
		Feeding problems	52/52	2/119 2/56	2/4	0.47 (0.07; 3.26)	-0.02 (-0.07; 0.03)	-53
		Depression	52/52	5/119 2/56	4/4	1.18 (0.24; 5.88)	0.01 (-0.05; 0.07)	159

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Decreased WBCs	52/52	1/119 0/56	1/0	1.43 (0.06; 34.44)	0.01 (-0.02; 0.04)	119
		Rheumatism	52/52	6/119 2/56	5/4	1.41 (0.29; 6.78)	0.01 (-0.05; 0.08)	68
		Diarrhea	52/52	15/119 0/56	13/0	14.73 (0.90; 241.77)	**0.13 (0.06; 0.19)**	8
		Abnormal ALT/AST	52/52	22/119 9/56	18/16	1.15 (0.57; 2.33)	0.02 (-0.09; 0.14)	41
		Pain	52/52	1/119 4/56	1/7	0.12 (0.01; 1.03)	-0.06 (-0.13; 0.01)	-16
		Musculoskeletal pain	52/52	1/119 2/56	1/4	0.24 (0.02; 2.54)	-0.03 (-0.08; 0.02)	-37
		Abnormal enzymes (amylase/CPK)	52/52	19/119 4/56	16/7	2.24 (0.80; 6.26)	0.09 (-0.01; 0.18)	11
		ALT >2 at baseline and >500U/l	52/52	9/119 4/56	8/7	1.06 (0.34; 3.29)	0.00 (-0.08; 0.09)	238
		ALT >2 at baseline and >500U/l	68/68	3/119 2/56	3/4	0.71 (0.12; 4.11)	-0.01 (-0.07; 0.05)	-95
		Histological response: reduction in HAI score >2	52/52	62/119 14/56	52/25	2.08 (1.28; 3.39)	**0.27 (0.13; 0.42)**	4
		Worsening in histology: increase in HAI by >2 scores	52/52	8/119 9/56	7/16	0.42 (0.17; 1.03)	-0.09 (-0.20; 0.01)	-11
		Improved necroinflammatory activity	52/52	63/119 16/56	53/29	1.85 (1.18; 2.90)	**0.24 (0.10; 0.39)**	4
		Worsening of fibrosis	52/52	4/119 3/56	3/5	0.63 (0.15; 2.71)	-0.02 (-0.09; 0.05)	-50
		HBeAg loss	52/52	38/119 7/56	32/12	2.55 (1.22; 5.36)	**0.19 (0.07; 0.31)**	5
		HBeAg loss	68/68	40/119 9/56	34/16	2.09 (1.09; 4.00)	**0.18 (0.05; 0.30)**	6

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		HBeAg seroconversion	52/52	19/119 7/56	16/12	1.28 (0.57; 2.86)	0.03 (-0.07; 0.14)	29
		HBeAg seroconversion	68/68	21/119 7/56	18/12	1.41 (0.64; 3.12)	0.05 (-0.06; 0.16)	19
		HBV DNA response: <3pg/ml	52/52	102/119 23/56	86/41	2.09 (1.51; 2.88)	**0.45 (0.30; 0.59)**	2
		Sustained HBV DNA response: no two consecutive detectable HBV DNA	52/52	60/119 9/56	50/16	3.14 (1.68; 5.86)	**0.34 (0.21; 0.48)**	3
		HBV DNA undetectable by PCR (<750 genomes/ml)	52/52	34/119 8/56	29/14	2.00 (0.99; 4.03)	**0.14 (0.02; 0.27)**	7
		HBsAg loss	52/52	2/119 0/56	2/0	2.38 (0.12; 48.66)	0.02 (-0.02; 0.05)	60
		HBsAg loss	68/68	3/119 0/56	3/0	3.33 (0.17; 63.30)	0.03 (-0.01; 0.06)	40
		Detectable YMDD-variant virus	52/52	52/119 0/56	44/0	49.88 (3.13; 793.61)	**0.44 (0.34; 0.53)**	2
Yao, 2000[108] Lamivudine, 100 mg/day, 12 weeks	Placebo, 12 weeks	ALT normalization	12/12	91/322 14/107	28/13	2.16 (1.29; 3.63)	**0.15 (0.07; 0.23)**	7
Yao, 2000[108] lamivudine, 100 mg/day, 60 weeks	Lamivudine, 100 mg/day, 48 weeks	ALT normalization	60/48	102/322 36/107	32/34	0.94 (0.69; 1.28)	-0.02 (-0.12; 0.08)	-51
Yao, 2000[108] Lamivudine, 100 mg/day, 12 weeks	Placebo, 12 weeks	>1 treatment-related event	12/12	58/322 13/107	18/12	1.48 (0.85; 2.60)	0.06 (-0.02; 0.13)	17
		Gastrointestinal events	12/12	25/322 6/107	8/6	1.38 (0.58; 3.28)	0.02 (-0.03; 0.07)	46
		Neurological events	39794	18/322 4/107	6/4	1.50 (0.52; 4.32)	0.02 (-0.03; 0.06)	54

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Yao, 2000[108] Lamivudine, 100 mg/day, 60 weeks	Lamivudine, 100 mg/day, 48 weeks	>1 drug-related event	60/48	86/322 23/107	27/21	1.24 (0.83; 1.86)	0.05 (-0.04; 0.14)	19
		Gastrointestinal events	60/48	35/322 11/107	11/10	1.06 (0.56; 2.01)	0.01 (-0.06; 0.07)	170
		Neurological events	60/48	21/322 9/107	7/8	0.78 (0.37; 1.64)	-0.02 (-0.08; 0.04)	-53
		Events of the hepatobiliary tract and pancreas	60/48	21/322 3/107	7/3	2.33 (0.71; 7.64)	**0.04 (0.00; 0.08)**	27
		Non-site specific events	60/48	20/322 7/107	6/7	0.95 (0.41; 2.18)	0.00 (-0.06; 0.05)	-302
Yao, 2000[108] Lamivudine, 100 mg/day, 12 weeks	Placebo, 12 weeks	Undetectable serum HBV DNA <1.6pg/ml	12/12	269/322 14/107	84/13	6.38 (3.91; 10.43)	**0.70 (0.63; 0.78)**	1
Yao, 2000[108] Lamivudine, 100 mg/day, 60 weeks	Lamivudine, 100 mg/day, 48 weeks	Undetectable serum HBV DNA <1.6pg/ml	60/48	207/322 77/107	64/72	0.89 (0.77; 1.03)	-0.08 (-0.18; 0.02)	-13
		Breakthrough in serum HBV DNA	60/48	65/266 7/82	24/9	2.86 (1.37; 6.00)	**0.16 (0.08; 0.24)**	6
		Mixed wild-type HBV plus pure YMDD variant	60/48	31/322 4/107	10/4	2.58 (0.93; 7.13)	**0.06 (0.01; 0.11)**	17
		Pure YMDD variant	60/48	12/322 1/107	4/1	3.99 (0.52; 30.31)	**0.03 (0.00; 0.06)**	36
Peters, 2004[43] Lamivudine, 100 mg/day, 48 weeks	Adefovir dipivoxil, 10 mg/day, 48 weeks	Normalization ALT	48/48	1/19 9/19	5/47	0.11 (0.02; 0.79)	**-0.42 (-0.67; -0.18)**	-2
		Any adverse event	48/48	19/19 18/19	100/95	1.05 (0.91; 1.22)	0.05 (-0.08; 0.19)	19
		Asthenia	48/48	6/19 9/19	32/47	0.67 (0.30; 1.50)	-0.16 (-0.46; 0.15)	-6
		Headache	48/48	5/19 5/19	26/26	1.00 (0.35; 2.90)	0.00 (-0.28; 0.28)	
		Pharyngitis	48/48	6/19 5/19	32/26	1.20 (0.44; 3.27)	0.05 (-0.24; 0.34)	19

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Abdominal pain	48/48	5/19 4/19	26/21	1.25 (0.40; 3.95)	0.05 (-0.22; 0.32)	19
		Insomnia	48/48	2/19 4/19	11/21	0.50 (0.10; 2.41)	-0.11 (-0.33; 0.12)	-9
		Rash	48/48	4/19 4/19	21/21	1.00 (0.29; 3.43)	0.00 (-0.26; 0.26)	
		Fever	48/48	1/19 3/19	5/16	0.33 (0.04; 2.93)	-0.11 (-0.30; 0.09)	-9
		Sinusitis	48/48	5/19 3/19	26/16	1.67 (0.46; 6.01)	0.11 (-0.15; 0.36)	9
		Arthralgia	48/48	3/19 2/19	16/11	1.50 (0.28; 7.99)	0.05 (-0.16; 0.27)	19
		Back pain	48/48	3/19 2/19	16/11	1.50 (0.28; 7.99)	0.05 (-0.16; 0.27)	19
		Increased cough	48/48	3/19 2/19	16/11	1.50 (0.28; 7.99)	0.05 (-0.16; 0.27)	19
		Nausea	48/48	1/19 2/19	5/11	0.50 (0.05; 5.06)	-0.05 (-0.22; 0.12)	-19
		Pain	48/48	4/19 2/19	21/11	2.00 (0.41; 9.65)	0.11 (-0.12; 0.33)	9
		Diarrhea	48/48	6/19 1/19	32/5	6.00 (0.80; 45.20)	**0.26 (0.03; 0.50)**	4
		Gastroenteritis	48/48	3/19 1/19	16/5	3.00 (0.34; 26.33)	0.11 (-0.09; 0.30)	9
		Infection	48/48	1/19 1/19	5/5	1.00 (0.07; 14.85)	0.00 (-0.14; 0.14)	
		Rhinitis	48/48	5/19 1/19	26/5	5.00 (0.64; 38.87)	0.21 (-0.01; 0.43)	5
		Bacterial infection	48/48	0/19 0/19			0.00 (-0.10; 0.10)	
		ALT Grade 3 (>5–10 times the ULN)	48/48	0/19 7/19	0/37	0.07 (0.00; 1.09)	**-0.37 (-0.59; -0.15)**	-3
		ALT Grade 4 >10 times the ULN)	48/48	3/19 0/19	16/0	7.00 (0.39; 126.92)	0.16 (-0.02; 0.34)	6

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		AST Grade3 (>5–10 times the ULN)	48/48	1/19 1/19	5/5	1.00 (0.07; 14.85)	0.00 (-0.14; 0.14)	
		Grade4 (>10 times the ULN)	48/48	2/19 0/19	11/0	5.00 (0.26; 97.70)	0.11 (-0.06; 0.27)	9
		Amylase Grade3 (>2-5 times the ULN)	48/48	3/19 0/19	16/0	7.00 (0.39; 126.92)	0.16 (-0.02; 0.34)	6
		Grade4 (5 times the ULN)	48/48	0/19 0/19			0.00 (-0.10; 0.10)	
		Serum Glucose Grade3 (30-39 mg/dL; 251–500 mg/dL)	48/48	3/19 2/19	16/11	1.50 (0.28; 7.99)	0.05 (-0.16; 0.27)	19
		Grade4 (>30 mg/dL; <500 mg/dL)	48/48	0/19 0/19			0.00 (-0.10; 0.10)	
		Urine Glucose Grade3 (3+)	48/48	4/19 2/19	21/11	2.00 (0.41; 9.65)	0.11 (-0.12; 0.33)	9
		Grade4 (4+)	48/48	0/19 0/19			0.00 (-0.10; 0.10)	
		HBV DNA undetectable	48/48	0/19 5/19	0/26	0.09 (0.01; 1.54)	**-0.26 (-0.47; -0.06)**	-4
		HBeAg	48/48	0/19 3/19	0/16	0.14 (0.01; 2.59)	-0.16 (-0.34; 0.02)	-6
		HBeAg seroconversion	48/48	0/19 2/19	0/11	0.20 (0.01; 3.91)	-0.11 (-0.27; 0.06)	-9
Yuen, 2005[111] Lamivudine, 100 mg/day, 48 weeks	Placebo, , 48 weeks	Improvement of necroinflammation	48/48	37/67 3/18	55/17	3.31 (1.15; 9.52)	**0.39 (0.18; 0.59)**	3
Ke, 2005[53] Lamivudine, 100 mg/day, 48 weeks	Routine medication with vitamin C and inosine, 48 weeks	HBV DNA became negative in serum	24/24	34/42 5/30	81/17	4.86 (2.15; 10.96)	**0.64 (0.46; 0.82)**	2
		HBV DNA negative in peripheral blood mononuclear cells	24/24	20/42 4/30	48/13	3.57 (1.36; 9.38)	**0.34 (0.15; 0.54)**	3

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		HBV DNA negative in serum	48/48	38/42 7/30	90/23	3.88 (2.01; 7.47)	**0.67 (0.50; 0.85)**	1
		HBV DNA negative in peripheral blood mononuclear cells	48/48	25/42 5/30	60/17	3.57 (1.54; 8.26)	**0.43 (0.23; 0.63)**	2
Nevins, 1997[55] Lamivudine, 300 mg/day, 24 weeks	Lamivudine, 25 mg/day, 24 weeks	ALT normalization in patients with abnormal ALT at baseline	24/24	5/19 7/16	26/44	0.60 (0.24; 1.53)	-0.17 (-0.49; 0.14)	-6
	Lamivudine, 100 mg/day, 24 weeks	ALT normalization in patients with abnormal ALT at baseline	24/24	5/19 5/16	26/31	0.84 (0.30; 2.40)	-0.05 (-0.35; 0.25)	-20
	Lamivudine, 25 mg/day, 24 weeks	ALT normalization in patients with abnormal ALT at baseline	24/24	5/16 7/16	31/44	0.71 (0.29; 1.78)	-0.13 (-0.46; 0.21)	-8
	Lamivudine, 25 mg/day, 24 weeks	Twofold increase of ALT	24/24	5/19 2/16	26/12	2.11 (0.47; 9.42)	0.14 (-0.12; 0.39)	7
	Lamivudine, 100 mg/day, 24 weeks	Twofold increase of ALT	24/24	5/19 4/16	26/25	1.05 (0.34; 3.27)	0.01 (-0.28; 0.30)	76
Nevins, 1997[55] Lamivudine, 100 mg/day, 24 weeks	Lamivudine, 25 mg/day, 24 weeks	Twofold increase of ALT	24/24	4/16 2/16	25/12	2.00 (0.42; 9.42)	0.13 (-0.14; 0.39)	8
Nevins, 1997[55] Lamivudine, 300 mg/day, 24 weeks	Lamivudine, 25 mg/day, 24 weeks	Any adverse event	24/24	5/19 5/16	26/31	0.84 (0.30; 2.40)	-0.05 (-0.35; 0.25)	-20
	Lamivudine, 100 mg/day, 24 weeks	Any adverse event	24/24	5/19 4/16	26/25	1.05 (0.34; 3.27)	0.01 (-0.28; 0.30)	76
Nevins, 1997[55] Lamivudine, 100 mg/day, 24 weeks	Lamivudine, 25 mg/day, 24 weeks	Any adverse event	24/24	4/16 5/16	25/31	0.80 (0.26; 2.45)	-0.06 (-0.37; 0.25)	-16
Nevins, 1997[55] Lamivudine, 300 mg/day,	Lamivudine, 25 mg/day, 24 weeks	Nausea and vomiting	24/24	2/19 2/16	11/12	0.84 (0.13; 5.32)	-0.02 (-0.23; 0.19)	-51

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24 weeks		Fatigue	24/24	2/19 0/16	11/0	4.25 (0.22; 82.57)	0.11 (-0.06; 0.27)	9
		Abdominal discomfort and pain	24/24	1/19 1/16	5/6	0.84 (0.06; 12.42)	-0.01 (-0.17; 0.15)	-101
		Skin rashes	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Diarrhea	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Dizziness	24/24	1/19 0/16	5/0	2.55 (0.11; 58.60)	0.05 (-0.09; 0.19)	19
		Hypoglycemia	24/24	1/19 0/16	5/0	2.55 (0.11; 58.60)	0.05 (-0.09; 0.19)	19
		Headache	24/24	0/19 0/16			0.00 (-0.11; 0.11)	
		Dyspepsia	24/24	0/19 0/16			0.00 (-0.11; 0.11)	
		Vertigo	24/24	0/19 0/16			0.00 (-0.11; 0.11)	
		Constipation	24/24	0/19 0/16			0.00 (-0.11; 0.11)	
		Acne and folliculitis	24/24	0/19 0/16			0.00 (-0.11; 0.11)	
		Eczema	24/24	0/19 0/16			0.00 (-0.11; 0.11)	
		Muscle pain	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Pigmentary skin disorders	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Amylase >2X upper limit of normal	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		CPK >5X upper limit of normal	24/24	2/19 0/16	11/0	4.25 (0.22; 82.57)	0.11 (-0.06; 0.27)	9

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	Lamivudine , 100 mg/day, 24 weeks	Nausea and vomiting	24/24	2/19 0/16	11/0	4.25 (0.22; 82.57)	0.11 (-0.06; 0.27)	9
		Fatigue	24/24	2/19 1/16	11/6	1.68 (0.17; 16.91)	0.04 (-0.14; 0.22)	23
		Abdominal discomfort and pain	24/24	1/19 0/16	5/0	2.55 (0.11; 58.60)	0.05 (-0.09; 0.19)	19
		Skin rashes	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Diarrhea	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Dizziness	24/24	1/19 0/16	5/0	2.55 (0.11; 58.60)	0.05 (-0.09; 0.19)	19
		Hypoglycemia	24/24	1/19 0/16	5/0	2.55 (0.11; 58.60)	0.05 (-0.09; 0.19)	19
		Headache	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Dyspepsia	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Vertigo	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Constipation	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Acne and folliculitis	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Eczema	24/24	0/19 1/16	0/6	0.28 (0.01; 6.51)	-0.06 (-0.21; 0.09)	-16
		Muscle pain	24/24	0/19 0/16			0.00 (-0.11; 0.11)	
		Pigmentary skin disorders	24/24	0/19 0/16			0.00 (-0.11; 0.11)	
		Amylase >2X upper limit of normal	24/24	0/19 0/16			0.00 (-0.11; 0.11)	

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		CPK >5X upper limit of normal	24/24	2/19 0/16	11/0	4.25 (0.22; 82.57)	0.11 (-0.06; 0.27)	9
Nevens, 1997[55] Lamivudine , 100 mg/day, 24 weeks	Lamivudine, 25 mg/day, 24 weeks	Nausea and vomiting	24/24	0/16 2/16	0/12	0.20 (0.01; 3.86)	-0.13 (-0.31; 0.06)	-8
		Fatigue	24/24	1/16 0/16	6/0	3.00 (0.13; 68.57)	0.06 (-0.09; 0.22)	16
		Abdominal discomfort and pain	24/24	0/16 1/16	0/6	0.33 (0.01; 7.62)	-0.06 (-0.22; 0.09)	-16
		Skin rashes	24/24	1/16 1/16	6/6	1.00 (0.07; 14.64)	0.00 (-0.17; 0.17)	
		Diarrhea	24/24	1/16 1/16	6/6	1.00 (0.07; 14.64)	0.00 (-0.17; 0.17)	
		Dizziness	24/24	0/16 0/16			0.00 (-0.11; 0.11)	
		Hypoglycemia	24/24	0/16 0/16			0.00 (-0.11; 0.11)	
		Headache	24/24	1/16 0/16	6/0	3.00 (0.13; 68.57)	0.06 (-0.09; 0.22)	16
		Dyspepsia	24/24	1/16 0/16	6/0	3.00 (0.13; 68.57)	0.06 (-0.09; 0.22)	16
		Vertigo	24/24	1/16 0/16	6/0	3.00 (0.13; 68.57)	0.06 (-0.09; 0.22)	16
		Constipation	24/24	1/16 0/16	6/0	3.00 (0.13; 68.57)	0.06 (-0.09; 0.22)	16
		Acne and folliculitis	24/24	1/16 0/16	6/0	3.00 (0.13; 68.57)	0.06 (-0.09; 0.22)	16
		Eczema	24/24	1/16 0/16	6/0	3.00 (0.13; 68.57)	0.06 (-0.09; 0.22)	16
		Muscle pain	24/24	0/16 1/16	0/6	0.33 (0.01; 7.62)	-0.06 (-0.22; 0.09)	-16
		Pigmentary skin disorders	24/24	0/16 1/16	0/6	0.33 (0.01; 7.62)	-0.06 (-0.22; 0.09)	-16
		Amylase >2X	24/24	0/16	0/6	0.33 (0.01; 7.62)	-0.06 (-0.22; 0.09)	-16

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		upper limit of normal		1/16				
		CPK >5X upper limit of normal	24/24	0/16 0/16			0.00 (-0.11; 0.11)	
Lai, 1998[50] Lamivudine, 25 mg/day, 48 weeks	Lamivudine , 100 mg/day, 48 weeks	ALT normalization	48/48	64/142 68/143	45/48	0.95 (0.74; 1.22)	-0.02 (-0.14; 0.09)	-40
	Placebo, 48 weeks	ALT normalization	48/48	64/142 12/73	45/16	2.74 (1.58; 4.74)	**0.29 (0.17; 0.40)**	3
Lai, 1998[50] Lamivudine, 100 mg/day, 48 weeks	Placebo, 48 weeks	ALT normalization	48/48	68/143 12/73	48/16	2.89 (1.68; 4.99)	**0.31 (0.19; 0.43)**	3
Lai, 1998[50] Lamivudine, 25 mg/day, 48 weeks	Lamivudine , 100 mg/day, 48 weeks	>1 adverse event	48/48	110/142 114/143	77/80	0.97 (0.86; 1.10)	-0.02 (-0.12; 0.07)	-44
	Placebo, 48 weeks	>1 adverse event	48/48	110/142 56/73	77/77	1.01 (0.87; 1.18)	0.01 (-0.11; 0.13)	133
Lai, 1998[50] Lamivudine, 100 mg/day, 48 weeks	Placebo, 48 weeks	>1 adverse event	48/48	114/143 56/73	80/77	1.04 (0.89; 1.21)	0.03 (-0.09; 0.15)	33
Lai, 1998[50] Lamivudine, 25 mg/day, 48 weeks	Lamivudine , 100 mg/day, 48 weeks	Respiratory infections	48/48	50/142 50/143	35/35	1.01 (0.73; 1.38)	0.00 (-0.11; 0.11)	406
		Headache	48/48	23/142 21/143	16/15	1.10 (0.64; 1.90)	0.02 (-0.07; 0.10)	66
		Cough	48/48	23/142 21/143	16/15	1.10 (0.64; 1.90)	0.02 (-0.07; 0.10)	66
		Abdominal discomfort or pain	48/48	26/142 19/143	18/13	1.38 (0.80; 2.37)	0.05 (-0.03; 0.13)	20
		Diarrhea	48/48	20/142 24/143	14/17	0.84 (0.49; 1.45)	-0.03 (-0.11; 0.06)	-37
		Malaise and fatigue	48/48	17/142 19/143	12/13	0.90 (0.49; 1.66)	-0.01 (-0.09; 0.06)	-76
		Throat discomfort or pain	48/48	18/142 23/143	13/16	0.79 (0.45; 1.40)	-0.03 (-0.12; 0.05)	-29
		Nasal signs and symptoms	48/48	10/142 10/143	7/7	1.01 (0.43; 2.34)	0.00 (-0.06; 0.06)	2030

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Dizziness	48/48	9/142 9/143	6/6	1.01 (0.41; 2.46)	0.00 (-0.06; 0.06)	2256
		Nausea and vomiting	48/48	4/142 11/143	3/8	0.37 (0.12; 1.12)	-0.05 (-0.10; 0.00)	-21
		Fever	48/48	9/142 9/143	6/6	1.01 (0.41; 2.46)	0.00 (-0.06; 0.06)	2256
		Chest symptoms	48/48	3/142 4/143	2/3	0.76 (0.17; 3.31)	-0.01 (-0.04; 0.03)	-146
		Abnormal liver-function results	48/48	6/142 3/143	4/2	2.01 (0.51; 7.90)	0.02 (-0.02; 0.06)	47
		Hair loss	48/48	0/142 3/143	0/2	0.14 (0.01; 2.76)	-0.02 (-0.05; 0.01)	-48
	Placebo, 48 weeks	Respiratory infections	48/48	50/142 21/73	35/29	1.22 (0.80; 1.87)	0.06 (-0.07; 0.19)	16
		Headache	48/48	23/142 14/73	16/19	0.84 (0.46; 1.54)	-0.03 (-0.14; 0.08)	-34
		Cough	48/48	23/142 12/73	16/16	0.99 (0.52; 1.87)	0.00 (-0.11; 0.10)	-415
		Abdominal discomfort or pain	48/48	26/142 9/73	18/12	1.49 (0.73; 3.00)	0.06 (-0.04; 0.16)	17
		Diarrhea	48/48	20/142 7/73	14/10	1.47 (0.65; 3.31)	0.04 (-0.04; 0.13)	22
		Malaise and fatigue	48/48	17/142 14/73	12/19	0.62 (0.33; 1.19)	-0.07 (-0.18; 0.03)	-14
		Throat discomfort or pain	48/48	18/142 6/73	13/8	1.54 (0.64; 3.72)	0.04 (-0.04; 0.13)	22
		Nasal signs and symptoms	48/48	10/142 6/73	7/8	0.86 (0.32; 2.26)	-0.01 (-0.09; 0.06)	-85
		Dizziness	48/48	9/142 3/73	6/4	1.54 (0.43; 5.52)	0.02 (-0.04; 0.08)	45
		Nausea and vomiting	48/48	4/142 1/73	3/1	2.06 (0.23; 18.07)	0.01 (-0.02; 0.05)	69
		Fever	48/48	9/142 2/73	6/3	2.31 (0.51; 10.43)	0.04 (-0.02; 0.09)	28

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Chest symptoms	48/48	3/142 5/73	2/7	0.31 (0.08; 1.25)	-0.05 (-0.11; 0.02)	-21
		Abnormal liver-function results	48/48	6/142 6/73	4/8	0.51 (0.17; 1.54)	-0.04 (-0.11; 0.03)	-25
		Hair loss	48/48	0/142 4/73	0/5	0.06 (0.00; 1.05)	-0.05 (-0.11; 0.00)	-18
Lai, 1998[50] Lamivudine , 100 mg/day, 48 weeks	Placebo, 48 weeks	Respiratory infections	48/48	50/143 21/73	35/29	1.22 (0.79; 1.86)	0.06 (-0.07; 0.19)	16
		Headache	48/48	21/143 14/73	15/19	0.77 (0.41; 1.42)	-0.04 (-0.15; 0.06)	-22
		Cough	48/48	21/143 12/73	15/16	0.89 (0.47; 1.71)	-0.02 (-0.12; 0.09)	-57
		Abdominal discomfort or pain	48/48	19/143 9/73	13/12	1.08 (0.51; 2.26)	0.01 (-0.08; 0.10)	104
		Diarrhea	48/48	24/143 7/73	17/10	1.75 (0.79; 3.87)	0.07 (-0.02; 0.16)	14
		Malaise and fatigue	48/48	19/143 14/73	13/19	0.69 (0.37; 1.30)	-0.06 (-0.16; 0.05)	-17
		Throat discomfort or pain	48/48	23/143 6/73	16/8	1.96 (0.83; 4.59)	0.08 (-0.01; 0.17)	13
		Nasal signs and symptoms	48/48	10/143 6/73	7/8	0.85 (0.32; 2.25)	-0.01 (-0.09; 0.06)	-82
		Dizziness	48/48	9/143 3/73	6/4	1.53 (0.43; 5.49)	0.02 (-0.04; 0.08)	46
		Nausea and vomiting	48/48	11/143 1/73	8/1	5.62 (0.74; 42.65)	**0.06 (0.01; 0.11)**	16
		Fever	48/48	9/143 2/73	6/3	2.30 (0.51; 10.36)	0.04 (-0.02; 0.09)	28
		Chest symptoms	48/48	4/143 5/73	3/7	0.41 (0.11; 1.48)	-0.04 (-0.10; 0.02)	-25
		Abnormal liver-function results	48/48	3/143 6/73	2/8	0.26 (0.07; 0.99)	-0.06 (-0.13; 0.01)	-16
		Hair loss	48/48	3/143 4/73	2/5	0.38 (0.09; 1.67)	-0.03 (-0.09; 0.02)	-30

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lai, 1998[50] Lamivudine, 25 mg/day, 48 weeks	Lamivudine , 100 mg/day, 48 weeks	Histological response was defined as a reduction of 2 or more points in the Knodell necroinflammatory score (components 1 through 3)	48/48	70/142 80/143	49/56	0.88 (0.71; 1.10)	-0.07 (-0.18; 0.05)	-15
		Worsening of Knodell necroinflammatory score	48/48	12/142 10/143	8/7	1.21 (0.54; 2.71)	0.01 (-0.05; 0.08)	69
	Placebo, 48 weeks	Histological response was defined as a reduction of 2 or more points in the Knodell necroinflammatory score (components 1 through 3)	48/48	70/142 18/73	49/25	2.00 (1.29; 3.09)	**0.25 (0.12; 0.37)**	4
		Worsening of Knodell necroinflammatory score	48/48	12/142 19/73	8/26	0.32 (0.17; 0.63)	**-0.18 (-0.29; -0.07)**	-6
Lai, 1998[50] Lamivudine, 100 mg/day, 48 weeks	Placebo, 48 weeks	Histological response was defined as a reduction of 2 or more points in the Knodell necroinflammatory score (components 1 through 3).	48/48	80/143 18/73	56/25	2.27 (1.48; 3.48)	**0.31 (0.18; 0.44)**	3

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Worsening of Knodell necroinflammatory score	48/48	10/143 19/73	7/26	0.27 (0.13; 0.55)	**-0.19 (-0.30; -0.08)**	-5
Lai, 1998[50] Lamivudine, 25 mg/day, 48 weeks	Lamivudine , 100 mg/day, 48 weeks	HBeAg seroconversion	48/48	17/142 22/143	12/15	0.78 (0.43; 1.40)	-0.03 (-0.11; 0.05)	-29
	Placebo, 48 weeks	HBeAg seroconversion	48/48	17/142 3/73	12/4	2.91 (0.88; 9.62)	**0.08 (0.01; 0.15)**	13
Lai, 1998[50] Lamivudine, 100 mg/day, 48 weeks	Placebo, 48 weeks	HBeAg seroconversion	48/48	22/143 3/73	15/4	3.74 (1.16; 12.10)	**0.11 (0.04; 0.19)**	9
Lai, 1998[50] Lamivudine, 25 mg/day, 48 weeks	Lamivudine , 100 mg/day, 48 weeks	Undetectable HBV DNA on at least one occasion	48/48	104/142 129/143	73/90	0.81 (0.73; 0.91)	**-0.17 (-0.26; -0.08)**	-6
	Placebo, 48 weeks	Undetectable HBV DNA on at least one occasion	48/48	104/142 17/73	73/23	3.14 (2.05; 4.83)	**0.50 (0.38; 0.62)**	2
Lai, 1998[50] lamivudine, 100 mg/day, 48 weeks	Placebo, , 48 weeks	Undetectable HBV DNA on at least one occasion	48/48	129/143 17/73	90/23	3.87 (2.55; 5.89)	**0.67 (0.56; 0.78)**	1
Honkoop, 1998[109] Lamivudine, 300 mg/day, 24 weeks	Lamivudine , 25 mg/day, 24 weeks	Undetectable with PCR HBV DNA	39794	15/19 7/16	79/44	1.80 (0.99; 3.30)	**0.35 (0.05; 0.66)**	3
	Lamivudine , 100 mg/day, 24 weeks	Undetectable with PCR HBV DNA	39794	15/19 14/16	79/88	0.90 (0.67; 1.21)	-0.09 (-0.33; 0.16)	-12
Honkoop, 1998[109] Lamivudine, 100 mg/day, 24 weeks	Lamivudine , 25 mg/day, 24 weeks	Undetectable with PCR HBV DNA	39794	14/16 7/16	88/44	2.00 (1.11; 3.59)	**0.44 (0.15; 0.73)**	2
Honkoop, 1998[109] Lamivudine, 300 mg/day, 24 weeks	Lamivudine , 25 mg/day, 24 weeks	Undetectable with PCR HBV DNA	24/24	13/19 6/16	68/38	1.82 (0.90; 3.68)	0.31 (-0.01; 0.63)	3
	Lamivudine , 100 mg/day, 24 weeks	Undetectable with PCR HBV DNA	24/24	13/19 12/16	68/75	0.91 (0.60; 1.38)	-0.07 (-0.36; 0.23)	-15
Honkoop, 1998[109] Lamivudine, 100 mg/day, 24 weeks	Lamivudine , 25 mg/day, 24 weeks	Undetectable with PCR HBV DNA	24/24	12/16 6/16	75/38	2.00 (1.00; 4.00)	**0.38 (0.06; 0.69)**	3

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Tassopoulos, 1999[49] Lamivudine, 100 mg/day after 6 months of previous LAM treatment, 52 weeks	Placebo, 26 weeks	HBV DNA <2.5 pg/mL and ALT normalization	24/24	34/60 3/65	57/5	12.28 (3.98; 37.90)	**0.52 (0.39; 0.66)**	2
		Headache	26/26	10/60 12/65	17/18	0.90 (0.42; 1.93)	-0.02 (-0.15; 0.12)	-56
		Malaise and fatigue	26/26	8/60 8/65	13/12	1.08 (0.43; 2.70)	0.01 (-0.11; 0.13)	98
		Abdominal discomfort and pain	26/26	4/60 8/65	7/12	0.54 (0.17; 1.71)	-0.06 (-0.16; 0.05)	-18
		Temperature regulation disturbance	26/26	5/60 4/65	8/6	1.35 (0.38; 4.81)	0.02 (-0.07; 0.11)	46
		Cough	26/26	4/60 3/65	7/5	1.44 (0.34; 6.19)	0.02 (-0.06; 0.10)	49
		Viral respiratory infections	26/26	3/60 2/65	5/3	1.63 (0.28; 9.39)	0.02 (-0.05; 0.09)	52
		Gastrointestinal infections	26/26	3/60 3/65	5/5	1.08 (0.23; 5.16)	0.00 (-0.07; 0.08)	260
		Musculoskeletal pain	26/26	2/60 4/65	3/6	0.54 (0.10; 2.85)	-0.03 (-0.10; 0.05)	-35
		Nausea and vomiting	26/26	5/60 1/65	8/2	5.42 (0.65; 45.04)	0.07 (-0.01; 0.14)	15
		Vertigo	26/26	1/60 4/65	2/6	0.27 (0.03; 2.36)	-0.04 (-0.11; 0.02)	-22
		Diarrhea	26/26	3/60 2/65	5/3	1.63 (0.28; 9.39)	0.02 (-0.05; 0.09)	52
		Tonsillitis	26/26	1/60 0/65	2/0	3.25 (0.13; 78.18)	0.02 (-0.03; 0.06)	60
		Dyspeptic symptoms	26/26	2/60 1/65	3/2	2.17 (0.20; 23.29)	0.02 (-0.04; 0.07)	56
		At least 1 adverse event	26/26	28/60 40/65	47/62	0.76 (0.54; 1.06)	-0.15 (-0.32; 0.02)	-7
		Headache	52/26	10/60	17/18	0.90 (0.42; 1.93)	-0.02 (-0.15; 0.12)	-56

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
				12/65				
		Malaise and fatigue	52/26	11/60 8/65	18/12	1.49 (0.64; 3.45)	0.06 (-0.07; 0.19)	17
		Abdominal discomfort and pain	52/26	6/60 8/65	10/12	0.81 (0.30; 2.21)	-0.02 (-0.13; 0.09)	-43
		Temperature regulation disturbance	52/26	5/60 4/65	8/6	1.35 (0.38; 4.81)	0.02 (-0.07; 0.11)	46
		Cough	52/26	5/60 3/65	8/5	1.81 (0.45; 7.23)	0.04 (-0.05; 0.12)	27
		Viral respiratory infections	52/26	4/60 2/65	7/3	2.17 (0.41; 11.40)	0.04 (-0.04; 0.11)	28
		Gastrointestinal infections	52/26	3/60 3/65	5/5	1.08 (0.23; 5.16)	0.00 (-0.07; 0.08)	260
		Musculoskeletal pain	52/26	2/60 4/65	3/6	0.54 (0.10; 2.85)	-0.03 (-0.10; 0.05)	-35
		Nausea and vomiting	52/26	5/60 1/65	8/2	5.42 (0.65; 45.04)	0.07 (-0.01; 0.14)	15
		Vertigo	52/26	2/60 4/65	3/6	0.54 (0.10; 2.85)	-0.03 (-0.10; 0.05)	-35
		Diarrhea	52/26	3/60 2/65	5/3	1.63 (0.28; 9.39)	0.02 (-0.05; 0.09)	52
		Tonsillitis	52/26	4/60 0/65	7/0	9.74 (0.54; 177.14)	**0.07 (0.00; 0.14)**	15
		Dyspeptic symptoms	52/26	3/60 1/65	5/2	3.25 (0.35; 30.40)	0.03 (-0.03; 0.10)	29
		At least 1 adverse event	52/26	32/60 40/65	53/62	0.87 (0.64; 1.18)	-0.08 (-0.26; 0.09)	-12
		HBV DNA <2.5 pg/mL	24/24	15/60 11/65	25/17	1.48 (0.74; 2.96)	0.08 (-0.06; 0.22)	12
		HBV DNA >2.5 pg/mL	24/24	5/60 40/65	8/62	0.14 (0.06; 0.32)	**-0.53 (-0.67; -0.39)**	-2
		HBsAg loss	24/24	0/60 1/65	0/2	0.36 (0.01; 8.69)	-0.02 (-0.06; 0.03)	-65

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Dienstag, 1999[48] Lamivudine, 100 mg/day, 52 weeks	Placebo, 52 weeks	ALT normalization	52/52	27/71 5/72	38/7	5.48 (2.23; 13.42)	**0.31 (0.18; 0.44)**	3
		Malaise or fatigue	52/52	13/71 14/72	19/20	0.94 (0.48; 1.86)	-0.01 (-0.14; 0.12)	-88
		Nausea or vomiting	52/52	6/71 11/72	9/15	0.55 (0.22; 1.41)	-0.07 (-0.17; 0.04)	-15
		Headache	52/52	6/71 6/72	9/8	1.01 (0.34; 3.00)	0.00 (-0.09; 0.09)	852
		Muscle pain	52/52	0/71 6/72	0/8	0.08 (0.00; 1.36)	**-0.08 (-0.15; -0.02)**	-12
		Abdominal discomfort	52/52	3/71 5/72	4/7	0.61 (0.15; 2.45)	-0.03 (-0.10; 0.05)	-37
		Sleep disorder	52/52	5/71 3/72	7/4	1.69 (0.42; 6.81)	0.03 (-0.05; 0.10)	35
		Paresthesias	52/52	2/71 5/72	3/7	0.41 (0.08; 2.02)	-0.04 (-0.11; 0.03)	-24
		Rash	52/52	4/71 6/72	6/8	0.68 (0.20; 2.29)	-0.03 (-0.11; 0.06)	-37
		Diarrhea	52/52	4/71 4/72	6/6	1.01 (0.26; 3.90)	0.00 (-0.07; 0.08)	1278
		Grade III or IV laboratory abnor-malities in ALT	52/52	7/71 9/72	10/13	0.79 (0.31; 2.00)	-0.03 (-0.13; 0.08)	-38
		Grade III or IV laboratory abnor-malities in albumin	52/52	0/71 2/72	0/3	0.20 (0.01; 4.15)	-0.03 (-0.07; 0.02)	-36
		Grade III or IV laboratory abnor-malities in amylase	52/52	0/71 1/72	0/1	0.34 (0.01; 8.16)	-0.01 (-0.05; 0.02)	-72
		Grade III or IV laboratory abnor-malities in lipase	52/52	6/71 5/72	9/7	1.22 (0.39; 3.81)	0.02 (-0.07; 0.10)	66
		Grade III or IV laboratory abnor-	52/52	6/71 3/72	9/4	2.03 (0.53; 7.80)	0.04 (-0.04; 0.12)	23

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		malities in creatine kinase						
		Grade III or IV laboratory abnor-malities in platelets	52/52	0/71 2/72	0/3	0.20 (0.01; 4.15)	-0.03 (-0.07; 0.02)	-36
		Grade III abnormality in ALT	52/52	7/71 9/72	10/12	0.79 (0.31; 2.00)	-0.03 (-0.13; 0.08)	-38
		Grade IV abnormality in ALT	52/52	0/71 0/72			0.00 (-0.03; 0.03)	
		ALT >2 times above baseline levels	52/52	18/71 19/72	25/26	0.96 (0.55; 1.67)	-0.01 (-0.15; 0.13)	-96
		ALT >3 times above baseline levels	52/52	7/71 9/72	10/12	0.79 (0.31; 2.00)	-0.03 (-0.13; 0.08)	-38
		ALT >2 times above baseline levels and >500 U/liter	52/52	1/71 7/72	1/10	0.14 (0.02; 1.15)	**-0.08 (-0.16; -0.01)**	-12
		ALT >2 times above baseline levels and bilirubin »2 times above baseline levels	52/52	0/71 0/72			0.00 (-0.03; 0.03)	
		Grade III abnormality in ALT	68/68	14/71 4/72	20/6	3.55 (1.23; 10.26)	**0.14 (0.04; 0.25)**	7
		Grade IV abnormality in ALT	68/68	2/71 1/72	3/1	2.03 (0.19; 21.87)	0.01 (-0.03; 0.06)	70
		ALT >2 times above baseline levels	68/68	19/71 13/72	27/18	1.48 (0.79; 2.77)	0.09 (-0.05; 0.22)	11
		ALT >3 times above baseline levels	68/68	16/71 5/72	23/7	3.25 (1.26; 8.38)	**0.16 (0.04; 0.27)**	6

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		ALT >2 times above baseline levels and >500 U/liter	68/68	12/71 6/72	17/8	2.03 (0.81; 5.11)	0.09 (-0.02; 0.19)	12
		ALT >2 times above baseline levels and bilirubin >2 times above baseline levels	68/68	1/71 1/72	1/1	1.01 (0.06; 15.90)	0.00 (-0.04; 0.04)	5112
		Reduction of at least 2 points in HAI score	52/52	34/71 16/72	48/22	2.15 (1.31; 3.54)	**0.26 (0.11; 0.41)**	4
		Histological worsening, defined as an increase of at least 2 points in HAI score	52/52	7/71 17/72	10/24	0.42 (0.18; 0.95)	**-0.14 (-0.26; -0.02)**	-7
		Decrease in necroinflammatory activity	52/52	42/71 24/72	59/33	1.77 (1.21; 2.59)	**0.26 (0.10; 0.42)**	4
		Increased fibrosis	52/52	3/71 14/72	4/19	0.22 (0.07; 0.72)	**-0.15 (-0.25; -0.05)**	-7
		Odds ratio of improvement of at least 2 points in the score on HAI after adjustment for the baseline ALT levels, serum HBV DNA levels, HAI score,and race	52/52	0/71 0/72		**7.50 (2.70; 20.90)**		
		Undetectable HBV DNA	52/52	62/71 23/72	87/32	2.73 (1.93; 3.87)	**0.55 (0.42; 0.69)**	2
		Sustained suppression of	52/52	28/71 11/72	39/15	2.58 (1.39; 4.78)	**0.24 (0.10; 0.38)**	4

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		serum HBV DNA levels						
		HBeAg seroconversion	52/52	11/71 4/72	15/6	2.79 (0.93; 8.35)	**0.10 (0.00; 0.20)**	10
		Lost serum HBeAg	52/52	21/71 8/72	30/11	2.66 (1.26; 5.61)	**0.18 (0.06; 0.31)**	5
		HBeAg seroconversion	68/68	11/71 6/72	15/8	1.86 (0.73; 4.76)	0.07 (-0.03; 0.18)	14
		Lost serum HBeAg	68/68	19/71 11/72	27/15	1.75 (0.90; 3.41)	0.11 (-0.02; 0.25)	9
		Loss of serum HBsAg	68/68	1/71 0/72	1/0	3.04 (0.13; 73.44)	0.01 (-0.02; 0.05)	71
Liaw, 2000[110] Lamivudine, 100 mg/day during second year after 100mg during the first year, 104 weeks	Lamivudine, 25 mg/day during the second year after 25mg/day LAM during the first year, 104 weeks	Viral respiratory infection	104/104	23/93 31/101	25/31	0.81 (0.51; 1.28)	-0.06 (-0.19; 0.07)	-17
		Malaise and fatigue	104/104	18/93 16/101	19/16	1.22 (0.66; 2.25)	0.04 (-0.07; 0.14)	28
		Abdominal discomfort and pain	104/104	18/93 23/101	19/23	0.85 (0.49; 1.47)	-0.03 (-0.15; 0.08)	-29
		Cough	104/104	21/93 26/101	23/26	0.88 (0.53; 1.45)	-0.03 (-0.15; 0.09)	-32
		Ear, nose, and throat infection	104/104	18/93 24/101	19/24	0.81 (0.47; 1.40)	-0.04 (-0.16; 0.07)	-23
		Headache	104/104	17/93 15/101	18/15	1.23 (0.65; 2.32)	0.03 (-0.07; 0.14)	29
		Throat and tonsil discomfort/pain	104/104	20/93 23/101	22/23	0.94 (0.56; 1.60)	-0.01 (-0.13; 0.10)	-79
		Abnormal liver function test results	104/104	13/93 12/101	14/12	1.18 (0.57; 2.45)	0.02 (-0.07; 0.12)	48
		Diarrhea	104/104	20/93 20/101	22/20	1.09 (0.63; 1.89)	0.02 (-0.10; 0.13)	59
		Nasal signs and symptoms	104/104	9/93 11/101	10/11	0.89 (0.39; 2.05)	-0.01 (-0.10; 0.07)	-82

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Temperature regulation disturbance	104/104	9/93 8/101	10/8	1.22 (0.49; 3.03)	0.02 (-0.06; 0.10)	57
		Dizziness	104/104	7/93 6/101	8/6	1.27 (0.44; 3.63)	0.02 (-0.05; 0.09)	63
		Abdominal distention	104/104	7/93 8/101	8/8	0.95 (0.36; 2.52)	0.00 (-0.08; 0.07)	-254
		Nausea and vomiting	104/104	10/93 7/101	11/7	1.55 (0.62; 3.91)	0.04 (-0.04; 0.12)	26
		Musculoskeletal pain	104/104	8/93 7/101	9/7	1.24 (0.47; 3.29)	0.02 (-0.06; 0.09)	60
	Placebo, during the second year after 100mg/day LAM during the first year, 52 weeks	Viral respiratory infection	104/104	23/93 16/41	25/40	0.63 (0.38; 1.07)	-0.14 (-0.32; 0.03)	-7
		Malaise and fatigue	104/104	18/93 7/41	19/18	1.13 (0.51; 2.50)	0.02 (-0.12; 0.16)	44
		Abdominal discomfort and pain	104/104	18/93 7/41	19/18	1.13 (0.51; 2.50)	0.02 (-0.12; 0.16)	44
		Cough	104/104	21/93 4/41	23/10	2.31 (0.85; 6.32)	**0.13 (0.00; 0.25)**	8
		Ear, nose, and throat infection	104/104	18/93 8/41	19/20	0.99 (0.47; 2.09)	0.00 (-0.15; 0.14)	-635
		Headache	104/104	17/93 6/41	18/15	1.25 (0.53; 2.94)	0.04 (-0.10; 0.17)	27
		Throat and tonsil discomfort/pain	104/104	20/93 7/41	22/18	1.26 (0.58; 2.74)	0.04 (-0.10; 0.19)	23
		Abnormal liver function test results	104/104	13/93 12/41	14/30	0.48 (0.24; 0.96)	-0.15 (-0.31; 0.00)	-7
		Diarrhea	104/104	20/93 9/41	22/23	0.98 (0.49; 1.96)	0.00 (-0.16; 0.15)	-224
		Nasal signs and symptoms	104/104	9/93 2/41	10/5	1.98 (0.45; 8.78)	0.05 (-0.04; 0.14)	21
		Temperature regulation disturbance	104/104	9/93 3/41	10/8	1.32 (0.38; 4.63)	0.02 (-0.08; 0.12)	42

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Dizziness	104/104	7/93 4/41	8/10	0.77 (0.24; 2.49)	-0.02 (-0.13; 0.08)	-45
		Abdominal distention	104/104	7/93 1/41	8/3	3.09 (0.39; 24.28)	0.05 (-0.02; 0.12)	20
		Nausea and vomiting	104/104	10/93 3/41	11/8	1.47 (0.43; 5.06)	0.03 (-0.07; 0.14)	29
		Musculoskeletal pain	104/104	8/93 1/41	9/3	3.53 (0.46; 27.29)	0.06 (-0.01; 0.14)	16
	Placebo, during the second year after 25mg/day LAM during the first year, 52 weeks	Viral respiratory infection	104/104	23/93 6/31	25/19	1.28 (0.57; 2.85)	0.05 (-0.11; 0.22)	19
		Malaise and fatigue	104/104	18/93 10/31	19/32	0.60 (0.31; 1.16)	-0.13 (-0.31; 0.05)	-8
		Abdominal discomfort and pain	104/104	18/93 7/31	19/23	0.86 (0.40; 1.86)	-0.03 (-0.20; 0.14)	-31
		Cough	104/104	21/93 5/31	23/16	1.40 (0.58; 3.40)	0.06 (-0.09; 0.22)	16
		Ear, nose, and throat infection	104/104	18/93 8/31	19/26	0.75 (0.36; 1.55)	-0.06 (-0.24; 0.11)	-16
		Headache	104/104	17/93 10/31	18/32	0.57 (0.29; 1.10)	-0.14 (-0.32; 0.04)	-7
		Throat and tonsil discomfort/pain	104/104	20/93 5/31	22/16	1.33 (0.55; 3.25)	0.05 (-0.10; 0.21)	19
		Abnormal liver function test results	104/104	13/93 9/31	14/29	0.48 (0.23; 1.02)	-0.15 (-0.33; 0.02)	-7
		Diarrhea	104/104	20/93 5/31	22/16	1.33 (0.55; 3.25)	0.05 (-0.10; 0.21)	19
		Nasal signs and symptoms	104/104	9/93 2/31	10/6	1.50 (0.34; 6.57)	0.03 (-0.07; 0.14)	31
		Temperature regulation disturbance	104/104	9/93 2/31	10/6	1.50 (0.34; 6.57)	0.03 (-0.07; 0.14)	31
		Dizziness	104/104	7/93 3/31	8/10	0.78 (0.21; 2.83)	-0.02 (-0.14; 0.10)	-46

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Abdominal distention	104/104	7/93 4/31	8/13	0.58 (0.18; 1.86)	-0.05 (-0.18; 0.08)	-19
		Nausea and vomiting	104/104	10/93 1/31	11/3	3.33 (0.44; 25.00)	0.08 (-0.01; 0.16)	13
		Musculoskeletal pain	104/104	8/93 2/31	9/6	1.33 (0.30; 5.95)	0.02 (-0.08; 0.13)	46
Liaw, 2000[110] Lamivudine, 25 mg/day during the second year after 25mg/day LAM during the first year, 104 weeks	Placebo, during the second year after 100mg/day LAM during the first year, 52 weeks	Viral respiratory infection	104/104	31/101 16/41	31/40	0.79 (0.49; 1.27)	-0.08 (-0.26; 0.09)	-12
		Malaise and fatigue	104/104	16/101 7/41	16/18	0.93 (0.41; 2.09)	-0.01 (-0.15; 0.12)	-81
		Abdominal discomfort and pain	104/104	23/101 7/41	23/18	1.33 (0.62; 2.86)	0.06 (-0.08; 0.20)	18
		Cough	104/104	26/101 4/41	26/10	2.64 (0.98; 7.09)	**0.16 (0.04; 0.28)**	6
		Ear, nose, and throat infection	104/104	24/101 8/41	24/20	1.22 (0.60; 2.48)	0.04 (-0.10; 0.19)	24
		Headache	104/104	15/101 6/41	15/15	1.01 (0.42; 2.43)	0.00 (-0.13; 0.13)	460
		Throat and tonsil discomfort/pain	104/104	23/101 7/41	23/18	1.33 (0.62; 2.86)	0.06 (-0.08; 0.20)	18
		Abnormal liver function test results	104/104	12/101 12/41	12/30	0.41 (0.20; 0.83)	**-0.17 (-0.33; -0.02)**	-6
		Diarrhea	104/104	20/101 9/41	20/23	0.90 (0.45; 1.81)	-0.02 (-0.17; 0.13)	-47
		Nasal signs and symptoms	104/104	11/101 2/41	11/5	2.23 (0.52; 9.64)	0.06 (-0.03; 0.15)	17
		Temperature regulation disturbance	104/104	8/101 3/41	8/8	1.08 (0.30; 3.88)	0.01 (-0.09; 0.10)	166
		Dizziness	104/104	6/101 4/41	6/10	0.61 (0.18; 2.05)	-0.04 (-0.14; 0.06)	-26
		Abdominal distention	104/104	8/101 1/41	8/3	3.25 (0.42; 25.15)	0.05 (-0.02; 0.13)	18

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Nausea and vomiting	104/104	7/101 3/41	7/8	0.95 (0.26; 3.49)	0.00 (-0.10; 0.09)	-259
		Musculoskeletal pain	104/104	7/101 1/41	7/3	2.84 (0.36; 22.38)	0.04 (-0.02; 0.11)	22
	Placebo, during the second year after 25mg/day LAM during the first year, 52 weeks	Viral respiratory infection	104/104	31/101 6/31	31/19	1.59 (0.73; 3.45)	0.11 (-0.05; 0.28)	9
		Malaise and fatigue	104/104	16/101 10/31	16/32	0.49 (0.25; 0.97)	-0.16 (-0.34; 0.02)	-6
		Abdominal discomfort and pain	104/104	23/101 7/31	23/23	1.01 (0.48; 2.12)	0.00 (-0.17; 0.17)	522
		Cough	104/104	26/101 5/31	26/16	1.60 (0.67; 3.80)	0.10 (-0.06; 0.25)	10
		Ear, nose, and throat infection	104/104	24/101 8/31	24/26	0.92 (0.46; 1.84)	-0.02 (-0.20; 0.15)	-49
		Headache	104/104	15/101 10/31	15/32	0.46 (0.23; 0.92)	-0.17 (-0.35; 0.00)	-6
		Throat and tonsil discomfort/pain	104/104	23/101 5/31	23/16	1.41 (0.59; 3.40)	0.07 (-0.09; 0.22)	15
		Abnormal liver function test results	104/104	12/101 9/31	12/29	0.41 (0.19; 0.88)	-0.17 (-0.34; 0.00)	-6
		Diarrhea	104/104	20/101 5/31	20/16	1.23 (0.50; 3.00)	0.04 (-0.11; 0.19)	27
		Nasal signs and symptoms	104/104	11/101 2/31	11/6	1.69 (0.40; 7.21)	0.04 (-0.06; 0.15)	23
		Temperature regulation disturbance	104/104	8/101 2/31	8/6	1.23 (0.27; 5.48)	0.01 (-0.09; 0.12)	68
		Dizziness	104/104	6/101 3/31	6/10	0.61 (0.16; 2.31)	-0.04 (-0.15; 0.08)	-27
		Abdominal distention	104/104	8/101 4/31	8/13	0.61 (0.20; 1.90)	-0.05 (-0.18; 0.08)	-20
		Nausea and vomiting	104/104	7/101 1/31	7/3	2.15 (0.27; 16.79)	0.04 (-0.04; 0.12)	27

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Musculoskeletal pain	104/104	7/101 2/31	7/6	1.07 (0.24; 4.91)	0.00 (-0.09; 0.10)	209
	Lamivudine , 25 mg/day during the second year after 25mg/day LAM during the first year, 104 weeks	Sustained suppression of serum HBV DNA levels	104/104	47/93 24/101	51/24	2.13 (1.42; 3.18)	0.27 (0.14; 0.40)	4
	Placebo, during the second year after 100mg/day LAM during the first year, 52 weeks	Sustained suppression of serum HBV DNA levels	104/104	47/93 2/41	51/5	10.36 (2.64; 40.63)	**0.46 (0.34; 0.58)**	2
	Placebo, during the second year after 25mg/day LAM during the first year, 52 weeks	Sustained suppression of serum HBV DNA levels	104/104	47/93 2/31	51/6	7.83 (2.02; 30.38)	**0.44 (0.31; 0.57)**	2
	Placebo, during the second year after 100mg/day LAM during the first year, 52 weeks	Sustained suppression of serum HBV DNA levels	104/104	24/101 2/41	24/5	4.87 (1.21; 19.68)	**0.19 (0.08; 0.29)**	5
	Placebo, during the second year after 25mg/day LAM during the first year, 52 weeks	Sustained suppression of serum HBV DNA levels	104/104	24/101 2/31	24/6	3.68 (0.92; 14.72)	**0.17 (0.05; 0.29)**	6
Yao, 1999[112] Lamivudine , 100 mg/day, 12 weeks	Placebo, 12 weeks	ALT Normalization	12/12	91/322 14/107	5/4	2.16 (1.29; 3.63)	**0.15 (0.07; 0.23)**	7
		At least one adverse effect	12/12	138/322 45/107	5/4	1.02 (0.79; 1.32)	0.01 (-0.10; 0.12)	125
		At least one drug related adverse effect	12/12	58/322 13/107	5/4	1.48 (0.85; 2.60)	0.06 (-0.02; 0.13)	17

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Fatigue	12/12	18/322 8/107	5/4	0.75 (0.33; 1.67)	-0.02 (-0.07; 0.04)	-53
		Abdominal pain and discomfort	12/12	17/322 3/107	5/4	1.88 (0.56; 6.30)	0.02 (-0.01; 0.06)	40
		Nausea, vomiting	12/12	13/322 6/107	5/4	0.72 (0.28; 1.85)	-0.02 (-0.06; 0.03)	-64
		Diarrhea	12/12	13/322 3/107	5/4	1.44 (0.42; 4.96)	0.01 (-0.03; 0.05)	81
		Constipation	12/12	1/322 1/107	5/4	0.33 (0.02; 5.27)	-0.01 (-0.03; 0.01)	-160
		Dizziness	12/12	16/322 4/107	5/4	1.33 (0.45; 3.89)	0.01 (-0.03; 0.06)	81
		Headache	12/12	14/322 5/107	5/4	0.93 (0.34; 2.52)	0.00 (-0.05; 0.04)	-308
		Sleep disturbance	12/12	6/322 2/107	5/4	1.00 (0.20; 4.87)	0.00 (-0.03; 0.03)	-17241
		Upper respiratory viral infection	12/12	11/322 6/107	5/4	0.61 (0.23; 1.61)	-0.02 (-0.07; 0.03)	-46
		Cough	12/12	13/322 2/107	5/4	2.16 (0.50; 9.42)	0.02 (-0.01; 0.06)	46
		Liver symptoms	12/12	13/322 5/107	5/4	0.86 (0.32; 2.37)	-0.01 (-0.05; 0.04)	-157
		Muscular or skeletal pain	12/12	4/322 4/107	5/4	0.33 (0.08; 1.31)	-0.02 (-0.06; 0.01)	-40
		Leucopenia	12/12	2/322 0/107	5/4	1.67 (0.08; 34.55)	0.01 (-0.01; 0.02)	161
		Rash	12/12	6/322 1/107	5/4	1.99 (0.24; 16.37)	0.01 (-0.01; 0.03)	108
		Pruritis	12/12	2/322 0/107	5/4	1.67 (0.08; 34.55)	0.01 (-0.01; 0.02)	161
		Negative HBeAg	12/12	23/322 5/107	7/5	1.53 (0.60; 3.92)	0.02 (-0.02; 0.07)	40
		HBeAg seroconversion	12/12	17/322 5/107	5/4	1.13 (0.43; 2.99)	0.01 (-0.04; 0.05)	165

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Dienstag, 2003[107] Lamivudine , 100 mg/day, 144 weeks	Lamivudine , 100 mg/day, 96 weeks	Improved (de-crease of 2 points) HAI necro-inflammatory score	144/96	12/152 36/152	8/24	0.33 (0.18; 0.62)	**-0.16 (-0.24; -0.08)**	-6
		No change	144/96	38/152 24/152	25/16	1.58 (1.00; 2.51)	**0.09 (0.00; 0.18)**	11
		Worsened	144/96	13/152 3/152	9/2	4.33 (1.26; 14.90)	**0.07 (0.02; 0.12)**	15
Liaw, 2004[51] Lamivudine, 100 mg/day, 130 weeks	Placebo, 130 weeks	Hepatocellular carcinoma	130/130	17/436 16/215	4/7	0.52 (0.27; 1.02)	-0.04 (-0.07; 0.00)	-28
		Liver-related death	130/130	0/436 0/215			0.00 (-0.01; 0.01)	
		Hazard ratio of Hepatocellular carcinoma adjusted for country, sex, baseline ALT level, Child–Pugh score, and Ishak fibrosis score	130/130	0/436 0/215		**0.49 (0.25; 0.99)**		
		Death	130/130	2/436 0/215		2.47 (0.12; 51.25)	**0.00 (0.00; 0.01)**	218
		Overall disease progression	130/130	34/436 38/215	8/18	0.44 (0.29; 0.68)	**-0.10 (-0.16; -0.04)**	-10
		Increase in Child–Pugh score	130/130	15/436 19/215	3/9	0.39 (0.20; 0.75)	**-0.05 (-0.10; -0.01)**	-19
		Hazard ratio of overall disease progression	130/130	0/436 0/215		0.45 (0.28; 0.73)		
		Hazard ratio of Increase in Child–Pugh score adjusted for country, sex,	130/130	0/436 0/215		**0.45 (0.22; 0.90)**		

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

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		baseline ALT, Child–Pugh score, and Ishak fibrosis score						
		Renal insufficiency	130/130	2/436 0/215		2.47 (0.12; 51.25)	**0.00 (0.00; 0.01)**	218
		Bleeding varices	130/130	2/436 3/215	0/1	0.33 (0.06; 1.95)	-0.01 (-0.03; 0.01)	-107
		Spontaneous bacterial peritonitis	130/130	0/436 0/215			0.00 (-0.01; 0.01)	
		Any serious adverse event	130/130	54/436 38/215	12/18	0.70 (0.48; 1.03)	-0.05 (-0.11; 0.01)	-19
		Any adverse event	130/130	335/436 178/215	77/83	0.93 (0.86; 1.01)	-0.06 (-0.12; 0.00)	-17
		Ear, nose, or throat infections	130/130	97/436 44/215	22/20	1.09 (0.79; 1.49)	0.02 (-0.05; 0.08)	56
		Abdominal discomfort or pain	130/130	77/436 43/215	18/20	0.88 (0.63; 1.24)	-0.02 (-0.09; 0.04)	-43
		Malaise or fatigue	130/130	65/436 42/215	15/20	0.76 (0.54; 1.09)	-0.05 (-0.11; 0.02)	-22
		Headache	130/130	64/436 21/215	15/10	1.50 (0.94; 2.39)	**0.05 (0.00; 0.10)**	20
		Cough	130/130	62/436 15/215	14/7	2.04 (1.19; 3.50)	**0.07 (0.03; 0.12)**	14
		Diarrhea	130/130	33/436 29/215	8/13	0.56 (0.35; 0.90)	**-0.06 (-0.11; -0.01)**	-17
		Viral respiratory infections	130/130	39/436 21/215	9/10	0.92 (0.55; 1.52)	-0.01 (-0.06; 0.04)	-122
		YMDD mutations	130/130	209/436 11/215	48/5	9.37 (5.23; 16.80)	**0.43 (0.37; 0.48)**	2
Kim, 2006[54] Lamivudine , 100 mg/day after 6 months of previous LAM treatment,	No treatment, 80 weeks	Flare - elevation of ALT >10 X ULN and to >2 the baseline value with	80/80	4/37 6/37	11/0	0.67 (0.20; 2.17)	-0.05 (-0.21; 0.10)	-18

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

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80 weeks		detectable HBV DNA						
		ALT normalization	80/80	2/37 2/37	5/5	1.00 (0.15; 6.73)	0.00 (-0.10; 0.10)	
		Hepatic decompen-sation change in the Child- Turcotte-Pugh score of 2 or more points	80/80	7/37 5/37	19/0	1.40 (0.49; 4.01)	0.05 (-0.11; 0.22)	18
		Severe decompensation with a Child-Turcotte-Pugh score of >9	80/80	3/37 3/37	8/0	1.00 (0.22; 4.64)	0.00 (-0.12; 0.12)	
		HBeAg seroconversion	80/80	3/37 6/37	8/16	0.50 (0.14; 1.85)	-0.08 (-0.23; 0.07)	-12
Chan, 2007[46] Lamivudine, 100 mg/day, 96 weeks	Placebo, 96 weeks	Normalization of ALT	96/96	66/89 17/47	74/36	2.05 (1.38; 3.06)	**0.38 (0.22; 0.54)**	3
		Normalization of ALT	120/120	53/89 18/47	60/38	1.55 (1.04; 2.32)	**0.21 (0.04; 0.38)**	5
		Undetectable HBV DNA and ALT normalization	96/96	50/89 5/47	56/11	5.28 (2.26; 12.34)	**0.46 (0.32; 0.59)**	2
		Adjusted for baseline HBV DNA and ALT odds ratio of undetectable HBV DNA and ALT normalization of	96/96	0/89 0/47		**10.80 (3.80; 30.20)**		
		Undetectable HBV DNA and ALT normalization	120/120	23/89 9/47	26/19	1.35 (0.68; 2.68)	0.07 (-0.08; 0.21)	15
		URTI symptoms	96/96	29/89 15/47	33/32	1.02 (0.61; 1.71)	0.01 (-0.16; 0.17)	149

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

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		Right upper quadrant discomfort	96/96	15/89 3/47	17/6	2.64 (0.80; 8.66)	**0.10 (0.00; 0.21)**	10
		Dyspepsia	96/96	8/89 4/47	9/9	1.06 (0.34; 3.33)	0.00 (-0.09; 0.10)	209
		Headache	96/96	7/89 3/47	8/6	1.23 (0.33; 4.55)	0.01 (-0.07; 0.10)	67
		Increased ALT	96/96	11/89 6/47	12/13	0.97 (0.38; 2.45)	0.00 (-0.12; 0.11)	-246
		Increased ALP	96/96	9/89 6/47	10/13	0.79 (0.30; 2.09)	-0.03 (-0.14; 0.09)	-38
		Increased bilirubin	96/96	1/89 1/47	1/2	0.53 (0.03; 8.25)	-0.01 (-0.06; 0.04)	-100
		Increased CPK	96/96	3/89 3/47	3/6	0.53 (0.11; 2.52)	-0.03 (-0.11; 0.05)	-33
		Increased amylase	96/96	3/89 0/47	3/0	3.73 (0.20; 70.79)	0.03 (-0.02; 0.08)	30
		Prolonged PT level	96/96	1/89 3/47	1/6	0.18 (0.02; 1.65)	-0.05 (-0.13; 0.02)	-19
		Low neutrophil count	96/96	0/89 1/47	0/2	0.18 (0.01; 4.28)	-0.02 (-0.07; 0.03)	-47
		Thrombocytopenia	96/96	7/89 3/47	8/6	1.23 (0.33; 4.55)	0.01 (-0.07; 0.10)	67
		>2 points improvement in necroinflammatory scores	96/96	14/89 2/47	16/4	3.70 (0.88; 15.58)	**0.11 (0.02; 0.21)**	9
		>2 points worsening in necroinflammatory scores	96/96	2/89 3/47	2/6	0.35 (0.06; 2.03)	-0.04 (-0.12; 0.04)	-24
		>2 points improvement in fibrosis scores	96/96	6/89 0/47	7/0	6.93 (0.40; 120.47)	**0.07 (0.01; 0.13)**	15
		>2 points	96/96	1/89	1/2	0.53 (0.03; 8.25)	-0.01 (-0.06; 0.04)	-100

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		worsening in fibrosis scores		1/47				
		HBV DNA <10,000 copies/ml	96/96	52/89 9/47	58/19	3.05 (1.65; 5.63)	**0.39 (0.24; 0.54)**	3
		Undetectable HBV DNA with PCR	96/96	23/89 3/47	26/6	4.05 (1.28; 12.79)	**0.19 (0.08; 0.31)**	5
		HBV DNA <10,000 copies/ml	120/120	29/89 12/47	33/26	1.28 (0.72; 2.26)	0.07 (-0.09; 0.23)	14
		Undetectable HBV DNA with PCR	120/120	9/89 1/47	10/2	4.75 (0.62; 36.39)	**0.08 (0.00; 0.15)**	13
		HBsAg loss	120/120	1/89 0/47	1/0	1.60 (0.07; 38.53)	0.01 (-0.03; 0.05)	89
		Genotypic resistance	96/96	16/89 1/47	18/2	8.45 (1.16; 61.76)	**0.16 (0.07; 0.25)**	6
Perrillo, 2002[104] Lamivudine, 100 mg/day, 52 weeks	Placebo, 52 weeks	HBeAg irrespective of HBV-DNA status	52/52	102/406 20/196	25/10	2.46 (1.57; 3.85)	**0.15 (0.09; 0.21)**	7
		HBeAg and HBV DNA loss	52/52	66/406 14/196	16/7	2.28 (1.31; 3.95)	**0.09 (0.04; 0.14)**	11
Lai, 2005[72] Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100 mg/day + Placebo, 52 weeks	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 400 mg/day, 52 weeks	ALT normalization	52/52	12/19 20/22	63/91	0.69 (0.48; 1.00)	**-0.28 (-0.53; -0.03)**	-4
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 600 mg/day, 52 weeks	ALT normalization	52/52	12/19 18/22	63/82	0.77 (0.52; 1.15)	-0.19 (-0.46; 0.08)	-5
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 500 mg/day, 52 weeks	ALT normalization	52/52	12/19 38/44	63/86	0.73 (0.51; 1.05)	-0.23 (-0.47; 0.01)	-4

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	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 500 mg/day, 52 weeks	HBV DNA <5 log10 copies/mL and HBeAg loss or normalization of ALT levels	52/52	10/19 34/44	53/77	0.68 (0.43; 1.07)	-0.25 (-0.50; 0.01)	-4
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 400 mg/day, 52 weeks	At least one adverse event	52/52	13/19 16/22	68/73	0.94 (0.63; 1.40)	-0.04 (-0.32; 0.24)	-23
		Influenza	52/52	4/19 4/22	21/18	1.16 (0.33; 4.01)	0.03 (-0.22; 0.27)	35
		Headache	52/52	5/19 1/22	26/5	5.79 (0.74; 45.31)	**0.22 (0.00; 0.43)**	5
		Fatigue	52/52	3/19 1/22	16/5	3.47 (0.39; 30.68)	0.11 (-0.07; 0.30)	9
		Cough	52/52	3/19 2/22	16/9	1.74 (0.32; 9.32)	0.07 (-0.14; 0.27)	15
		Pharyngolaryngeal pain	52/52	3/19 2/22	16/9	1.74 (0.32; 9.32)	0.07 (-0.14; 0.27)	15
		Upper respiratory tract infection	52/52	1/19 3/22	5/14	0.39 (0.04; 3.41)	-0.08 (-0.26; 0.09)	-12
		Nasopharyngitis	52/52	1/19 1/22	5/5	1.16 (0.08; 17.28)	0.01 (-0.13; 0.14)	139
		Diarrhea	52/52	1/19 2/22	5/9	0.58 (0.06; 5.89)	-0.04 (-0.19; 0.12)	-26
		Upper abdominal pain	52/52	1/19 1/22	5/5	1.16 (0.08; 17.28)	0.01 (-0.13; 0.14)	139
		Back pain	52/52	0/19 0/22			0.00 (-0.09; 0.09)	
		Dyspepsia	52/52	4/19 0/22	21/0	10.35 (0.59; 180.66)	**0.21 (0.02; 0.40)**	5
		Dizziness	52/52	1/19 0/22	5/0	3.45 (0.15; 80.03)	0.05 (-0.08; 0.18)	19
		Increased creatine phosphokinase level	52/52	1/19 1/22	5/5	1.16 (0.08; 17.28)	0.01 (-0.13; 0.14)	139

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		Nausea	52/52	1/19 1/22	5/5	1.16 (0.08; 17.28)	0.01 (-0.13; 0.14)	139
		Depression	52/52	2/19 0/22	11/0	5.75 (0.29; 112.83)	0.11 (-0.05; 0.26)	9
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 600 mg/day, 52 weeks	At least one adverse event	52/52	13/19 15/22	68/68	1.00 (0.66; 1.52)	0.00 (-0.28; 0.29)	418
		Influenza	52/52	4/19 4/22	21/18	1.16 (0.33; 4.01)	0.03 (-0.22; 0.27)	35
		Headache	52/52	5/19 3/22	26/14	1.93 (0.53; 7.03)	0.13 (-0.12; 0.37)	8
		Fatigue	52/52	3/19 4/22	16/18	0.87 (0.22; 3.40)	-0.02 (-0.25; 0.21)	-42
		Cough	52/52	3/19 1/22	16/5	3.47 (0.39; 30.68)	0.11 (-0.07; 0.30)	9
		Pharyngolaryngeal pain	52/52	3/19 1/22	16/5	3.47 (0.39; 30.68)	0.11 (-0.07; 0.30)	9
		Upper respiratory tract infection	52/52	1/19 0/22	5/0	3.45 (0.15; 80.03)	0.05 (-0.08; 0.18)	19
		Nasopharyngitis	52/52	1/19 1/22	5/5	1.16 (0.08; 17.28)	0.01 (-0.13; 0.14)	139
		Diarrhea	52/52	1/19 1/22	5/5	1.16 (0.08; 17.28)	0.01 (-0.13; 0.14)	139
		Upper abdominal pain	52/52	1/19 2/22	5/9	0.58 (0.06; 5.89)	-0.04 (-0.19; 0.12)	-26
		Back pain	52/52	0/19 1/22	0/5	0.38 (0.02; 8.89)	-0.05 (-0.17; 0.08)	-22
		Dyspepsia	52/52	4/19 1/22	21/5	4.63 (0.57; 37.96)	0.17 (-0.04; 0.37)	6
		Dizziness	52/52	1/19 1/22	5/5	1.16 (0.08; 17.28)	0.01 (-0.13; 0.14)	139
		Increased creatine phosphokinase level	52/52	1/19 1/22	5/5	1.16 (0.08; 17.28)	0.01 (-0.13; 0.14)	139

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		Nausea	52/52	1/19 1/22	5/5	1.16 (0.08; 17.28)	0.01 (-0.13; 0.14)	139
		Depression	52/52	2/19 0/22	11/0	5.75 (0.29; 112.83)	0.11 (-0.05; 0.26)	9
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 500 mg/day, 52 weeks	HBV DNA PCR non detectable	52/52	6/19 27/44	32/61	0.51 (0.26; 1.04)	**-0.30 (-0.55; -0.04)**	-3
		HBeAg loss	52/52	5/19 15/44	28/33	0.77 (0.33; 1.82)	-0.08 (-0.32; 0.16)	-13
		HBeAg seroconversion	52/52	4/19 14/44	22/31	0.66 (0.25; 1.75)	-0.11 (-0.34; 0.12)	-9
		HBeAg loss and HBV DNA <5 log10 copies/mL	52/52	5/19 14/44	26/32	0.83 (0.35; 1.97)	-0.06 (-0.30; 0.19)	-18
		Virologic break through on treat-ment increase in HBV DNA levels to >5 log10 copies/mL	52/52	3/19 2/44	16/5	3.47 (0.63; 19.14)	0.11 (-0.06; 0.29)	9
Hadziyannis, 2005[98] Placebo, 0 placebo after 48 weeks of adefovir therapy, 96 weeks	Adefovir dipivoxil, 10 mg daily after 48 weeks of placebo therapy, 96 weeks	ALT normalization	96/96	12/40 40/60	30/67	0.45 (0.27; 0.75)	**-0.37 (-0.55; -0.18**)	-3
		Any adverse events	96/96	32/40 41/60	80/68	1.17 (0.93; 1.48)	0.12 (-0.05; 0.29)	9
		Headache	96/96	4/40 5/60	10/8	1.20 (0.34; 4.20)	0.02 (-0.10; 0.13)	60
		Abdominal pain	96/96	7/40 5/60	18/8	2.10 (0.72; 6.16)	0.09 (-0.05; 0.23)	11
		Asthenia	96/96	6/40 3/60	15/5	3.00 (0.80; 11.31)	0.10 (-0.02; 0.22)	10
		Flu-like syndrome	96/96	4/40 5/60	10/8	1.20 (0.34; 4.20)	0.02 (-0.10; 0.13)	60
		Back pain	96/96	5/40 3/60	12/5	2.50 (0.63; 9.88)	0.08 (-0.04; 0.19)	13
		Pain	96/96	2/40 4/60	5/7	0.75 (0.14; 3.90)	-0.02 (-0.11; 0.08)	-60

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Accidental injury	96/96	2/40 2/60	5/3	1.50 (0.22; 10.22)	0.02 (-0.06; 0.10)	60
		Diarrhea	96/96	4/40 1/60	10/2	6.00 (0.70; 51.74)	0.08 (-0.02; 0.18)	12
		Dyspepsia	96/96	5/40 1/60	12/2	7.50 (0.91; 61.83)	**0.11 (0.00; 0.22)**	9
		Pharyngitis	96/96	8/40 8/60	20/13	1.50 (0.61; 3.67)	0.07 (-0.08; 0.22)	15
		Increased cough	96/96	4/40 2/60	10/3	3.00 (0.58; 15.61)	0.07 (-0.04; 0.17)	15
		Bronchitis	96/96	1/40 1/60	2/2	1.50 (0.10; 23.30)	0.01 (-0.05; 0.07)	120
		Increased ALT levels	96/96	6/40 1/60	15/2	9.00 (1.13; 71.96)	**0.13 (0.02; 0.25)**	8
		Arthralgia	96/96	5/40 1/60	12/2	7.50 (0.91; 61.83)	**0.11 (0.00; 0.22)**	9
		Increased creatinine levels	96/96	0/40 0/60			0.00 (-0.04; 0.04)	
		Hematuria	96/96	0/40 1/60	0/2	0.50 (0.02; 11.88)	-0.02 (-0.07; 0.03)	-60
		Kidney calculus	96/96	0/40 1/60	0/2	0.50 (0.02; 11.88)	-0.02 (-0.07; 0.03)	-60
		Kidney pain	96/96	0/40 1/60	0/2	0.50 (0.02; 11.88)	-0.02 (-0.07; 0.03)	-60
		Improvement in Histological scores	96/96	4/40 14/60	10/23	0.43 (0.15; 1.21)	-0.13 (-0.28; 0.01)	-8
		Serum HBV DNA level <1000 log copies/ml	96/96	3/40 37/60	8/62	0.12 (0.04; 0.37)	**-0.54 (-0.69; -0.39)**	-2
		HBsAg seroconversion	96/96	0/40 1/60	0/2	0.50 (0.02; 11.88)	-0.02 (-0.07; 0.03)	-60
Lai, 2005[72] Telbivudine Idenix Pharmaceuticals Inc	Telbivudine Idenix Pharmaceuticals Inc (Cambridge,	ALT normalization	52/52	17/21 15/20	81/74	1.08 (0.78; 1.50)	0.06 (-0.19; 0.31)	17

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
(Cambridge, MA), 400 mg/day lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100mg/day52 weeks	MA), 600 mg/day, 52 weeks							
	Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100 mg/day, 52 weeks	ALT normalization	52/52	17/21 12/19	81/63	1.28 (0.86; 1.91)	0.18 (-0.10; 0.45)	6
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 400 mg/day, 52 weeks	ALT normalization	52/52	17/21 20/22	81/91	0.89 (0.70; 1.14)	-0.10 (-0.31; 0.11)	-10
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 600 mg/day, 52 weeks	ALT normalization	52/52	17/21 18/22	81/82	0.99 (0.74; 1.32)	-0.01 (-0.24; 0.22)	-116
Lai, 2005[72] Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 600 mg/day lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100mg/day52 weeks	Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100 mg/day, 52 weeks	ALT normalization	52/52	15/20 12/19	74/63	1.19 (0.78; 1.82)	0.12 (-0.17; 0.41)	8
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 400 mg/day, 52 weeks	ALT normalization	52/52	15/20 20/22	74/91	0.83 (0.62; 1.10)	-0.16 (-0.38; 0.07)	-6
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 600 mg/day, 52 weeks	ALT normalization	52/52	15/20 18/22	74/82	0.92 (0.67; 1.26)	-0.07 (-0.32; 0.18)	-15
Lai, 2005[72] Telbivudine Idenix Pharmaceuticals Inc	Telbivudine Idenix Pharmaceuticals Inc (Cambridge,	ALT normalization	52/52	20/22 18/22	91/82	1.11 (0.88; 1.41)	0.09 (-0.11; 0.29)	11

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
(Cambridge, MA), 400 mg/day +Placebo, 52 weeks	MA), 600 mg/day, 52 weeks							
Lai, 2005[72] Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 500 mg/day (both 400mg or 600 mg/day) lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100mg/day 52 weeks	Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100 mg/day, 52 weeks	ALT normalization	52/52	32/41 12/19	78/63	1.24 (0.85; 1.81)	0.15 (-0.10; 0.40)	7
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 500 mg/day, 52 weeks	ALT normalization	52/52	32/41 38/44	78/86	0.90 (0.74; 1.10)	-0.08 (-0.25; 0.08)	-12
	Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100 mg/day, 52 weeks	HBV DNA <5 log 10 copies/mL coupled with HBeAg loss or normalization of ALT levels	52/52	26/41 10/19	63/53	1.20 (0.74; 1.96)	0.11 (-0.16; 0.38)	9
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 500 mg/day, 52 weeks	HBV DNA < 5 log 10 copies/mL coupled with HBeAg loss or normal-ization of ALT levels	52/52	26/41 34/44	63/77	0.82 (0.62; 1.09)	-0.14 (-0.33; 0.05)	-7
Lai, 2005[72] Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 400 mg/day lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100mg/day52 weeks	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 600 mg/day, 52 weeks	At least one adverse event	52/52	15/21 14/20	71/70	1.02 (0.69; 1.51)	0.01 (-0.26; 0.29)	70
		Influenza	52/52	4/21 6/20	19/30	0.63 (0.21; 1.92)	-0.11 (-0.37; 0.15)	-9
		Headache	52/52	4/21 2/20	19/10	1.90 (0.39; 9.28)	0.09 (-0.12; 0.30)	11
		Fatigue	52/52	1/21 2/20	5/10	0.48 (0.05; 4.85)	-0.05 (-0.21; 0.11)	-19
		Cough	52/52	2/21 1/20	10/5	1.90 (0.19; 19.40)	0.05 (-0.11; 0.20)	22

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Pharyngolaryngeal pain	52/52	0/21 3/20	0/15	0.14 (0.01; 2.48)	-0.15 (-0.32; 0.02)	-7
		Upper respiratory tract infection	52/52	2/21 2/20	10/10	0.95 (0.15; 6.13)	0.00 (-0.19; 0.18)	-210
		Nasopharyngitis	52/52	2/21 1/20	10/5	1.90 (0.19; 19.40)	0.05 (-0.11; 0.20)	22
		Diarrhea	52/52	1/21 1/20	5/5	0.95 (0.06; 14.22)	0.00 (-0.13; 0.13)	-420
		Upper abdominal pain	52/52	0/21 2/20	0/10	0.19 (0.01; 3.75)	-0.10 (-0.25; 0.05)	-10
		Back pain	52/52	2/21 2/20	10/10	0.95 (0.15; 6.13)	0.00 (-0.19; 0.18)	-210
		Dyspepsia	52/52	0/21 0/20			0.00 (-0.09; 0.09)	
		Dizziness	52/52	1/21 2/20	5/10	0.48 (0.05; 4.85)	-0.05 (-0.21; 0.11)	-19
		Increased creatine phosphokinase level	52/52	1/21 1/20	5/5	0.95 (0.06; 14.22)	0.00 (-0.13; 0.13)	-420
		Nausea	52/52	0/21 2/20	0/10	0.19 (0.01; 3.75)	-0.10 (-0.25; 0.05)	-10
		Depression	52/52	1/21 1/20	5/5	0.95 (0.06; 14.22)	0.00 (-0.13; 0.13)	-420
	Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100 mg/day, 52 weeks	At least one adverse event	52/52	15/21 13/19	71/68	1.04 (0.69; 1.57)	0.03 (-0.25; 0.31)	33
		Influenza	52/52	4/21 4/19	19/21	0.90 (0.26; 3.12)	-0.02 (-0.27; 0.23)	-50
		Headache	52/52	4/21 5/19	19/26	0.72 (0.23; 2.31)	-0.07 (-0.33; 0.19)	-14
		Fatigue	52/52	1/21 3/19	5/16	0.30 (0.03; 2.66)	-0.11 (-0.30; 0.08)	-9
		Cough	52/52	2/21 3/19	10/16	0.60 (0.11; 3.23)	-0.06 (-0.27; 0.14)	-16
		Pharyngolaryngeal pain	52/52	0/21 3/19	0/16	0.13 (0.01; 2.36)	-0.16 (-0.34; 0.02)	-6

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Upper respiratory tract infection	52/52	2/21 1/19	10/5	1.81 (0.18; 18.39)	0.04 (-0.12; 0.20)	23
		Nasopharyngitis	52/52	2/21 1/19	10/5	1.81 (0.18; 18.39)	0.04 (-0.12; 0.20)	23
		Diarrhea	52/52	1/21 1/19	5/5	0.90 (0.06; 13.48)	-0.01 (-0.14; 0.13)	-200
		Upper abdominal pain	52/52	0/21 1/19	0/5	0.30 (0.01; 7.02)	-0.05 (-0.18; 0.08)	-19
		Back pain	52/52	2/21 0/19	10/0	4.55 (0.23; 89.08)	0.10 (-0.05; 0.24)	10
		Dyspepsia	52/52	0/21 4/19	0/21	0.10 (0.01; 1.76)	**-0.21 (-0.40; -0.02)**	-5
		Dizziness	52/52	1/21 1/19	5/5	0.90 (0.06; 13.48)	-0.01 (-0.14; 0.13)	-200
		Increased creatine phosphokinase level	52/52	1/21 1/19	5/5	0.90 (0.06; 13.48)	-0.01 (-0.14; 0.13)	-200
		Nausea	52/52	0/21 1/19	0/5	0.30 (0.01; 7.02)	-0.05 (-0.18; 0.08)	-19
		Depression	52/52	1/21 2/19	5/11	0.45 (0.04; 4.60)	-0.06 (-0.22; 0.11)	-17
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 400 mg/day, 52 weeks	At least one adverse event	52/52	15/21 16/22	71/73	0.98 (0.68; 1.43)	-0.01 (-0.28; 0.26)	-77
		Influenza	52/52	4/21 4/22	19/18	1.05 (0.30; 3.66)	0.01 (-0.22; 0.24)	116
		Headache	52/52	4/21 1/22	19/5	4.19 (0.51; 34.50)	0.15 (-0.04; 0.33)	7
		Fatigue	52/52	1/21 1/22	5/5	1.05 (0.07; 15.69)	0.00 (-0.12; 0.13)	462
		Cough	52/52	2/21 2/22	10/9	1.05 (0.16; 6.77)	0.00 (-0.17; 0.18)	231
		Pharyngolaryngeal pain	52/52	0/21 2/22	0/9	0.21 (0.01; 4.11)	-0.09 (-0.23; 0.05)	-11
		Upper respiratory tract infection	52/52	2/21 3/22	10/14	0.70 (0.13; 3.77)	-0.04 (-0.23; 0.15)	-24

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Nasopharyngitis	52/52	2/21 1/22	10/5	2.10 (0.20; 21.42)	0.05 (-0.10; 0.20)	20
		Diarrhea	52/52	1/21 2/22	5/9	0.52 (0.05; 5.36)	-0.04 (-0.19; 0.11)	-23
		Upper abdominal pain	52/52	0/21 1/22	0/5	0.35 (0.01; 8.11)	-0.05 (-0.16; 0.07)	-22
		Back pain	52/52	2/21 0/22	10/0	5.23 (0.27; 102.87)	0.10 (-0.05; 0.24)	10
		Dyspepsia	52/52	0/21 0/22			0.00 (-0.09; 0.09)	
		Dizziness	52/52	1/21 0/22	5/0	3.14 (0.13; 72.96)	0.05 (-0.07; 0.17)	21
		Increased creatine phosphokinase level	52/52	1/21 1/22	5/5	1.05 (0.07; 15.69)	0.00 (-0.12; 0.13)	462
		Nausea	52/52	0/21 1/22	0/5	0.35 (0.01; 8.11)	-0.05 (-0.16; 0.07)	-22
		Depression	52/52	1/21 0/22	5/0	3.14 (0.13; 72.96)	0.05 (-0.07; 0.17)	21
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 600 mg/day, 52 weeks	At least one adverse event	52/52	15/21 15/22	71/68	1.05 (0.71; 1.55)	0.03 (-0.24; 0.31)	31
		Influenza	52/52	4/21 4/22	19/18	1.05 (0.30; 3.66)	0.01 (-0.22; 0.24)	116
		Headache	52/52	4/21 3/22	19/14	1.40 (0.35; 5.51)	0.05 (-0.17; 0.27)	18
		Fatigue	52/52	1/21 4/22	5/18	0.26 (0.03; 2.16)	-0.13 (-0.32; 0.05)	-7
		Cough	52/52	2/21 1/22	10/5	2.10 (0.20; 21.42)	0.05 (-0.10; 0.20)	20
		Pharyngolaryngeal pain	52/52	0/21 1/22	0/5	0.35 (0.01; 8.11)	-0.05 (-0.16; 0.07)	-22
		Upper respiratory tract infection	52/52	2/21 0/22	10/0	5.23 (0.27; 102.87)	0.10 (-0.05; 0.24)	10
		Nasopharyngitis	52/52	2/21 1/22	10/5	2.10 (0.20; 21.42)	0.05 (-0.10; 0.20)	20

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Diarrhea	52/52	1/21 1/22	5/5	1.05 (0.07; 15.69)	0.00 (-0.12; 0.13)	462
		Upper abdominal pain	52/52	0/21 2/22	0/9	0.21 (0.01; 4.11)	-0.09 (-0.23; 0.05)	-11
		Back pain	52/52	2/21 1/22	10/5	2.10 (0.20; 21.42)	0.05 (-0.10; 0.20)	20
		Dyspepsia	52/52	0/21 1/22	0/5	0.35 (0.01; 8.11)	-0.05 (-0.16; 0.07)	-22
		Dizziness	52/52	1/21 1/22	5/5	1.05 (0.07; 15.69)	0.00 (-0.12; 0.13)	462
		Increased creatine phosphokinase level	52/52	1/21 1/22	5/5	1.05 (0.07; 15.69)	0.00 (-0.12; 0.13)	462
		Nausea	52/52	0/21 1/22	0/5	0.35 (0.01; 8.11)	-0.05 (-0.16; 0.07)	-22
		Depression	52/52	1/21 0/22	5/0	3.14 (0.13; 72.96)	0.05 (-0.07; 0.17)	21
Lai, 2005[72] Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 600 mg/day lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100mg/day52 weeks	Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100 mg/day, 52 weeks	At least one adverse event	52/52	14/20 13/19	70/68	1.02 (0.67; 1.56)	0.02 (-0.27; 0.31)	63
		Influenza	52/52	6/20 4/19	30/21	1.43 (0.48; 4.27)	0.09 (-0.18; 0.36)	11
		Headache	52/52	2/20 5/19	10/26	0.38 (0.08; 1.73)	-0.16 (-0.40; 0.07)	-6
		Fatigue	52/52	2/20 3/19	10/16	0.63 (0.12; 3.38)	-0.06 (-0.27; 0.15)	-17
		Cough	52/52	1/20 3/19	5/16	0.32 (0.04; 2.79)	-0.11 (-0.30; 0.08)	-9
		Pharyngolaryngeal pain	52/52	3/20 3/19	15/16	0.95 (0.22; 4.14)	-0.01 (-0.23; 0.22)	-127
		Upper respiratory tract infection	52/52	2/20 1/19	10/5	1.90 (0.19; 19.27)	0.05 (-0.12; 0.21)	21
		Nasopharyngitis	52/52	1/20 1/19	5/5	0.95 (0.06; 14.13)	0.00 (-0.14; 0.14)	-380
		Diarrhea	52/52	1/20 1/19	5/5	0.95 (0.06; 14.13)	0.00 (-0.14; 0.14)	-380

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Upper abdominal pain	52/52	2/20 1/19	10/5	1.90 (0.19; 19.27)	0.05 (-0.12; 0.21)	21
		Back pain	52/52	2/20 0/19	10/0	4.76 (0.24; 93.19)	0.10 (-0.05; 0.25)	10
		Dyspepsia	52/52	0/20 4/19	0/21	0.11 (0.01; 1.84)	**-0.21 (-0.40; -0.02)**	-5
		Dizziness	52/52	2/20 1/19	10/5	1.90 (0.19; 19.27)	0.05 (-0.12; 0.21)	21
		Increased creatine phosphokinase level	52/52	1/20 1/19	5/5	0.95 (0.06; 14.13)	0.00 (-0.14; 0.14)	-380
		Nausea	52/52	2/20 1/19	10/5	1.90 (0.19; 19.27)	0.05 (-0.12; 0.21)	21
		Depression	52/52	1/20 2/19	5/11	0.48 (0.05; 4.82)	-0.06 (-0.22; 0.11)	-18
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 400 mg/day, 52 weeks	At least one adverse event	52/52	14/20 16/22	70/73	0.96 (0.66; 1.41)	-0.03 (-0.30; 0.25)	-37
		Influenza	52/52	6/20 4/22	30/18	1.65 (0.54; 5.01)	0.12 (-0.14; 0.38)	8
		Headache	52/52	2/20 1/22	10/5	2.20 (0.22; 22.45)	0.05 (-0.10; 0.21)	18
		Fatigue	52/52	2/20 1/22	10/5	2.20 (0.22; 22.45)	0.05 (-0.10; 0.21)	18
		Cough	52/52	1/20 2/22	5/9	0.55 (0.05; 5.61)	-0.04 (-0.19; 0.11)	-24
		Pharyngolaryngeal pain	52/52	3/20 2/22	15/9	1.65 (0.31; 8.89)	0.06 (-0.14; 0.26)	17
		Upper respiratory tract infection	52/52	2/20 3/22	10/14	0.73 (0.14; 3.95)	-0.04 (-0.23; 0.16)	-28
		Nasopharyngitis	52/52	1/20 1/22	5/5	1.10 (0.07; 16.45)	0.00 (-0.12; 0.13)	220
		Diarrhea	52/52	1/20 2/22	5/9	0.55 (0.05; 5.61)	-0.04 (-0.19; 0.11)	-24
		Upper abdominal pain	52/52	2/20 1/22	10/5	2.20 (0.22; 22.45)	0.05 (-0.10; 0.21)	18

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Back pain	52/52	2/20 0/22	10/0	5.48 (0.28; 107.62)	0.10 (-0.05; 0.25)	10
		Dyspepsia	52/52	0/20 0/22			0.00 (-0.09; 0.09)	
		Dizziness	52/52	2/20 0/22	10/0	5.48 (0.28; 107.62)	0.10 (-0.05; 0.25)	10
		Increased creatine phosphokinase level	52/52	1/20 1/22	5/5	1.10 (0.07; 16.45)	0.00 (-0.12; 0.13)	220
		Nausea	52/52	2/20 1/22	10/5	2.20 (0.22; 22.45)	0.05 (-0.10; 0.21)	18
		Depression	52/52	1/20 0/22	5/0	3.29 (0.14; 76.33)	0.05 (-0.08; 0.18)	20
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 600 mg/day, 52 weeks	At least one adverse event	52/52	14/20 15/22	70/68	1.03 (0.68; 1.54)	0.02 (-0.26; 0.30)	55
		Influenza	52/52	6/20 4/22	30/18	1.65 (0.54; 5.01)	0.12 (-0.14; 0.38)	8
		Headache	52/52	2/20 3/22	10/14	0.73 (0.14; 3.95)	-0.04 (-0.23; 0.16)	-28
		Fatigue	52/52	2/20 4/22	10/18	0.55 (0.11; 2.69)	-0.08 (-0.29; 0.13)	-12
		Cough	52/52	1/20 1/22	5/5	1.10 (0.07; 16.45)	0.00 (-0.12; 0.13)	220
		Pharyngolaryngeal pain	52/52	3/20 1/22	15/5	3.30 (0.37; 29.21)	0.10 (-0.07; 0.28)	10
		Upper respiratory tract infection	52/52	2/20 0/22	10/0	5.48 (0.28; 107.62)	0.10 (-0.05; 0.25)	10
		Nasopharyngitis	52/52	1/20 1/22	5/5	1.10 (0.07; 16.45)	0.00 (-0.12; 0.13)	220
		Diarrhea	52/52	1/20 1/22	5/5	1.10 (0.07; 16.45)	0.00 (-0.12; 0.13)	220
		Upper abdominal pain	52/52	2/20 2/22	10/9	1.10 (0.17; 7.09)	0.01 (-0.17; 0.19)	110
		Back pain	52/52	2/20 1/22	10/5	2.20 (0.22; 22.45)	0.05 (-0.10; 0.21)	18

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Dyspepsia	52/52	0/20 1/22	0/5	0.37 (0.02; 8.48)	-0.05 (-0.17; 0.07)	-22
		Dizziness	52/52	2/20 1/22	10/5	2.20 (0.22; 22.45)	0.05 (-0.10; 0.21)	18
		Increased creatine phosphokinase level	52/52	1/20 1/22	5/5	1.10 (0.07; 16.45)	0.00 (-0.12; 0.13)	220
		Nausea	52/52	2/20 1/22	10/5	2.20 (0.22; 22.45)	0.05 (-0.10; 0.21)	18
		Depression	52/52	1/20 0/22	5/0	3.29 (0.14; 76.33)	0.05 (-0.08; 0.18)	20
Lai, 2005[72] Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 400 mg/day + Placebo, 52 weeks	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 600 mg/day, 52 weeks	At least one adverse event	52/52	16/22 15/22	73/68	1.07 (0.73; 1.57)	0.05 (-0.22; 0.31)	22
		Influenza	52/52	4/22 4/22	18/18	1.00 (0.29; 3.50)	0.00 (-0.23; 0.23)	
		Headache	52/52	1/22 3/22	5/14	0.33 (0.04; 2.96)	-0.09 (-0.26; 0.08)	-11
		Fatigue	52/52	1/22 4/22	5/18	0.25 (0.03; 2.06)	-0.14 (-0.32; 0.05)	-7
		Cough	52/52	2/22 1/22	9/5	2.00 (0.20; 20.49)	0.05 (-0.10; 0.19)	22
		Pharyngolaryngeal pain	52/52	2/22 1/22	9/5	2.00 (0.20; 20.49)	0.05 (-0.10; 0.19)	22
		Upper respiratory tract infection	52/52	3/22 0/22	14/0	7.00 (0.38; 128.02)	0.14 (-0.02; 0.29)	7
		Nasopharyngitis	52/52	1/22 1/22	5/5	1.00 (0.07; 15.00)	0.00 (-0.12; 0.12)	
		Diarrhea	52/52	2/22 1/22	9/5	2.00 (0.20; 20.49)	0.05 (-0.10; 0.19)	22
		Upper abdominal pain	52/52	1/22 2/22	5/9	0.50 (0.05; 5.12)	-0.05 (-0.19; 0.10)	-22
		Back pain	52/52	0/22 1/22	0/5	0.33 (0.01; 7.76)	-0.05 (-0.16; 0.07)	-22
		Dyspepsia	52/52	0/22 1/22	0/5	0.33 (0.01; 7.76)	-0.05 (-0.16; 0.07)	-22

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Dizziness	52/52	0/22 1/22	0/5	0.33 (0.01; 7.76)	-0.05 (-0.16; 0.07)	-22
		Increased creatine phosphokinase level	52/52	1/22 1/22	5/5	1.00 (0.07; 15.00)	0.00 (-0.12; 0.12)	
		Nausea	52/52	1/22 1/22	5/5	1.00 (0.07; 15.00)	0.00 (-0.12; 0.12)	
		Depression	52/52	0/22 0/22			0.00 (-0.08; 0.08)	
Lai, 2005[72] Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 500 mg/day (both 400mg or 600 mg/day) lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100mg/day, 52 weeks	Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100 mg/day, 52 weeks	HBV DNA PCR non detectable	52/52	20/41 6/19	49/32	1.54 (0.74; 3.21)	0.17 (-0.09; 0.43)	6
		HBeAg loss	52/52	7/41 5/19	17/28	0.65 (0.24; 1.78)	-0.09 (-0.32; 0.14)	-11
		HBeAg seroconversion	52/52	6/41 4/19	15/22	0.70 (0.22; 2.18)	-0.06 (-0.28; 0.15)	-16
		HBeAg loss and HBV DNA <5 log10 copies/mL	52/52	8/41 5/19	20/26	0.74 (0.28; 1.97)	-0.07 (-0.30; 0.16)	-15
		Virologic break through on treat-ment increase in HBV DNA levels to >5 log10 copies/mL	52/52	5/41 3/19	12/16	0.77 (0.21; 2.90)	-0.04 (-0.23; 0.16)	-28
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 500 mg/day, 52 weeks	HBV DNA PCR non detectable	52/52	20/41 27/44	49/61	0.79 (0.54; 1.18)	-0.13 (-0.34; 0.08)	-8
		HBeAg loss	52/52	7/41 15/44	17/33	0.50 (0.23; 1.10)	-0.17 (-0.35; 0.01)	-6
		HBeAg seroconversion	52/52	6/41 14/44	15/31	0.46 (0.20; 1.08)	-0.17 (-0.35; 0.00)	-6
		HBeAg loss and HBV DNA <5 log10 copies/mL	52/52	8/41 14/44	20/32	0.61 (0.29; 1.31)	-0.12 (-0.31; 0.06)	-8
		Virologic breakthrough on	52/52	5/41 2/44	12/5	2.68 (0.55; 13.07)	0.08 (-0.04; 0.19)	13

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		treatment increase in HBV DNA levels to >5 log10 copies/mL						
Lai, 2007[71] Telbivudine (Idenix Pharmaceuticals Inc Cambridge, MA), 600 mg/day, 52 weeks	Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100 mg/day, 52 weeks	Discontinuation due to adverse events, clinical disease progression, or lack of efficacy	52/52	2/680 8/687	0/1	0.25 (0.05; 1.19)	-0.01 (-0.02; 0.00)	-115
		Any adverse event	52/52	496/680 474/687	73/69	1.06 (0.99; 1.13)	0.04 (-0.01; 0.09)	25
		Upper respiratory tract infection	52/52	82/680 82/687	12/12	1.01 (0.76; 1.35)	0.00 (-0.03; 0.04)	814
		Headache	52/52	68/680 82/687	10/12	0.84 (0.62; 1.13)	-0.02 (-0.05; 0.01)	-52
		Nasopharyngitis	52/52	68/680 69/687	10/10	1.00 (0.72; 1.37)	0.00 (-0.03; 0.03)	-2290
		Fatigue	52/52	68/680 62/687	10/9	1.11 (0.80; 1.54)	0.01 (-0.02; 0.04)	103
		Increased blood creatine kinase	52/52	54/680 41/687	8/6	1.33 (0.90; 1.97)	0.02 (-0.01; 0.05)	51
		Post procedure pain	52/52	41/680 34/687	6/5	1.22 (0.78; 1.90)	0.01 (-0.01; 0.03)	93
		Cough	52/52	41/680 41/687	6/6	1.01 (0.66; 1.54)	0.00 (-0.02; 0.03)	1628
		Upper abdominal pain	52/52	34/680 48/687	5/7	0.72 (0.47; 1.10)	-0.02 (-0.05; 0.01)	-50
		Influenza	52/52	34/680 34/687	5/5	1.01 (0.64; 1.61)	0.00 (-0.02; 0.02)	1963
		Diarrhea	52/52	34/680 27/687	5/4	1.27 (0.78; 2.08)	0.01 (-0.01; 0.03)	93
		Nausea	52/52	34/680 27/687	5/4	1.27 (0.78; 2.08)	0.01 (-0.01; 0.03)	93

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Dizziness	52/52	27/680 34/687	4/5	0.80 (0.49; 1.31)	-0.01 (-0.03; 0.01)	-102
		Dyspepsia	52/52	14/680 34/687	2/5	0.42 (0.23; 0.77)	**-0.03 (-0.05; -0.01)**	-35
		Grade 3 or 4 laboratory abnormalities in ALT	52/52	25/680 43/687	4/6	0.59 (0.36; 0.95)	-0.03 (-0.05; 0.00)	-39
		Grade 3 or 4 laboratory abnormalities in AST	52/52	18/680 32/687	3/5	0.57 (0.32; 1.00)	-0.02 (-0.04; 0.00)	-50
		Grade 3 or 4 laboratory abnormalities in creatine kinase	52/52	51/680 21/687	8/3	2.45 (1.49; 4.03)	**0.04 (0.02; 0.07)**	23
		Grade 3 or 4 laboratory abnormalities in Lipase	52/52	12/680 22/687	2/3	0.55 (0.27; 1.10)	-0.01 (-0.03; 0.00)	-70
		Grade 3 or 4 laboratory abnormalities in amylase	52/52	1/680 2/687		0.51 (0.05; 5.56)	0.00 (-0.01; 0.00)	-694
		Grade 3 or 4 laboratory abnormalities in absolute neutrophil count	52/52	13/680 9/687	2/1	1.46 (0.63; 3.39)	0.01 (-0.01; 0.02)	166
		Grade 3 or 4 laboratory abnormalities in platelet count	52/52	5/680 4/687	1/1	1.26 (0.34; 4.68)	0.00 (-0.01; 0.01)	653
		Grade 3 or 4 laboratory abnormalities in total bilirubin	52/52	0/680 2/687		0.20 (0.01; 4.20)	0.00 (-0.01; 0.00)	-344
Chan, 2007[44] Telbivudine (Idenix	Adefovir (Hepsera, Gilead Sciences,	ALT normalization	24/24	26/45 56/91	58/61	0.94 (0.70; 1.26)	-0.04 (-0.21; 0.14)	-27

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Pharmaceuticals, Cambridge, MA), 600 mg/day in 3 tablets, 24 weeks	Foster City, CA), 10 mg/day, 24 weeks	Adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site) odds ratio of ALT normalization	24/24	0/45 0/91		1.81 (0.56; 5.85)		
Chan, 2007[44] Telbivudine (Idenix Pharmaceuticals, Cambridge, MA), 600 mg/day in 3 tablets, 52 weeks	Adefovir (Hepsera, Gilead Sciences, Foster City, CA), 10 mg/day, 52 weeks	Serum ALT normalization	52/52	36/45 38/45	79/85	0.95 (0.78; 1.15)	-0.04 (-0.20; 0.11)	-23
	Adefovir (Hepsera, Gilead Sciences, Foster City, CA) for 24 weeks and then telbivudine(Idenix Pharmaceuticals, Cambridge, MA) for the remaining 28 weeks, 10 mg/day, 52 weeks	Serum ALT normalization	52/52	36/45 39/46	79/85	0.94 (0.78; 1.14)	-0.05 (-0.20; 0.11)	-21
	Adefovir (Hepsera, Gilead Sciences, Foster City, CA), 10 mg/day, 52 weeks	Adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site) odds ratio of serum ALT normalization	52/52	0/45 0/45		0.61 (0.18; 2.08)		
		Total adverse effects	52/52	34/45 27/45	76/61	1.26 (0.94; 1.68)	0.16 (-0.03; 0.35)	6
		Upper respiratory tract infection	52/52	5/45 5/45	11/11	1.00 (0.31; 3.22)	0.00 (-0.13; 0.13)	

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Headache	52/52	5/45 3/45	11/7	1.67 (0.42; 6.56)	0.04 (-0.07; 0.16)	23
		Back pain	52/52	6/45 3/45	13/7	2.00 (0.53; 7.51)	0.07 (-0.06; 0.19)	15
		Diarrhea	52/52	6/45 1/45	13/2	6.00 (0.75; 47.85)	**0.11 (0.00; 0.22)**	9
		Influenza	52/52	5/45 3/45	11/7	1.67 (0.42; 6.56)	0.04 (-0.07; 0.16)	23
		Upper abdominal pain	52/52	3/45 2/45	7/5	1.50 (0.26; 8.55)	0.02 (-0.07; 0.12)	45
		Nasopharyngitis	52/52	1/45 5/45	2/11	0.20 (0.02; 1.64)	-0.09 (-0.19; 0.01)	-11
		Cough	52/52	1/45 0/45	2/0	3.00 (0.13; 71.74)	0.02 (-0.04; 0.08)	45
		Arthralgia	52/52	2/45 2/45	4/5	1.00 (0.15; 6.79)	0.00 (-0.09; 0.09)	
		Fatigue	52/52	2/45 0/45	4/0	5.00 (0.25; 101.31)	0.04 (-0.03; 0.12)	23
		Dizziness	52/52	1/45 0/45	2/0	3.00 (0.13; 71.74)	0.02 (-0.04; 0.08)	45
		Malaise	52/52	3/45 0/45	7/0	7.00 (0.37; 131.73)	0.07 (-0.02; 0.15)	15
		Nausea	52/52	2/45 2/45	4/5	1.00 (0.15; 6.79)	0.00 (-0.09; 0.09)	
		Pharyngolaryngeal pain	52/52	1/45 3/45	2/7	0.33 (0.04; 3.08)	-0.04 (-0.13; 0.04)	-23
		Abdominal pain	52/52	2/45 1/45	4/2	2.00 (0.19; 21.28)	0.02 (-0.05; 0.10)	45
		Epigastric discomfort	52/52	2/45 0/45	4/0	5.00 (0.25; 101.31)	0.04 (-0.03; 0.12)	23
		Gastritis	52/52	3/45 0/45	7/0	7.00 (0.37; 131.73)	0.07 (-0.02; 0.15)	15
		Hepatic steatosis	52/52	2/45 1/45	4/2	2.00 (0.19; 21.28)	0.02 (-0.05; 0.10)	45

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Mouth ulceration	52/52	0/45 2/45	0/5	0.20 (0.01; 4.05)	-0.04 (-0.12; 0.03)	-23
		Myalgia	52/52	1/45 0/45	2/0	3.00 (0.13; 71.74)	0.02 (-0.04; 0.08)	45
		Toothache	52/52	2/45 1/45	4/2	2.00 (0.19; 21.28)	0.02 (-0.05; 0.10)	45
		Hepatitis B	52/52	0/45 2/45	0/5	0.20 (0.01; 4.05)	-0.04 (-0.12; 0.03)	-23
		Hordeolum	52/52	2/45 0/45	4/0	5.00 (0.25; 101.31)	0.04 (-0.03; 0.12)	23
		Allergic rhinitis	52/52	0/45 2/45	0/5	0.20 (0.01; 4.05)	-0.04 (-0.12; 0.03)	-23
	Adefovir (Hepsera, Gilead Sciences, Foster City, CA) for 24 weeks and then telbivudine(Idenix Pharmaceuticals, Cambridge, MA) for the remaining 28 weeks, 10 mg/day, 52 weeks	Total adverse effects	52/52	34/45 31/46	76/67	1.12 (0.86; 1.46)	0.08 (-0.10; 0.27)	12
		Upper respiratory tract infection	52/52	5/45 6/46	11/13	0.85 (0.28; 2.59)	-0.02 (-0.15; 0.11)	-52
		Headache	52/52	5/45 6/46	11/13	0.85 (0.28; 2.59)	-0.02 (-0.15; 0.11)	-52
		Back pain	52/52	6/45 3/46	13/7	2.04 (0.54; 7.68)	0.07 (-0.05; 0.19)	15
		Diarrhea	52/52	6/45 5/46	13/11	1.23 (0.40; 3.73)	0.02 (-0.11; 0.16)	41
		Influenza	52/52	5/45 4/46	11/9	1.28 (0.37; 4.46)	0.02 (-0.10; 0.15)	41
		Upper abdominal pain	52/52	3/45 5/46	7/11	0.61 (0.16; 2.42)	-0.04 (-0.16; 0.07)	-24
		Nasopharyngitis	52/52	1/45 2/46	2/4	0.51 (0.05; 5.44)	-0.02 (-0.09; 0.05)	-47
		Cough	52/52	1/45 6/46	2/13	0.17 (0.02; 1.36)	-0.11 (-0.21; 0.00)	-9
		Arthralgia	52/52	2/45 2/46	4/4	1.02 (0.15; 6.95)	0.00 (-0.08; 0.09)	1035
		Fatigue	52/52	2/45 4/46	4/9	0.51 (0.10; 2.65)	-0.04 (-0.14; 0.06)	-24

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Dizziness	52/52	1/45 4/46	2/9	0.26 (0.03; 2.20)	-0.06 (-0.16; 0.03)	-15
		Malaise	52/52	3/45 2/46	7/4	1.53 (0.27; 8.75)	0.02 (-0.07; 0.12)	43
		Nausea	52/52	2/45 1/46	4/2	2.04 (0.19; 21.76)	0.02 (-0.05; 0.10)	44
		Pharyngolaryngeal pain	52/52	1/45 1/46	2/2	1.02 (0.07; 15.85)	0.00 (-0.06; 0.06)	2070
		Abdominal pain	52/52	2/45 0/46	4/0	5.11 (0.25; 103.54)	0.04 (-0.03; 0.12)	23
		Epigastric discomfort	52/52	2/45 1/46	4/2	2.04 (0.19; 21.76)	0.02 (-0.05; 0.10)	44
		Gastritis	52/52	3/45 0/46	7/0	7.15 (0.38; 134.64)	0.07 (-0.02; 0.15)	15
		Hepatic steatosis	52/52	2/45 0/46	4/0	5.11 (0.25; 103.54)	0.04 (-0.03; 0.12)	23
		Mouth ulceration	52/52	0/45 1/46	0/2	0.34 (0.01; 8.15)	-0.02 (-0.08; 0.04)	-46
		Myalgia	52/52	1/45 2/46	2/4	0.51 (0.05; 5.44)	-0.02 (-0.09; 0.05)	-47
		Toothache	52/52	2/45 0/46	4/0	5.11 (0.25; 103.54)	0.04 (-0.03; 0.12)	23
		Hepatitis B	52/52	0/45 0/46			0.00 (-0.04; 0.04)	
		Hordeolum	52/52	2/45 0/46	4/0	5.11 (0.25; 103.54)	0.04 (-0.03; 0.12)	23
		Allergic rhinitis	52/52	0/45 0/46			0.00 (-0.04; 0.04)	
Chan, 2007[44] Telbivudine (Idenix Pharmaceuticals, Cambridge, MA), 600 mg/day in 3 tablets, 24 weeks	Adefovir (Hepsera, Gilead Sciences, Foster City, CA), 10 mg/day, 24 weeks	HBV DNA PCR-negative	24/24	18/45 11/91	39/12	3.31 (1.71; 6.40)	**0.28 (0.12; 0.44)**	4
		HBeAg loss	24/24	7/45 10/91	16/11	1.42 (0.58; 3.47)	0.05 (-0.08; 0.17)	22
		Adjusted for baseline covariates	24/24	7/45 9/91	16/10	**6.03 (2.20; 16.52)**	0.06 (-0.07; 0.18)	18

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		(baseline HBV DNA level, age, body mass index, sex, and study site),OR of HBeAg seroconversion						
		Adjusted for baseline covariates odds ratio of HBV DNA PCR-negative	24/24	0/45 0/91		**0.07 (0.02; 0.29)**		
		Adjusted for baseline covariates odds ratio of HBV DNA <5 log10 copies/mL	24/24	0/45 0/91		0.91 (0.41; 2.04)		
		Adjusted for base-line covariates odds ratio of HBeAg loss	24/24	0/45 0/91		2.30 (0.69; 7.70)		
		HBV DNA PCR-negative	52/52	27/45 18/45	60/40	1.50 (0.98; 2.31)	**0.20 (0.00; 0.40)**	5
Chan, 2007[44] Telbivudine (Idenix Pharmaceuticals, Cambridge, MA), 600 mg/day in 3 tablets, 52 weeks	Adefovir (Hepsera, Gilead Sciences, Foster City, CA), 10 mg/day, 52 weeks	HBeAg loss	52/52	14/45 9/45	30/21	1.52 (0.73; 3.16)	0.10 (-0.07; 0.28)	10
		HBeAg seroconversion	52/52	13/45 9/45	28/19	1.44 (0.69; 3.04)	0.09 (-0.09; 0.27)	11
		Primary treatment failure	52/52	1/45 13/45	2/29	0.08 (0.01; 0.56)	**-0.27 (-0.41; -0.13)**	-4
		HBV DNA PCR-negative	52/52	27/45 25/46	60/54	1.10 (0.77; 1.58)	0.06 (-0.15; 0.26)	18
	Adefovir (Hepsera, Gilead Sciences, Foster City, CA) for 24 weeks and then	HBeAg loss	52/52	14/45 12/46	30/26	1.17 (0.61; 2.24)	0.04 (-0.14; 0.23)	23
		HBeAg seroconversion	52/52	13/45 11/46	28/24	1.21 (0.61; 2.41)	0.05 (-0.13; 0.23)	20

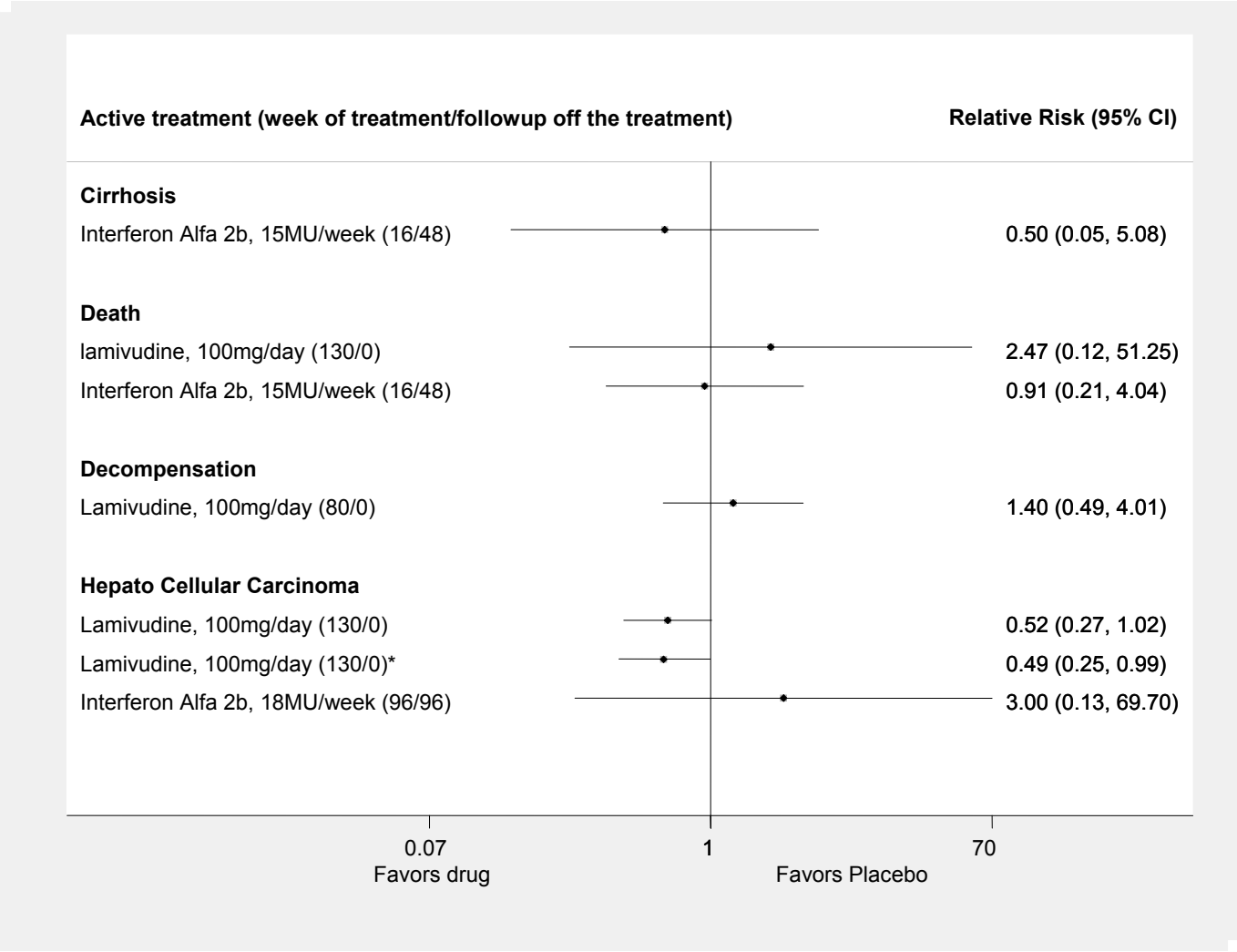
Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
	telbivudine (Idenix Pharmaceuticals, Cambridge, MA) for the remaining 28 weeks, 10 mg/day, 52 weeks	Primary treatment failure	52/52	1/45 5/46	2/11	0.20 (0.02; 1.68)	-0.09 (-0.19; 0.01)	-12
		Adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site) odds ratio of HBV DNA PCR-negative	52/52	0/45 0/45		1.89 (0.72; 4.94)		
	Adefovir (Hepsera, Gilead Sciences, Foster City, CA), 10 mg/day, 52 weeks	Adjusted for baseline covariates odds ratio of HBeAg loss	52/52	0/45 0/45		1.42 (0.50; 4.07)		
		Adjusted for baseline covariates odds ratio of HBeAg seroconversion	52/52	0/45 0/45		1.49 (0.51; 4.39)		
		Adjusted for baseline covariates odds ratio of primary treatment failure	52/52	0/45 0/45		0.05 (0.00; 0.45)		
		Viral breakthrough, defined as a confirmed increase in serum HBV DNA levels of greater than 1 log above the nadir value	24/24	3/45 4/45	7/9	0.75 (0.18; 3.16)	-0.02 (-0.13; 0.09)	-45

Appendix E. Table 4. Evidence tables of the effects of antiviral drugs on patient outcomes (individual randomized controlled clinical trials)

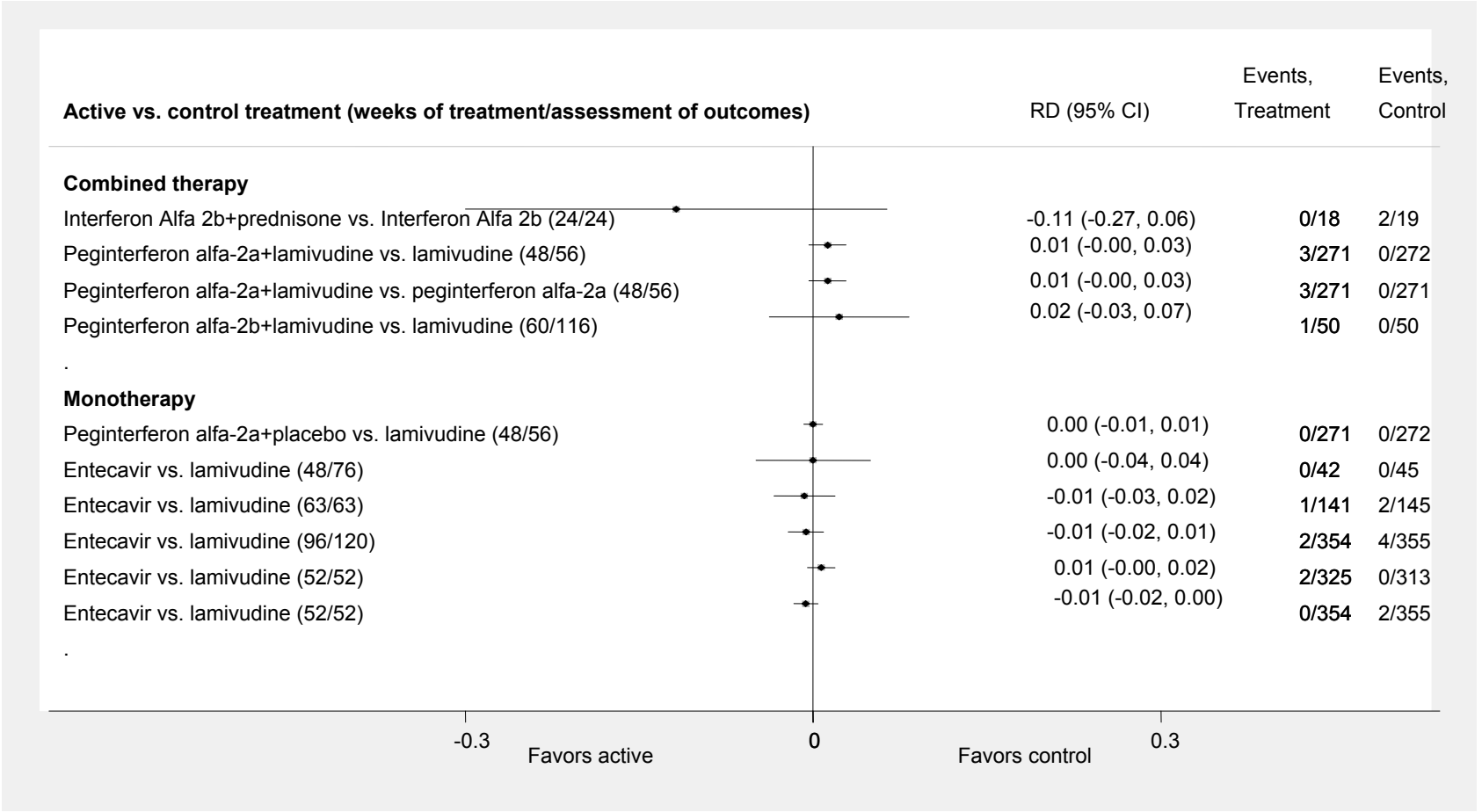
Author Active Drug, Daily Dose Mg/Day, Combined Active Drug, Daily Dose Mg/Day, Length of Active Treatment (Weeks)	Control Intervention, Daily Dose Mg/Day Length of Control Intervention	Outcome	Length of Treatment/ Followup (Weeks)	Cases/ Randomized Active Control	Rates of Outcomes Active/ Control (%)	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Viral breakthrough was defined as an increase of serum HBV DNA to 5 log10 copies/mL or greater after a decrease to below	24/24	2/45 1/45	4/2	2.00 (0.19; 21.28)	0.02 (-0.05; 0.10)	45

Appendix E. Figure 2. Effects of interferon alfa-2b and reverse transcriptase inhibitors on clinical outcomes compared to placebo or no active treatment—Relative risk from four individual RCTs[51,54,84,89]

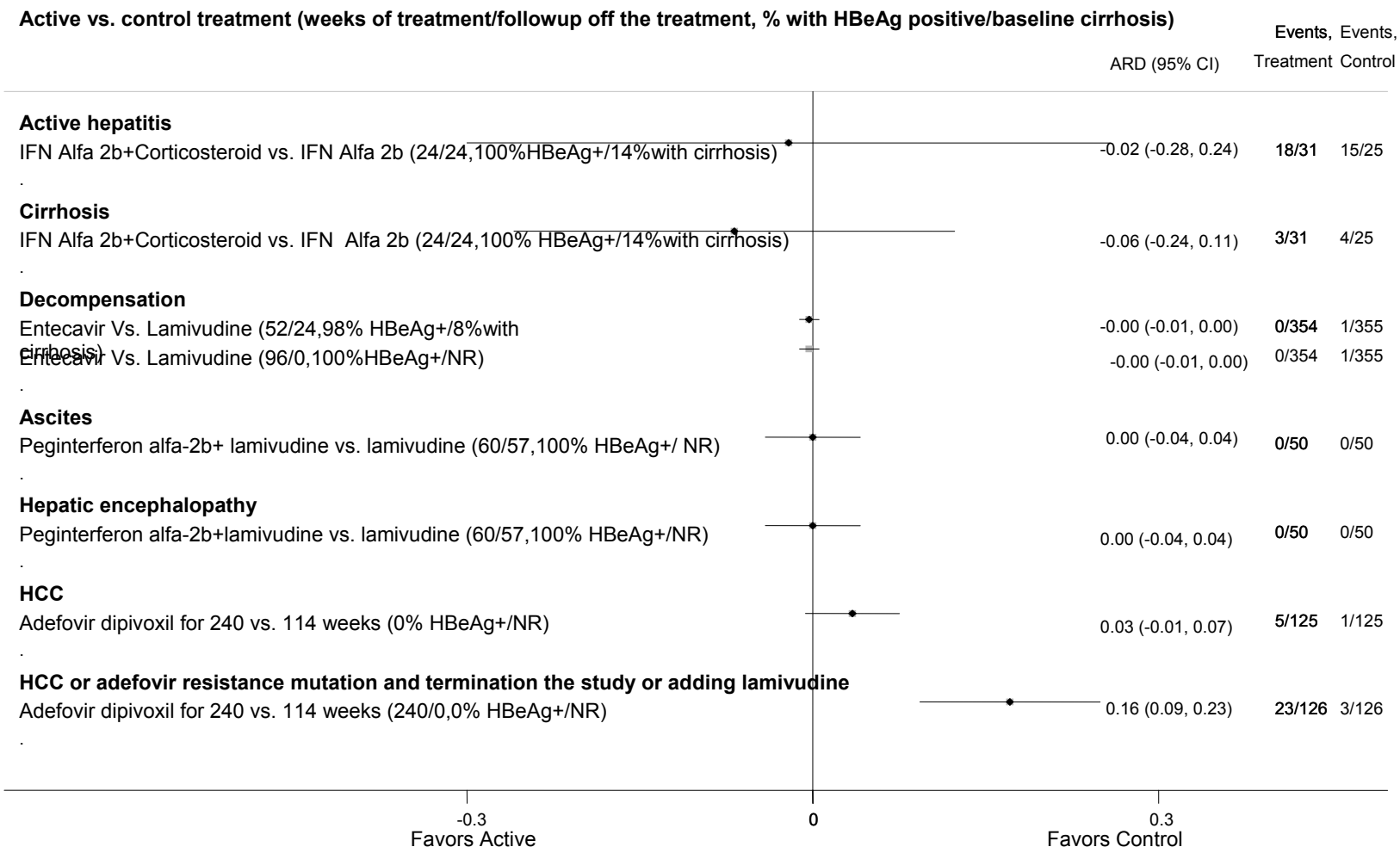


*Hazard ratio of hepatocellular carcinoma adjusted for country, sex, baseline Alanine aminotransferase level, Child–Pugh score, and Ishak fibrosis scor

Appendix E. Figure 3. Comparative effectiveness of interferon alfa-2b and reverse transcriptase inhibitors on mortality, results from individual randomized controlled clinical trials [73-76,90,101]



Appendix E. Figure 4. Comparative effectiveness of active drugs on clinical outcomes, results from individual RCTs.



Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

(A) Virological Outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
HBeAg loss at the end of treatment				
Adefovir dipivoxil vs. placebo[40,42]	48-52/0	2/995	**0.11 (0.06; 0.16)** (RD) 0.122/48.2 % No *	Moderate. Adefovir dipivoxil vs. placebo resulted in increased rates of HBeAg loss without dose response association
Adefovir dipivoxil+ lamivudine vs. adefovir dipivoxil[43]	48/0	1/39	-0.01 (-0.23; 0.22) (RD)	Low. Sparse data (small N of events) No differences between adefovir dipivoxil combined with lamivudine vs. adefovir dipivoxil on HBeAg loss
Adefovir dipivoxil vs. adefovir dipivoxil then telbivudine[44]	52/0	1/91	-0.06 (-0.23; 0.11) (RD)	Low. No differences between adefovir dipivoxil vs. adefovir dipivoxil followed by telbivudine on HBeAg loss
Adefovir dipivoxil+ lamivudine vs. lamivudine[43,58]	48-52/0	2/134	**0.12 (0.03; 0.21)** (RD) 0.699/0%	Moderate. Consistent results that adefovir dipivoxil combined with lamivudine vs. lamivudine resulted in 0.12 increase in absolute rate of HBeAg loss
Adefovir dipivoxil (10 vs.30mg)[42]	48/0	1/344	-0.01 (-0.11; 0.08) (RD) No*	Low. Random differences between 10 and 30mg/day of adefovir dipivoxil
Adefovir dipivoxil (40 vs. 52 weeks)[40]	40-52/0	1/360	0.08 (-0.01; 0.16) (RD)	Low. Random differences between 40 vs. 52 weeks of adefovir dipivoxil administration
Entecavir[77]	24/0	1/76	NS differences for all comparisons No * when 0.01; 0.1; or 0.5g were compared	Low. Sparse data (small N of events) No dose response association of entecavir on HBeAg loss.
Entecavir vs. lamivudine[73,75,77]	24-63/0	3/1112	0.03 (-0.03; 0.08) (RD) 0.13/46.9 %	Low. No differences between entecavir vs. lamivudine on HBeAg loss
Interferon alfa 2b+corticosteroid vs. interferon alfa 2b[90,94]	16-24/0	2/77	NS differences for all comparisons	Low. No differences between interferon Alfa 2b combined with pretreatment using corticosteroid vs. interferon Alfa 2b on HBeAg loss
Interferon alfa 2b+lamivudine vs. interferon alfa 2b[67]	24/0	1/144	0.00 (-0.12; 0.12) (RD)	Low. No difference between interferon Alfa 2b combined with lamivudine vs. interferon Alfa 2b on HBeAg loss
Interferon alfa 2b+lamivudine vs. interferon alfa 2b then lamivudine[80]	16/0	1/20	0.29 (-0.01; 0.59) (RD)	Low. No difference between interferon Alfa 2b combined with lamivudine vs. interferon Alfa 2b followed by lamivudine on HBeAg loss
Interferon alfa 2b+lamivudine vs. lamivudine[47,67,69]	24-52/0	3/414	-0.05 (-0.13; 0.03) (RD) 0.499/0%	Moderate. No difference between interferon Alfa 2b combined with lamivudine vs. lamivudine alone on HBeAg loss

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Interferon alfa 2b+lamivudine vs. placebo[47]	52/0	1/118	0.08 (-0.05; 0.21) (RD)	Low. No effect of interferon Alfa 2b combined with lamivudine on HBeAg loss
Interferon alfa 2b vs. no treatment[89]	16/0	1/40	**0.55 (0.29; 0.81)** (RD)	Low. Interferon Alfa 2 b resulted in increased HBeAg loss compared to no treatment
Interferon alfa 2b+placebo vs. lamivudine[67]	24-52/0	1/151	-0.03 (-0.15; 0.09) (RD)	Low. No differences between interferon Alfa 2b vs. lamivudine on HBeAg loss
Interferon alfa 2b for 48 weeks vs. interferon alfa 2b for 24 weeks[82]	24-48/0	1/65	-0.14 (-0.36; 0.07) (RD)	Low. Treatment duration with interferon Alfa 2b did not have any effects on HBeAg loss
Lamivudine vs. adefovir dipivoxil[43]	48/0	1/38	-0.16 (-0.34; 0.02) (RD)	Low. Sparse data (0 events in active group) No difference between lamivudine vs. adefovir dipivoxil on HBeAg loss
Lamivudine vs. placebo[47,48,104,112]	12-52/0	4/1349	**0.13 (0.04; 0.22)** (RD) 0.001/81%	Moderate. Non consistent effect of lamivudine on HBeAg loss
Lamivudine vs. telbivudine[72]	52/0	1/63	-0.08 (-0.32; 0.16) (RD)	Low. No differences between lamivudine vs. telbivudine on HBeAg loss
Peginterferon alfa-2a+lamivudine vs. lamivudine[56]	48/0	1/543	0.05 (-0.02; 0.12) (RD)	Low. No differences between peginterferon alfa-2a combined with lamivudine vs. lamivudine on HBeAg loss
Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a[56]	48/0	1/542	-0.03 (-0.11; 0.05) (RD)	Low. No differences between peginterferon alfa-2a combined with lamivudine vs. peginterferon alfa-2a on HBeAg loss
Peginterferon alfa-2a+placebo vs. lamivudine[56]	48/0	1/543	**0.08 (0.01; 0.16)** (RD)	Moderate. Peginterferon alfa-2a vs. lamivudine resulted in increased absolute rate of HBeAg loss
Peginterferon alfa-2b+lamivudine vs. lamivudine[117]	52-60/0	1/100	**0.34 (0.16; 0.52)** (RD)	Moderate. Peginterferon alfa-2b combined with lamivudine vs. lamivudine resulted in increased absolute rate of HBeAg loss
Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b[78]	52/0	1/307	**0.12 (0.01; 0.22)** (RD)	Moderate. Peginterferon alfa-2b combined with lamivudine vs. peginterferon alfa-2b resulted in increased absolute rate of HBeAg loss
Telbivudine + lamivudine vs. lamivudine[72]	52/0	1/60	-0.09 (-0.32; 0.14) (RD)	Low. No differences between telbivudine combined with lamivudine vs. lamivudine alone on HBeAg loss
Telbivudine+lamivudine vs. telbivudine[72]	52/0	1/85	-0.17 (-0.35; 0.01) (RD)	Low. No differences between telbivudine combined with lamivudine vs. telbivudine alone on HBeAg loss

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Telbivudinevs. adefovir dipivoxil[44]	24-52/0	1/135	NS differences for all comparisons	Low. No differences between telbivudine vs. adefovir dipivoxil alone or followed by telbivudine on HBeAg loss
HBeAg loss at the end of followup				
Interferon alfa 2b+corticosteroid vs. interferon alfa 2b[90,92,95]	16-40/24-26	3/122	NS differences for all comparisons	Moderate. No differences between interferon Alfa 2b with pretreatment of corticosteroid vs. interferon Alfa 2b on HBeAg loss
Interferon alfa 2b+lamivudine vs. interferon alfa 2b[67,104]	24/28-40	2/347	NS differences for all comparisons	Moderate. No differences between interferon Alfa 2b combined with lamivudine vs. interferon Alfa 2b on HBeAg loss
Interferon alfa 2b+lamivudine vs. lamivudine[47,65,67,69,104]	37-135/16-144	5/1167	1 RCT in 5 reported significant improvement after combined therapy	Moderate. No differences between interferon Alfa 2b combined with lamivudine vs. lamivudine alone on HBeAg loss
Interferon alfa 2b+lamivudine vs. placebo[47,104]	24-52/16-28	2/450	0.10 (-0.04; 0.23) (RD) 0.077/68%	Moderate. No effects of interferon Alfa 2b combined with lamivudine on HBeAg loss
Interferon alfa 2b vs. lamivudine[67,104]	24/28-40	2/625	NS differences for all comparisons	Moderate. No differences between interferon Alfa 2b and lamivudine on HBeAg loss
Interferon alfa 2b vs. interferon Alfa 2b (dose, time) [82,90]	24-48/24-72	2/103	NS differences for dose and duration of time comparisons	Moderate. Dose, length of treatment ,or followup did not result in different effects of interferon Alfa 2b on HBeAg loss
Interferon alfa 2b vs. placebo or no treatment[86,89,104]	16-24/8-48	3/351	**0.28 (0.07; 0.50)** (RD) 0.025/73 % **2.52 (1.55;4.1)** (RR) 0.359/2.4 %	Moderate. All RCTs reported significant increase in HBeAg loss after interferon Alfa 2b with consistent effect size in relative risk but inconsistent increase in absolute risk
Lamivudine vs. placebo[47,48]	52/16	2/318	**0.15 (0.05; 0.24)** (RD) 0.519/0 %	Moderate. Lamivudine increased absolute rates of HBeAg loss at followup
Peginterferon alfa-2a+lamivudine vs. lamivudine[56]	48/24	1/543	**0.07 (0.00; 0.15)** (RD)	Moderate. No differences between peginterferon alfa-2a combined with lamivudine vs. lamivudine alone on HBeAg loss at followup
Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a[56]	48/24	1/542	-0.05 (-0.13; 0.03) (RD)	Moderate. No differences between peginterferon alfa-2a combined with lamivudine vs. peginterferon alfa-2a on HBeAg loss at time of followup
Peginterferon alfa-2a+placebo vs. lamivudine[56]	48/24	1/543	**0.13 (0.05; 0.20)** (RD)	Moderate. Peginterferon alfa-2a increased HBeAg loss compared to lamivudine at time of followup

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Peginterferon alfa-2a vs. peginterferon alfa-2a[116]	24/24	1/194	NS differences for dose and duration of time comparisons (RD)	Low. No differences between doses and length of treatment with peginterferon alfa-2a on HBeAg loss at time of followup
Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b[78,122]	52/26	2/614	-0.01 (-0.09; 0.06) (RD) 0.991/0%	Moderate. No difference between peginterferon alfa-2b combined with lamivudine vs. peginterferon alfa-2b alone on HBeAg loss at time of followup
Peginterferon alfa-2b+vs interferon Alfa 2b[81]	24/24	1/230	0.10 (0.00; 0.21) (RD)	Low. No differences between peginterferon alfa-2b vs. interferon Alfa 2b on HBeAg loss at time of followup
HBeAg seroconversion at the end of treatment				
Adefovir dipivoxil +lamivudine vs. adefovir dipivoxil[43]	48/0	1/39	-0.06 (-0.22; 0.11) (RD)	Low. Sparse data (small number of events) No differences between adefovir dipivoxil combined with lamivudine vs. adefovir dipivoxil in HBeAg seroconversion
Adefovir dipivoxil+ lamivudine vs. lamivudine[43,58]	48-52/0	2/134	Random differences in both RCTs	Low. Sparse data (small number of events) No differences between adefovir dipivoxil combined with lamivudine vs. lamivudine on HBeAg seroconversion
Adefovir dipivoxil (dose, duration of treatment)[40,42,44]	48-52/0	3/795	Random differences in 2 RCTs from 3 (RD) No *	Low. Sparse data (small number of events) Dose and duration of treatment did not result in consistent increased rates of HBeAg seroconversion
Adefovir dipivoxil vs. placebo[40,42]	48-52/0	2/700	**0.05 (0.01; 0.09)** (RD) No * 0.25/28 %	High. Adefovir dipivoxil resulted in increased rates of HBeAg seroconversion without dose response association
Entecavir (dose response association)[77]	24/0	1/177	NS differences for all comparisons (RD) No * association with HBeAg loss	Low. No dose response association with HBeAg loss
Entecavir vs. lamivudine[73,75,77]	24-96/0	3/1185	Random differences in 2 RCTs of 3	Moderate. No differences between entecavir vs. lamivudine on HBeAg seroconversion
Interferon alfa 2b+lamivudine vs. interferon alfa 2b[67]	24/0	1/144	-0.02 (-0.11; 0.07) (RD)	Low. No differences between interferon Alfa 2b combined with lamivudine vs. interferon Alfa 2b on HBeAg seroconversion

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Interferon alfa 2b+lamivudine vs. lamivudine[47,66,67,69]	52/0	4/565	Random differences in 3 RCTs of 4	High. No differences between Interferon Alfa 2b combined with lamivudine vs. lamivudine alone on HBeAg seroconversion
Interferon alfa 2b+lamivudine vs. placebo[47]	52/0	1/119	-0.01 (-0.13; 0.10) (RD)	Low. No effects from Interferon Alfa 2b+lamivudine on HBeAg seroconversion
Interferon alfa 2b+placebo vs. lamivudine[67]	52/0	1/151	-0.05 (-0.12; 0.02) (RD)	Low. No differences between Interferon Alfa 2b and lamivudine on HBeAg seroconversion
Interferon alfa 2b [82]	24/0	1/65	-0.10 (-0.33; 0.12) (RD)	Low. No differences between length of treatment with interferon Alfa 2b on HBeAg seroconversion
Interferon alfa 2b vs. placebo[89]	16/0	1/40	NS differences for dose comparisons (0.00; 0.00) (RD)	Low. No consistency across doses of interferon Alfa 2b effects on HBeAg seroconversion
Lamivudine vs. telbivudine[72]	52/0	1/63	-0.11 (-0.34; 0.12) (RD)	Low. No differences between lamivudine vs. telbivudine on HBeAg seroconversion
Lamivudine vs. adefovir dipivoxil[43]	48/0	1/38	-0.11 (-0.27; 0.06) (RD)	Low. No differences between lamivudine vs. adefovir dipivoxil on HBeAg seroconversion
Lamivudine [50]	48/0	1/285	-0.03 (-0.11; 0.05) (RD)	Low. No differences between doses of lamivudine on HBeAg seroconversion
Lamivudine vs. placebo[47,48,50,54,104,112]	12-80 /0	6/1638	0.05 (0.00; 0.10) (RD) 0.028/60 % **1.69 (1.05;2.74**) (RR) 0.153/38 %	High. Lamivudine resulted in increased rate of HBeAg seroconversion with consistent across the RCTs results in multiplicative scale. Rate in placebo group and duration of treatments could not explain the heterogeneity in absolute rates.
Peginterferon alfa-2a+lamivudine vs. lamivudine[56]	48/0	1/543	0.03 (-0.04; 0.10) (RD)	Low. No differences between peginterferon alfa-2a combined with lamivudine vs. lamivudine alone on HBeAg seroconversion
Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a[56]	48/0	1/542	-0.03 (-0.10; 0.04) (RD)	Low. No differences between peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a
Peginterferon alfa-2a+placebo vs. lamivudine[56]	48/0	1/543	0.06 (-0.01; 0.13) (RD)	Low. No differences between peginterferon alfa-2a vs. lamivudine on HBeAg seroconversion
Peginterferon alfa-2b+lamivudine vs. lamivudine[117]	60/0	1/100	**0.32 (0.14; 0.50)** (RD)	Low. Peginterferon alfa-2b combined with lamivudine resulted in increase HBeAg seroconversion compared to lamivudine alone
Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b[78]	52/0	1/307	0.02 (-0.07; 0.11) (RD)	Low. No differences between peginterferon alfa-2b combined with lamivudine vs. peginterferon alfa-2b alone on HBeAg seroconversion
Telbivudine+lamivudine vs. lamivudine[72]	52/0	1/60	-0.06 (-0.28; 0.15) (RD)	Low. No differences between telbivudine combined with lamivudine vs. lamivudine on HBeAg seroconversion

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Telbivudine+lamivudine vs. telbivudine[72]	52/0	1/85	-0.17 (-0.35; 0.00) (RD)	Low. No differences between telbivudine combined with lamivudine vs. telbivudine on HBeAg seroconversion
Telbivudine vs. adefovir dipivoxil[44]	24-52/0	1/136	**6.03 (2.20; 16.52)** (RR)	Low. Telbivudine compared to adefovir dipivoxil resulted in increased relative risk of HBeAg seroconversion at 24 but not at 52 weeks of therapy without statistically significant differences in absolute rate
HBeAg seroconversion at time of followup				
Interferon alfa 2b+corticosteroid vs. interferon alfa 2b[92,95]	24/24-26	2/85	0.10 (-0.11; 0.31) (RD) 0.792/0%	Low. No differences between Interferon Alfa 2b with Corticosteroid pretreatments vs. Interferon Alfa 2b on HBeAg seroconversion
Interferon alfa 2b+lamivudine vs. interferon alfa 2b[67,79,104]	24-48/4-56	3/482	Random difference in all comparisons. Active treatment at the longest 56 weeks of followup in 1 RCT resulted in increase of **0.36 (95 % CI 0.10; 0.61)** in rate of the outcome	Low. No differences between interferon Alfa 2b combined with lamivudine vs. interferon Alfa 2b alone at followup. Limited evidence from 1 RCT suggest increase in HBeAg seroconversion at the longest 56 weeks of followup
Interferon alfa 2b+lamivudine vs. lamivudine[47,66,67]	24-52 /16-48	3/490	0.00 (-0.15; 0.14) (RD) 0.002/84 %	Moderate. No differences between interferon Alfa 2b combined with lamivudine vs. lamivudine on HBeAg seroconversion (1 RCT from 3 reported significant increase in (0.182; 95% 0.050; 0.315)
Interferon alfa 2b+lamivudine vs. placebo[47,104]	24-52 /16-28	2/450	0.05 (-0.12; 0.22) (RD) 0.011/85 %	Low. No consistent effects of interferon Alfa 2b+lamivudine on HBeAg seroconversion at time of followup, secondary analysis of 4 RCTs reported significant increase (**0.13; 95% 0.05: 0.21**)
Interferon alfa 2b vs. lamivudine[67,104]	24-52 /12-40	3/776	Random difference in all comparisons	Moderate. No differences between interferon Alfa 2b vs. lamivudine on HBeAg seroconversion at time of followup
Interferon alfa 2b vs. placebo[89,104]	16-96 /28-64	2/346	**0.120 (0.03; 0.21)** (RD) 0.353/0 %	Moderate Interferon Alfa 2b increased rates of HBeAg seroconversion at time of followup
Lamivudine vs. placebo[47,48]	52 /16	2/318	Random difference in all comparisons	Low. No effects from lamivudine vs. placebo on HBeAg seroconversion at time of followup
Peginterferon alfa-2a+lamivudine vs. lamivudine[56]	48/24	1/814	**0.08 (0.01; 0.15)** (RD)	Low. Peginterferon alfa-2a combined with lamivudine vs. lamivudine results in increased rates of HBeAg seroconversion at time of followup

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a[56]	48/24	1/814	-0.05 (-0.12; 0.03) (RD)	Low. No differences between peginterferon alfa-2a combined with lamivudine vs. peginterferon alfa-2a alone on HBeAg seroconversion at time of followup
Peginterferon alfa-2a+placebo vs. lamivudine[56]	48/24	1/814	**0.13 (0.06; 0.20)** (RD)	Moderate. Peginterferon alfa-2a resulted in increased rates of HBeAg seroconversion at time of followup compared to Lamivudine
Peginterferon alfa-2a vs. peginterferon alfa-2a[116]	24/24	1/194	Random difference in all dose comparisons. No *	Low. No dose response association between peginterferon alfa-2a and HBeAg seroconversion at time of followup
Peginterferon alfa-2b+lamivudine vs. lamivudine[117]	52-60 /40-96	1/100	Random difference in all time of followup comparisons.	Low. No differences between peginterferon alfa-2b combined with lamivudine vs. lamivudine on HBeAg seroconversion at time of followup
Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b[78]	52/26	1/307	Random difference in all comparisons	Low. No differences between peginterferon alfa-2b combined with lamivudine vs. peginterferon alfa-2b on HBeAg seroconversion at time of followup
HBsAg loss at the end of treatment				
Adefovir dipivoxil+ lamivudine vs. adefovir dipivoxil[43]	48/0	1/39	0.05 (-0.08; 0.18) (RD)	Low. No differences between adefovir dipivoxil + lamivudine vs. adefovir dipivoxil on HBsAg loss
Adefovir dipivoxil+ Lamivudine vs. lamivudine[43]	48/0	1/39	0.05 (-0.08; 0.18) (RD)	Low. No differences between adefovir dipivoxil+ lamivudine vs. lamivudine on HBsAg loss
Adefovir dipivoxil (240 vs. 114 weeks)[97]	240 vs. 114	1/250	**-0.048 (-0.088; -0.008)** (RD)	Low. Treatment with adefovir for 240 weeks resulted in decreased rates of HBsAg loss compared to 114 weeks.
Entecavir vs. lamivudine[73,101]	52-96 /0	2/1117	Random difference in all comparisons.	Moderate. No differences between entecavir vs. lamivudine on HBsAg loss
Interferon alfa 2b+corticosteroid vs. interferon alfa 2b[94,96]	16-24 /0	2/125	Random difference in all comparisons	Moderate. No differences between Interferon Alfa 2b with corticosteroid pretreatment vs. Interferon Alfa 2b
Interferon alfa 2b+corticosteroid vs. no treatment[96,103]	24/0	2/103	**0.11 (0.02; 0.20)** (RD) 0.917/0 %	Moderate. Interferon alfa 2b with corticosteroid pretreatment resulted in increased rates of HBsAg loss
Interferon alfa 2b+lamivudine vs. lamivudine[47,64]	52-96 /0	2/262	Random difference in all comparisons	Moderate. No differences between interferon Alfa 2b combined with lamivudine vs. lamivudine alone on HBsAg loss

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Interferon alfa 2b+lamivudine vs. placebo[47]	52/0	1/119	0.06 (0.00; 0.13) (RD)	Low. No differences between interferon Alfa 2b combined with lamivudine vs. placebo on HBsAg loss
Interferon alfa 2b vs. interferon alfa 2b[96]	24/0	1/82	0.10 (-0.01; 0.21) (RD) No *	Low. No dose response association with interferon Alfa 2b and HBsAg loss
Interferon alfa 2b vs. no treatment[84,89,96]	16-96 /0	3/166	0.06 (-0.03; 0.15) (RD) 0.209/36.2 %	Moderate. No effects of interferon alfa 2b vs. no treatment on HBsAg loss
Lamivudine vs. placebo[47]	52/0	1/175	0.02 (-0.02; 0.05) (RD)	Low. Sparse data (0 events in control group) No effects of lamivudine on HBsAg loss
Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b[78]	52/0	1/307	0.01 (-0.04; 0.06) (RD)	Low. No differences between peginterferon alfa-2b combined with lamivudine vs. peginterferon alfa-2b alone on HBsAg loss
HBsAg loss at followup				
Interferon alfa 2b vs. no treatment[83,84,86,89]	16-96 /8-48	4/247	Random difference in all comparisons. (RD)	Low. Sparse data (0 events in control group) No effects from interferon Alfa 2b vs. no treatment on HBsAg loss
Interferon alfa 2b+lamivudine vs. lamivudine[47,62,66]	24-52 /16-48	3/495	Random difference in all comparisons	Low. Sparse data (0 events in both group) No differences between interferon Alfa 2b combined with lamivudine vs. lamivudine on HBsAg loss
Interferon alfa 2b+lamivudine vs. placebo[47]	52/16	1/119	0.05 (-0.01; 0.11) (RD)	Low. Sparse data (0 events in control group) No effects from Interferon alfa 2b combined with lamivudine vs. placebo on HBsAg loss
Interferon alfa 2b vs. interferon Alfa 2b[82,85]	24-48 /48	2/103	Random difference in all comparisons. No *	Low. Sparse data (0 events in both group) No dose response and time to treat association of Interferon alfa 2b on HBsAg loss
Interferon alfa 2b+corticosteroid vs. interferon alfa 2b[91,92,95]	24/24-26	3/141	Random difference in all comparisons	Low. Sparse data (small number of events) No differences between interferon alfa 2b with corticosteroid pretreatment vs. interferon Alfa 2b on HBsAg loss
Lamivudine vs. placebo[46-48]	52-96 /16-26	3/1068	Random difference in all comparisons. (RD)	Low. Sparse data (small number of events) No effects from lamivudine vs. placebo on HBsAg loss at time of followup
HBsAg seroconversion – end of treatment				
Adefovir dipivoxil vs. placebo[98]	96 weeks/0	1/120	0.01 (-0.03; 0.06) (RD)	Low. Adefovir dipivoxil did not increase rates of HBsAg seroconversion

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Adefovir dipivoxil (longer treatment)[97,98]	48-240weeks/0	2/390	Random difference in all comparisons. (RD)	Low. Adefovir dipivoxil administration for 96 vs.48 and for 240 vs. 114 weeks did not increase HBsAg seroconversion
Entecavir vs. lamivudine[101]	96/0	1/408	-0.02 (-0.06; 0.01)	Low. Random differences between entecavir vs. lamivudine on HBsAg seroconversion
HBsAg seroconversion at followup				
Peginterferon alfa-2b vs. interferon alfa 2b[81]	24/24	1/230	Random difference in all comparisons	Low. No differences between peginterferon alfa-2b and interferon alfa 2b on HBsAg seroconversion at time of followup
Interferon alfa 2b vs. placebo[84]	96/48	1/42	0.10 (-0.05; 0.24) (RD)	Low. Interferon alfa 2b did not increase HBsAg seroconversion
Interferon alfa 2b vs. no treatment[89]	16/48-64	1/40	0.15 (-0.05; 0.35) (RD)	Low. Interferon alfa 2b did not increase HBsAg seroconversion
HBV DNA loss—end of treatment				
Adefovir dipivoxil+ lamivudine vs. lamivudine[43,58]	48-52/0	2/134	**0.25 (0.10; 0.39)** (RD) 0.219/34 %	Low. Sparse data (0 events in control group) Adefovir dipivoxil+ lamivudine vs. lamivudine resulted in increased rates of HBV DNA loss
Adefovir dipivoxil vs. adefovir dipivoxil[40,42,44,97,98]	48-240/0	5/1520	-0.08 (-0.16; 0.01) (RD) 0.049/58 % 0.84 (0.68; 1.04) (RR) 0.034/62 %	Moderate. Duration of treatment with adefovir dipivoxil was not association with increased rates of HBV DNA loss. One RCT reported greater HBV DNA loss after 30 vs. 10 mg (**0.18; 95% CI 0.08; 0.27**)
Adefovir dipivoxil+ lamivudine vs. adefovir dipivoxil[43]	48/0	1/39	0.09 (-0.20; 0.37) (RD)	Low. No differences between adefovir dipivoxil+ lamivudine vs. adefovir dipivoxil on HBV DNA loss
Adefovir dipivoxil vs. placebo[40-42,98]	48-96 /0	4/1002	**0.38 (0.23; 0.53)** (RD) 0/93 % **20.41 (6.79; 61.32)** (RR) 0.267/24 %	High. Adefovir dipivoxil vs. placebo resulted in increased HBV DNA loss
Entecavir (dose)[77]	24/0	1/177	Random difference in all dose comparisons. No *	Low. No dose response association with HBV DNA loss
Entecavir vs. lamivudine[73,74,77,101]	24-96/0	4/1636	**0.23 (0.11; 0.35) (RD)** 0/89 % No *	Low. Entecavir vs. lamivudine resulted in greater HBV DNA loss
			1.64 (1.22; 2.22) (RR) 0/92 % No *	Rate in control group and dose of entecavir could not explain heterogeneity across the studies.
			0.30 (0.16; 0.44) (RD > 1 year of active treatment) 0.09 (-0.04; 0.21) (RD, 6 months of active treatment)	Moderate .Length of active treatment was associated with greater differences in absolute rates of HBV DNA loss with significant differences after >1 year of treatment

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Interferon alfa 2b+corticosteroid vs. interferon alfa 2b[90,94]	16-24/0	2/77	Random difference in all dose comparisons	Low. No differences between interferon alfa 2b with corticosteroid pretreatments vs. interferon alfa 2b alone on HBV DNA loss
Interferon alfa 2b+corticosteroid vs. no treatment[94]	16/0	1/34	**0.25 (0.04; 0.46)** (RD)	Low. Interferon alfa 2b with corticosteroid pretreatments vs. no treatment increased rates of HBV DNA loss
Interferon alfa 2b+lamivudine vs. interferon alfa 2b[67]	24/0	1/144	0.00 (-0.12; 0.12) (RD)	Low. No differences between interferon alfa 2b+lamivudine vs. interferon Alfa 2b alone on HBV DNA loss
Interferon alfa 2b+lamivudine vs. interferon alfa 2b+lamivudine[80]	16/0	1/20	0.00 (-0.21; 0.21) (RD)	Low. No differences between Interferon alfa 2b+lamivudine for 20 weeks vs. interferon alfa 2b +4 weeks placebo then 12 weeks lamivudine on HBV DNA loss
Interferon alfa 2b+lamivudine vs. lamivudine[47,63,64,66-69]	24-96/0	7/786	0.03 (-0.11; 0.17) (RD) 0/81%	High. No differences between interferon alfa 2b+lamivudine vs. lamivudine alone on HBV DNA loss
Interferon alfa 2b+lamivudine vs. placebo[47]	52/0	1/119	**0.48 (0.33; 0.63)** (RD in HBV DNA response: <3pg/ml) 0.05 (-0.09; 0.18) (RD in sustained HBV DNA response: no two consecutive detectable HBV DNA)	Low. Inconsistent effect of interferon alfa 2b+lamivudine vs. placebo in one RCT: significant increase in rate of HBV <3pg/ml with random differences in sustained HBV DNA response
Interferon alfa 2b+placebo vs. lamivudine[67]	24/0	1/76	-0.03 (-0.15; 0.09) (RD)	
Interferon alfa 2b vs. interferon alfa 2b[82,85,90]	0/0	3/141	Random difference in all dose comparisons. No *	Moderate. Different length of treatment and doses of Interferon alfa 2b were associated with random changes in HBV DNA loss
Interferon alfa 2b vs. no treatment[94]	16/0	1/34	**0.45 (0.22; 0.68)** (RD)	Low. Interferon alfa 2b vs. no treatment increased rate of HBV DNA loss
Lamivudine vs. adefovir dipivoxil[43]	48/0	1/38	**-0.26 (-0.47; -0.06)** (RD)	Low. Adefovir dipivoxil vs. lamivudine increased rate of HBV DNA loss
Lamivudine[50,109,110]	24-104/0	3/581	**0.21 (0.10; 0.31)** (RD) 0.187/35 % * association	Moderate. Larger doses of lamivudine resulted in greater HBV DNA loss, the length of treatment was not associated with greater dose response
Lamivudine 60 vs.48 weeks[108]	60/0	1/429	-0.08 (-0.08; 0.2) (RD)	Low. Longer treatment did not increase HBV DNA loss
Lamivudine vs. placebo or usual care[46-48,50,53,108,110]	12-104 /0	7/1305	**0.48 (0.31; 0.66)** (RD) 0/94 % **3.79 (2.71; 5.30)** (RR) 0.046/53 %	High. Lamivudine vs. placebo or usual care increased HBV DNA loss in all RCT with consistent effect size in relative but not absolute

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
				scale (heterogeneity significant and cannot be explained by length of treatment or control rate of HBV DNA loss)
Peginterferon alfa-2a+ lamivudine vs. lamivudine[56]	48/0	1/543	**0.29 (0.21; 0.37)** (RD)	Moderate. Peginterferon alfa-2a+ lamivudine vs. lamivudine alone increased HBV DNA loss
Peginterferon alfa-2a+ lamivudine vs. peginterferon alfa-2a[56]	48/0	1/542	**0.44 (0.36; 0.51)** (RD)	Moderate. Peginterferon alfa-2a+ lamivudine vs. peginterferon alfa-2a alone increased HBV DNA loss
Peginterferon alfa-2a+ placebo vs. lamivudine[56]	48/0	1/543	**-0.15 (-0.22; -0.07)** (RD)	Moderate. Rate of HBV DNA loss was lower after peginterferon alfa-2a+ placebo vs. lamivudine
Peginterferon alfa-2b+ lamivudine vs. lamivudine[59]	60/0	1/100	0.06 (-0.04; 0.16) (RD)	Low. No differences between peginterferon alfa-2b+ lamivudine vs. lamivudine alone on HBV DNA loss
Lamivudine vs. telbivudine[72]	52/0	1/63	**-0.30 (-0.55; -0.04)** (RD)	Low. Rate of HBV DNA loss was lower after lamivudine vs. telbivudine
Telbivudine+lamivudine vs. lamivudine[72]	52/0	1/60	0.17 (-0.09; 0.43) (RD)	Low. No differences between telbivudine + lamivudine vs. lamivudine alone on HBV DNA loss
Telbivudine+lamivudine vs. telbivudine[72]	52/0	1/85	-0.13 (-0.34; 0.08) (RD)	Low. No difference between telbivudine + lamivudine vs. telbivudine alone on HBV DNA loss
Telbivudine vs. adefovir dipivoxil[44]	24-52/0	1/136	**0.28 (0.12; 0.44)** (RD)	Low. Telbivudine resulted in greater HBV DNA loss compared to adefovir dipivoxil at 24 but not 52 weeks of treatment
HBV DNA loss at time of followup				
Adefovir dipivoxil vs. placebo[98]	96/18	1/120	**0.59 (0.46; 0.72)** (RD)	Low. Adefovir dipivoxil vs. placebo increased HBV DNA loss
Entecavir vs. lamivudine[73]	52/24	1/709	0.01 (-0.02; 0.05) (RD)	Low. No differences between entecavir vs. lamivudine on HBV DNA loss
Interferon alfa 2b+corticosteroid vs. interferon alfa 2b[90-92,94-96]	16-24 /24-72	6/322	Random differences in all comparisons	High. No differences between interferon alfa 2b+corticosteroid vs. interferon Alfa 2b alone on HBV DNA loss
Interferon alfa 2b+corticosteroid vs. no treatment[94,96]	16-96 /24	2/121	Random differences in all comparisons	Moderate. No effects from Interferon alfa 2b+ corticosteroid vs. no treatment on HBV DNA loss
Interferon alfa 2b+lamivudine vs. interferon alfa 2b[67,79]	24-48 /4-56	2/278	0.15 (-0.06; 0.35) (RD) 0.002/80.4 %	Low. No differences between interferon alfa 2b+ lamivudine vs. interferon alfa 2b alone. One RCT of treatment with lamivudine followed by combined therapy reported random differences in HBV DNA. Heterogeneity cannot be explained by the length of the treatment or followup.

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Interferon alfa 2b+lamivudine vs. lamivudine[63,65,67,69]	24-176/12-40	4/365	0.04 (-0.07; 0.14) (RD) 0.071/57 %	Moderate. No differences between interferon alfa 2b + lamivudine vs. lamivudine alone on HBV DNA
Interferon alfa 2b+placebo vs. lamivudine[67]	24-52 /12-40	1/151	Random differences in all followup comparisons	Low. No differences between interferon alfa 2b+ placebo vs. lamivudine on HBV DNA loss
Interferon alfa 2b vs. interferon alfa 2b[82,85,90,96]	24-48 /24-72	4/297	Random differences in all dose, length of treatment, and followup comparisons	Moderate. No differences between doses and length of treatment of interferon alfa 2b on HBV DNA loss
Interferon alfa 2b vs. no treatment[86,94]	16/8-24	3/168	**0.44 (0.27; 0.60)** (RD) 0.573/0 %	Low. Interferon Alfa 2b vs. no treatment resulted in HBV DNA loss.
[96]			0.28 (-0.04; 0.60) (RD) 0/89 %	The effects were attenuated at longer followup
Lamivudine vs. placebo[46]	96/24	1/136	**0.08 (0.01; 0.15)** (RD)	Low. Lamivudine vs. placebo increased HBV DNA loss at time of followup
Peginterferon alfa-2a+lamivudine vs. lamivudine[56]	48/24	1/543	**0.09 (0.04; 0.13)** (RD)	Low. Peginterferon alfa-2a+lamivudine vs. lamivudine increased HBV DNA loss at time of followup
Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a[56]	48/24	1/542	-0.01 (-0.07; 0.05) (RD)	Low. No differences between peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a alone on HBV DNA loss at time of followup
Peginterferon alfa-2a+placebo vs. lamivudine[56]	48/24	1/543	**0.09 (0.04; 0.14)** (RD)	Low. Peginterferon alfa-2a+placebo vs. lamivudine increased rate of HBV DNA loss at followup
Peginterferon alfa-2b+lamivudine vs. lamivudine[117]	52-60/24-57	1/100	0.00 (-0.04; 0.04) (RD)	Low. No differences between peginterferon alfa-2b+ lamivudine vs. lamivudine on HBV DNA loss at followup

Bold- significant differences at 95% confidence level

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

(B) Histological Outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95% CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Histological improvement at end of treatment				
Adefovir dipivoxil vs. placebo[41,42,98]	48-96/0	3/819	**0.26 (0.17; 0.34)** (RD) 0.086/55 %. No *	High. Adefovir dipivoxil improved necroinflammatory scores compared to placebo
Adefovir dipivoxil vs. placebo[41,42]	48-96/0	2/699	**0.20 (0.14; 0.26)** (RD) 0.395/0 % No *	Moderate. Adefovir dipivoxil vs. placebo improved fibrosis scores without dose response association
Lamivudine vs. placebo[46,48,50,111]	48-96/0	4/580	**0.25 (0.13; 0.38)** (RD) 0.025/68 % **2.09 (1.60; 2.74)** (RR)	Moderate. Lamivudine improved necroinflammatory scores in all RCT with consistent increase in relative risk and significant heterogeneity in pooled absolute risk
Adefovir dipivoxil vs. adefovir dipivoxil, 30[42,97,98]	48-240/0	3/905	Random difference in all comparisons. No *	Moderate. Dose and duration of treatments with adefovir were not associated with improved histology
Entecavir vs. lamivudine[73-75]	52-63/0	3/1633	**0.14 (0.04; 0.24)** (RD) 0.003/83 % No *	Moderate. Entecavir compared to lamivudine improved necroinflammatory scores without dose response association
Entecavir vs. lamivudine[73,75]	52-63/0	2/995	0.10 (-0.02; 0.22) (RD) 0.008/86 % No *	Moderate. No differences between entecavir vs. lamivudine on fibrosis scores
Interferon Alfa 2b +lamivudine vs. lamivudine[47,68,69]	24-52/0	3/327	-0.04 (-0.17; 0.09) (RD) 0.185/36 %	Moderate. No differences between interferon Alfa 2b combined with lamivudine vs. lamivudine on HAI scores
Interferon Alfa 2b +lamivudine vs. lamivudine[47,66]	52/0	2/389	0.00 (-0.38; 0.38) (RD) 0/93 %	Low. No differences between Interferon Alfa 2b combined with lamivudine vs. lamivudine on necroinflammatory scores
Lamivudine for 144 vs. 96 weeks[107]	96-144/0	1/250	**-0.16 (-0.24; -0.08)** (RD)	Low. Lamivudine treatment for 144 vs. 96 weeks resulted in lower rates of Improved necroinflammatory scores.
Interferon Alfa 2b+lamivudine vs. interferon Alfa 2b[79]	48/0	1/48	**0.54 (0.28; 0.79)** (RD)	Low. Interferon Alfa 2b+lamivudine vs. interferon Alfa 2b improved HAI scores
Interferon Alfa 2b+lamivudine vs. placebo[47]	52/0	1/119	Random difference in total and inflammatory scores	Low. Interferon Alfa 2b+lamivudine vs. placebo did not improve total and inflammatory scores
Interferon Alfa 2b vs. no treatment[84]	96/0	1/72	0.24 (0.00; 0.48) (RD)	Low. Interferon Alfa 2b vs. no treatment did not improve HAI scores
Peginterferon alfa-2b+lamivudine vs. lamivudine[59]	52-60/0	1/100	Random difference in inflammatory and fibrosis scores	Low. No differences between peginterferon alfa-2b combined with lamivudine vs. lamivudine alone on inflammatory and fibrosis scores

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95% CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b[78]	52/0	1/307	-0.04 (-0.12; 0.05) (RD)	Low. No differences between peginterferon alfa-2b+ lamivudine vs. peginterferon alfa-2b on inflammatory scores
Histological improvement at followup				
Interferon alfa 2b+lamivudine vs. interferon alfa 2b[67]	24/28	1/144	-0.08 (-0.23; 0.07) (RD)	Low. No differences between interferon alfa 2b+lamivudine vs. interferon alfa 2b on Knodell scores
Interferon alfa 2b+lamivudine vs. lamivudine[67]	24/28	1/157	-0.10 (-0.24; 0.05) (RD)	Low. No differences between interferon alfa 2b+lamivudine vs. lamivudine on Knodell scores
Interferon alfa 2b+placebo vs. lamivudine[67]	24/28	1/151	-0.02 (-0.17; 0.14) (RD)	Low. Interferon alfa 2b vs. lamivudine did not improve Knodell scores
Interferon alfa 2b vs. no treatment[89]	16/48	1/40	0.15 (-0.05; 0.35) (RD)	Low. Interferon alfa 2b vs. no treatment did not improve total scores
Peginterferon alfa-2a+lamivudine vs. lamivudine[56,57]	48/24	2/1366	Random difference in all comparisons	High. No differences between peginterferon alfa-2a+lamivudine vs. lamivudine on histological improvement
Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a[56]	48/24	1/96	0.04 (-0.05; 0.12) (RD)	Low. No differences between peginterferon alfa-2a + lamivudine vs. peginterferon alfa-2a on histological improvement
Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b[78]	52/26	1/307	0.03 (-0.04; 0.09) (RD)	Low. No differences between peginterferon alfa-2b + lamivudine vs. peginterferon alfa-2b on fibrosis scores
Peginterferon alfa-2+placebo vs. lamivudine[57]	48/24	1/552	-0.01 (-0.07; 0.06) (RD)	Low. No differences between peginterferon alfa-2a vs. lamivudine on fibrosis scores
Peginterferon alfa-2a+placebo vs. lamivudine[56,57]	48/24	2/1366	Random difference in all comparisons	Moderate. No differences between peginterferon alfa-2a vs. lamivudine on HAI scores
Peginterferon alfa-2a+placebo vs. lamivudine[57]	48/24	1/552	**0.12 (0.02; 0.22)** (RD)	Low. Peginterferon alfa-2a vs. lamivudine improved necroinflammatory scores

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

(C) Biochemical Outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/Comments
ALT normalization end of treatment				
Adefovir dipivoxil+ lamivudine vs. adefovir dipivoxil[43]	48/0	1/39	0.03 (-0.29; 0.34) (RD)	Low. No difference between Adefovir dipivoxil+ Lamivudine vs. Adefovir dipivoxil alone on ALT normalization
Adefovir dipivoxil+ lamivudine vs. lamivudine[43,58]	48-52/0	2/134	**0.32 (0.13; 0.52)** (RD) 0.158/50%	Moderate. Adefovir dipivoxil+ lamivudine vs. lamivudine increased ALT normalization
Adefovir dipivoxil (dose or duration)[40,42,44,97,98]	48-240/0	5/173	**-0.06 (-0.12; -0.01)** (RD for shorter treatment vs. longest) 0.709/0% No *	Longer treatment with adefovir associated with increased rate of ALT normalization
Adefovir dipivoxil vs. placebo[4140,42,98]	48-96/0	5/1342	**0.40 (0.30; 0.49)** (RD) 0.007/72% No *	High. Adefovir dipivoxil vs. placebo increased rates of ALT normalization in all RCT. The effect size was consistent in multiplicative scale. Heterogeneity in ARD could not be explained by the dose, control rate, duration of the treatment, % of HBeAg + patients
			2.97 (2.38; 3.69) (RR) 0.219/30 %	
Entecavir (dose)[76,77]	24-48/0	2/359	Random differences in all dose comparisons No *	Moderate. No dose response association of entecavir on ALT normalization
Entecavir vs. lamivudine[73-77,101]	24-96/0	6/2423	**0.22 (0.11; 0.32)** (RD) 0/87%	High. Entecavir vs. lamivudine increased rate of ALT normalization. Heterogeneity was significant in relative and absolute risk differences. Heterogeneity did not depend on dose of entecavir, duration of treatment, or % of HBeAg + patients.
			1.62 (1.28; 2.06) (RR) 0/87%	The effect of entecavir on ARD of ALT normalization was lower in RCTs with higher rates of the outcome after lamivudine administration (meta-regression -0.004, p=0.005)
Interferon alfa 2b+lamivudine vs. interferon alfa 2b[67]	24/0	1/144	-0.01 (-0.14; 0.11) (RD)	Low. No differences between interferon alfa 2b+lamivudine vs. interferon alfa 2b on ALT normalization
Interferon alfa 2b+lamivudine vs. interferon alfa 2b+lamivudine[80]	16/0	1/20	-0.05 (-0.42; 0.32) (RD)	Low. No differences between interferon alfa 2b+lamivudine vs. interferon alfa 2b followed by lamivudine on ALT normalization
Interferon alfa 2b+lamivudine vs. lamivudine[47,62,63,67,69]	24-96/0	5/626	-0.02 (-0.16; 0.12) (RD) 0.004/74%	Moderate. No differences between interferon alfa 2b+lamivudine vs. lamivudine alone on ALT normalization

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/Comments
Interferon alfa 2b+lamivudine vs. placebo[47]	52/0	1/119	0.03 (-0.10; 0.16) (RD)	Low. Interferon alfa 2b+lamivudine vs. placebo did not increase rates of ALT normalization
Interferon alfa 2b+placebo vs. lamivudine[67]	24/0	1/151	-0.04 (-0.15; 0.07) (RD)	Low. No differences between Interferon alfa 2b+placebo vs. lamivudine on ALT normalization
Interferon alfa 2b [82,85]	24-48/0	2/103	Random differences in all dose and time comparisons	Low. Dose and duration of interferon alfa 2b therapy was not associated with increased rates of ALT normalization
Lamivudine vs. adefovir dipivoxil[43]	48/0	1/38	**-0.42 (-0.67; -0.18)** (RD)	Low. Adefovir dipivoxil increased rates of ALT normalization compared to lamivudine
Lamivudine [5055,108]	48-52/0	3/838	Random differences in all dose and time comparisons	Moderate. Dose and duration of lamivudine therapy was not associated with increased rates of ALT normalization
Lamivudine vs. no treatment or placebo[5446-48,50,108,112]	12-96 /0	7/1602	**0.22 (0.13; 0.31)** (RD) 0/78% **2.42 (1.94; 3.01)** (RR) 0.44/0%	Moderate. Lamivudine increased ALT normalization with consistent effect size in relative risk. An increase in absolute risk was inconsistent across the studies; heterogeneity cannot be explained by the length of the treatment, control rate, or % of HBeAg + patients.
Lamivudine vs. telbivudine[72]	52/0	1/85	Random differences in two of three dose comparisons	Low. No differences between lamivudine vs. different doses of telbivudine on ALT normalization
Peginterferon alfa-2a+lamivudine vs. lamivudine[56,57]	48/0	2/905	**-0.20 (-0.29; -0.10)** (RD) 0.141/54%	High. Peginterferon alfa-2a+lamivudine vs. lamivudine resulted in lower rates of ALT normalization
Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a[56]	48/0	1/542	0.08 (-0.01; 0.16) (RD)	Low. No differences between peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a alone on ALT normalization
Peginterferon alfa-2a+placebo vs. lamivudine[5756]	48/0	2/905	**-0.29 (-0.42; -0.17)** (RD) 0.045/75% **0.57 (0.46; 0.70)** (RR) 0.13/56%	Moderate. Peginterferon alfa-2a+placebo vs. lamivudine alone reduced rates of ALT normalization with consistent effect size in relative risk and significant heterogeneity in pooled ARD
Peginterferon alfa-2b+lamivudine vs. lamivudine[59]	60/0	1/100	0.12 (-0.02; 0.26) (RD)	Low. No differences between peginterferon alfa-2b+lamivudine vs. lamivudine alone on ALT normalization
Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b[78]	52/0	1/307	**0.14 (0.03; 0.24)** (RD)	Low. Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b alone increased rate of ALT normalization

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/Comments
Telbivudine+lamivudine vs. lamivudine[72]	52/0	1/101	Random differences in all 3 dose comparisons	Low. Three tested doses of telbivudine + lamivudine vs. lamivudine alone did not increase rates of ALT normalization
Telbivudine+lamivudine vs. telbivudine[72]	52/0	1/101	Random differences in all 3 dose comparisons	Low. Three tested doses of Telbivudine + lamivudine vs. telbivudine alone did not increase rates of ALT normalization
Telbivudine vs. telbivudine[72]	52/0	1/44	0.09 (-0.11; 0.29) (RD) No * association	Low. Telbivudine 600mg vs. telbivudine 400mg did not improve rates of ALT normalization
Telbivudine vs. adefovir dipivoxil[44]	24-52/0	1/135	Random differences in all dose and time comparisons	Low. No differences between telbivudine vs. adefovir dipivoxil on ALT normalization
ALT normalization at followup				
Adefovir dipivoxil vs. placebo[40,98]	12-96/18-40	2/600	**0.26 (0.19; 0.33)** (RD) 0.791/0%	Moderate. Adefovir dipivoxil vs. placebo increased rates of ALT normalization at followup
Interferon alfa 2b+corticosteroid vs. interferon alfa 2b[92,95,96]	24/24-26	3/170	Random differences in all comparisons	Moderate. No differences between interferon Alfa 2b+corticosteroid vs. interferon alfa 2b alone on ALT normalization at time of followup
Interferon alfa 2b+corticosteroid vs. no treatment[96]	24/24	1/87	**0.25 (0.06; 0.43)** (RD)	Low. Interferon Alfa 2b+corticosteroid vs. no treatment increased rate of ALT normalization
Interferon alfa 2b+lamivudine vs. interferon alfa 2b[67,79]	24-48 /4-56	2/192	Random differences in all time of followup comparisons, significant increase in RD at the onset 56 week time of followup	Low. No differences between interferon alfa 2b+lamivudine vs. interferon Alfa 2b on ALT normalization at4-40 weeks of followup, a significant increase in the outcome at 56 weeks
Interferon alfa 2b+lamivudine vs. lamivudine[63]	24-176 /24-96	6/751	0.03 (-0.03; 0.08) (RD) 0.014/58.3%	Moderate. No differences between interferon alfa 2b+lamivudine vs. lamivudine on ALT normalization at time of followup
[62,65-67,69]				2 of 6 RCT reported an increase in rate, heterogeneity cannot be explained by length of the treatment and followup, or dose of interferon alfa 2b
Interferon alfa 2b+placebo vs. lamivudine[67]	24/12-40	2/151	Random differences at different time of followup	Low. No differences between interferon alfa 2b+placebo vs. lamivudine on ALT normalization at time of followup
Interferon alfa 2b vs. interferon alfa 2b[82,85,96]	24-48 /24-48	3/185	Random differences at different doses and time of followup	Moderate. No difference between different doses or time of treatment and followup of interferon alfa 2b on ALT normalization

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95 % CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/Comments
Interferon alfa 2b vs. no treatment[86,96]	16-24 /8-24	2/131	**0.31 (0.17; 0.44)** (RD) 0.442/0%	Moderate. Interferon Alfa 2b at doses 35 but not 7MU/week vs. no treatment increased rates of ALT normalization at time of followup
Lamivudine vs. placebo[46]	96/24	1/136	**0.21 (0.04; 0.38)** (RD)	Low. Lamivudine vs. placebo increased rates of ALT normalization at time of followup
Peginterferon alfa 2a+lamivudine vs. lamivudine[56,57]	48/24	2/905	**0.13 (0.06; 0.19)** (RD) 0.569/0%	High. Peginterferon alfa 2a+lamivudine vs. lamivudine increased rate of ALT normalization at time of followup
Peginterferon alfa 2a+lamivudine vs. peginterferon alfa-2a[56]	48/24	1/542	-0.02 (-0.10; 0.06) (RD)	Low. No differences between peginterferon alfa-2a+lamivudine vs. peginterferon alfa 2a on ALT normalization at time of followup
Peginterferon alfa 2a+placebo vs. lamivudine[56,57]	48/24	2/905	**0.13 (0.07; 0.20)** (RD) 0.904/0%	High. Peginterferon alfa-2a+placebo vs. lamivudine alone increased rates of ALT normalization at time of followup
Peginterferon alfa 2a vs. peginterferon alfa-2a[116]	24/24	1/194	Random differences at all dose comparisons No *	Low. No dose response association of peginterferon alfa-2a on ALT normalization at time of followup
Peginterferon alfa 2b+lamivudine vs. peginterferon alfa 2b[78]	52/26	1/307	0.02 (-0.08; 0.12) (RD)	Low. No differences between peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b alone on ALT normalization at time of followup
Peginterferon alfa-2b vs. interferon alfa 2b[81]	24/24	1/230	-0.01 (-0.13; 0.11) (RD)	Low. No differences between peginterferon alfa-2b vs. interferon alfa 2b on ALT normalization at time of followup

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

(D) Relapse and Mutation

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95% CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Relapse end of treatment				
Adefovir dipivoxil vs. placebo[40,100]	48-52/0	2/1055	-0.08 (-0.37; 0.21) (RD) 0.000/99%	Low. Adefovir dipivoxil in dose of 10mg/day increased rates of relapse. Adefovir dipivoxil in adjusted dose (10 or 30 mg/day) reduced the rate of relapse.
Entecavir vs. lamivudine[74,101]	52-96/0	2/1347	-0.01 (-0.11; 0.09) (RD) 0/96%	Low. Entecavir vs. lamivudine reduced relapse in HBeAg negative patients but increase in HBeAg positive.
Interferon Alfa 2b+lamivudine vs. lamivudine[60,63,64,66]	24-96 /0	4/326	-0.06 (-0.16; 0.04) (RD) 0.063/59%	High. No differences between interferon Alfa 2b+lamivudine vs. lamivudine alone on relapse
Lamivudine[108]	48-60/0	1/348	**0.16 (0.08; 0.24)** (RD)	Low. Lamivudine for 60 weeks vs. lamivudine for 48 weeks increased rates of virological relapse
Lamivudine vs. telbivudine[72]	52/0	1/63	0.11 (-0.06; 0.29) (RD)	Low. No differences between lamivudine vs. telbivudine on virological relapse
Peginterferon alfa-2b+lamivudine vs. lamivudine[59]	60/0	1/100	Random differences for virological and biochemical outcomes	Low. No differences between peginterferon alfa-2b+lamivudine vs. lamivudine alone on relapse
Telbivudine+lamivudine vs. lamivudine[72]	52/0	1/60	-0.04 (-0.23; 0.16) (RD)	Low. No differences between telbivudine + lamivudine vs. lamivudine on relapse
Telbivudine+lamivudine vs. telbivudine[72]	52/0	1/85	0.08 (-0.04; 0.19) (RD)	Low. No differences between telbivudine+ lamivudine vs. telbivudine on relapse
Relapse at followup				
Entecavir vs. lamivudine[73]	52/24	1/709	**-0.16 (-0.20; -0.12)** (RD)	Low. Entecavir vs. lamivudine reduced virological relapse
Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b[91,96]	24/24	2/141	Random differences for all comparisons	Low. No differences between interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b alone on relapse
Interferon Alfa 2b+corticosteroid vs. no treatment[96]	24/24	1/87	0.02 (-0.04; 0.08) (RD)	Low. Interferon Alfa 2b+ corticosteroid vs. no treatment did not increase rates of relapse
Interferon Alfa 2b+lamivudine vs. lamivudine[65,69]	52-176/24-192	2/158	Random differences in all but at 96 and 144 weeks of followup comparisons	Low. No differences between Interferon Alfa 2b + lamivudine vs. lamivudine alone on relapse at weeks 24, 48, and 192 of followup. One RCT reported a significant decrease in relapse at weeks 96 and 144 of followup

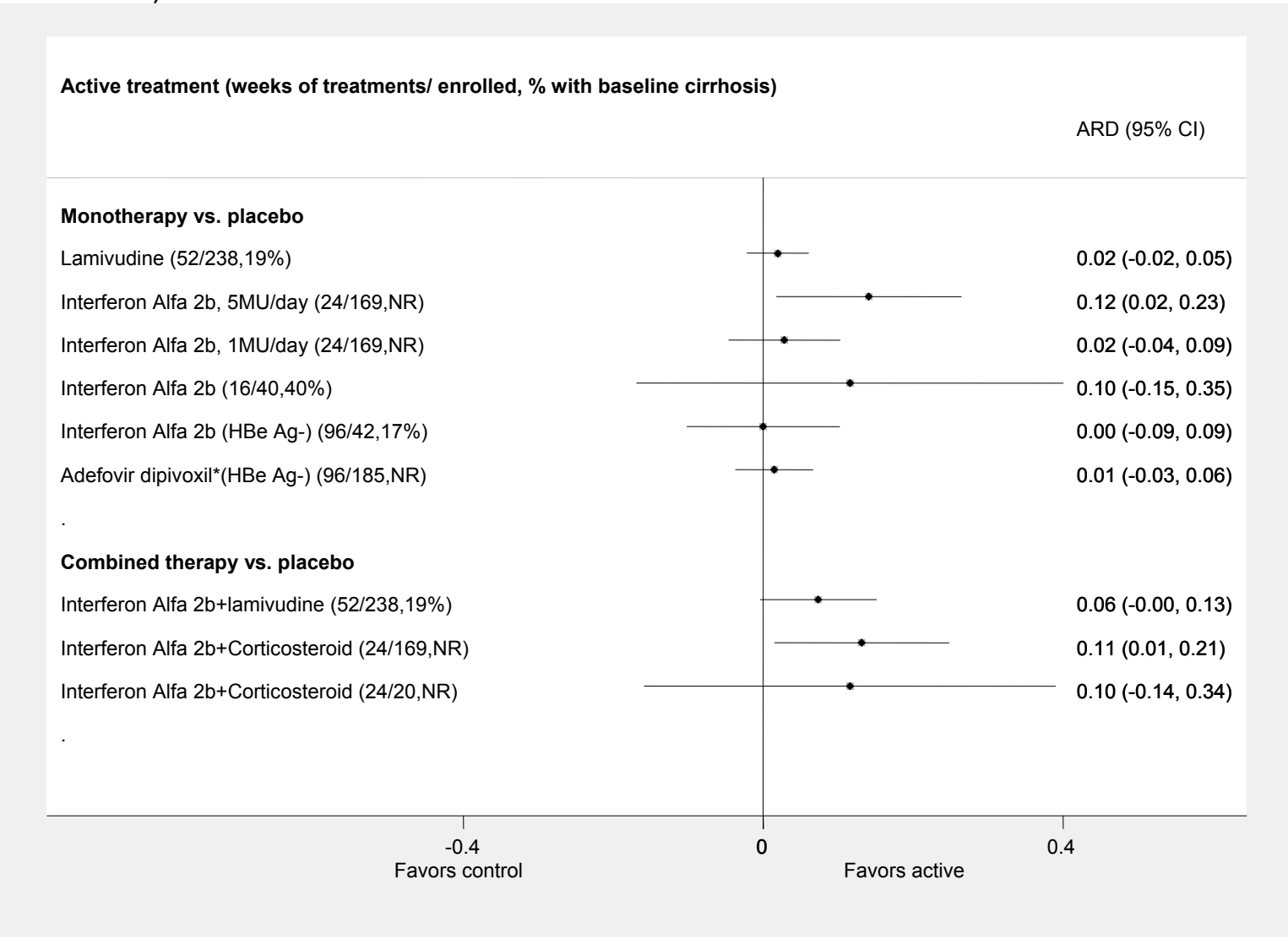
Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95% CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Interferon alfa 2b vs. interferon Alfa 2b[96]	24/24	1/82	-0.02 (-0.09; 0.04)	Low. No differences between 5 or 1 MU/day of interferon Alfa 2b on relapse at followup
Interferon alfa 2b vs. no treatment[83,84,88,96]	16-96/20-96	5/378	Random differences for all comparisons	High. Interferon Alfa 2b vs. no treatment did not increase rates of relapse
Peginterferon alfa 2b+lamivudine vs. lamivudine[117]	52-60/24-72	1/100	Random differences for all time of followup comparisons (0.00; 0.00) (RD)	Low. No differences between peginterferon alfa-2b+lamivudine vs. lamivudine on relapse in all time of followup
Mutation end of treatment				
Adefovir dipivoxil+lamivudine vs. lamivudine[58]	52/0	1/95	**-0.33 (-0.50; -0.17)** (RD) 0.04 (-0.03; 0.11) (RD)	Low. Adefovir dipivoxil+ lamivudine vs. lamivudine decreased rates of YMDD but not wild type mutation
Adefovir dipivoxil vs. adefovir dipivoxil[97]	114-240/0	1/250	**0.18 (0.08; 0.27)** (RD) **0.12 (0.04; 0.20)** (RD)	Low. Adefovir dipivoxil for 240 vs. 114 weeks increased rates of adefovir resistant mutation
Adefovir dipivoxil vs. placebo[41,100]	48/0	2/879	Random differences for all but 1 amino acid substitution rt221Y	Low. Adefovir dipivoxil vs. placebo increased rates of emerging amino acid substitutions in the HBV-RT domain and rates of rt221Y amino acid substitution but not rt134D; rt219A; rt91I;rt134N; rt54H; rt145M substitutions
Interferon alfa 2b+lamivudine vs. lamivudine[66] [47,60,62,63,69]	24-96 /0	6/721	**-0.18 (-0.35; -0.01)** (RD) 0/91% **0.42 (0.16; 1.09)** (RR) 0.003/72.2%	Moderate. Interferon alfa 2b+lamivudine vs. lamivudine reduced rate of mutation with inconsistent effect size. Heterogeneity cannot be explained by the dose of Interferon alfa 2b, length of treatment, or % of HBeAg + patients at baseline
Interferon Alfa 2b+lamivudine vs. placebo[47]	52/0	1/118	0.00 (-0.03; 0.03) (RD)	Low. No differences between interferon Alfa 2b+lamivudine vs. placebo on mutation
Lamivudine for 60 weeks vs. lamivudine for 48 weeks[108]	48-60/0	1/429	**0.06 (0.01; 0.11)** (RD) **0.03 (0.00; 0.06)** (RD)	Low. Lamivudine for 60 weeks vs. lamivudine for 48 weeks increased rates of mixed and pure YMDD mutation
Lamivudine vs. placebo[47,51]	52-130/0	2/826	**0.43 (0.38; 0.48)** (RD) 0.873/0%	High. Lamivudine vs. placebo increased rates of YMDD mutation
Peginterferon alfa 2a+lamivudine vs. lamivudine[56]	48/0	1/543	**-0.22 (-0.28; -0.16)** (RD)	Low. Peginterferon alfa-2a+lamivudine vs. lamivudine reduced rate of mutation
Peginterferon alfa 2a+lamivudine vs. peginterferon alfa 2a[56]	48/0	1/542	**0.03 (0.01; 0.06)** (RD)	Low. Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a alone increased rate of mutation

Appendix E. Table 5. Summary tables of the effects of drug therapies for chronic hepatitis B on outcomes

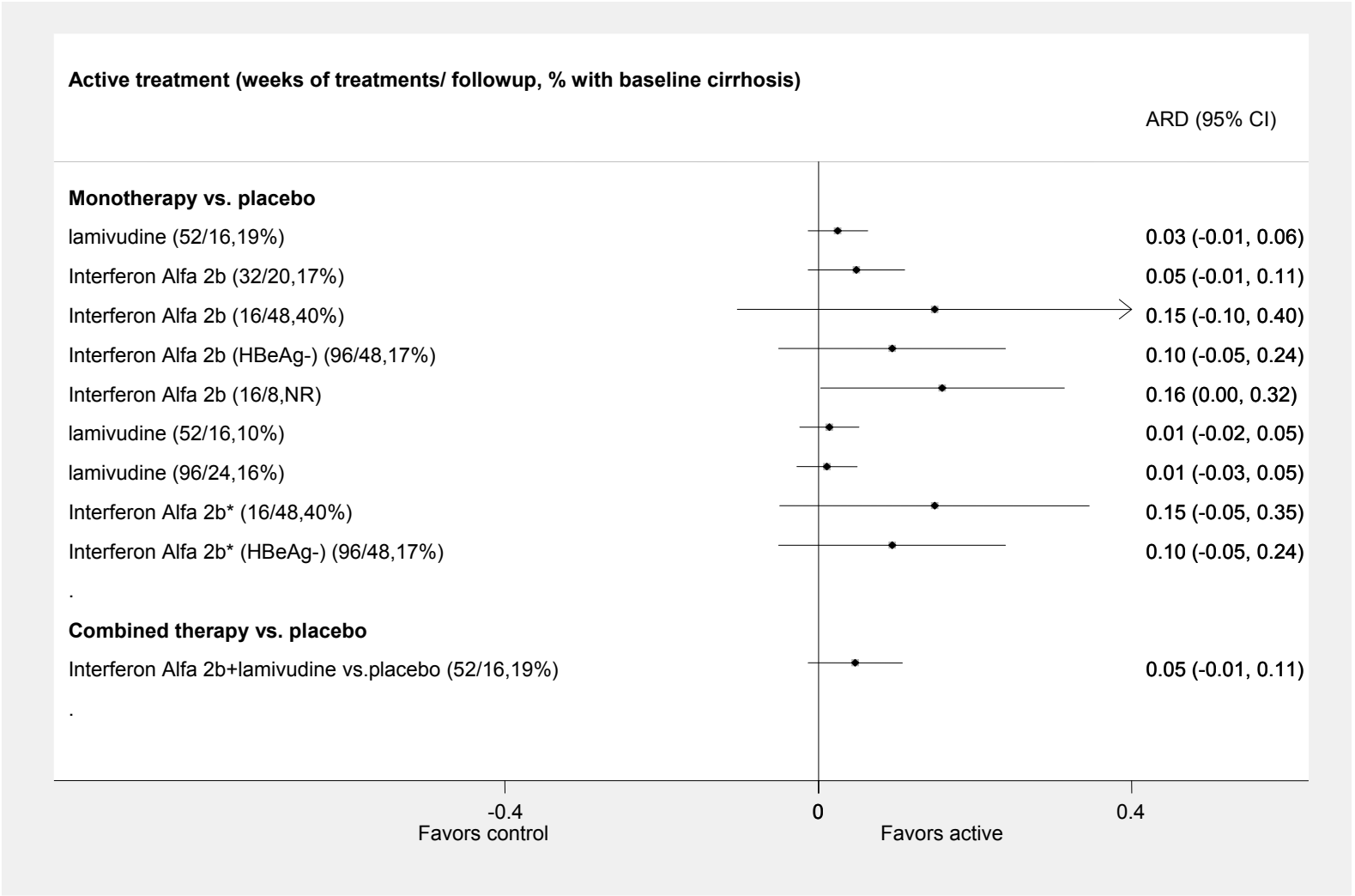
Active Treatments vs. Control Treatment	Treatment Duration/ Followup Off Therapy, Weeks	Studies/ Subjects Enrolled	Estimates (95% CI) *-Dose Response Heterogeneity: p Value/I Squared, %	Level of Evidence/ Comments
Peginterferon alfa 2a+placebo vs. lamivudine[56]	48/0	1/543	**-0.25 (-0.31; -0.20)** (RD)	Low. Peginterferon alfa 2a+ placebo vs. lamivudine alone reduced rate of mutation
Peginterferon alfa 2b+lamivudine vs. lamivudine[59]	60/0	1/100	**-0.18 (-0.35; -0.01)** (RD)	Low. Peginterferon alfa 2b+lamivudine vs. lamivudine alone reduced rate of mutation
Peginterferon alfa 2b+lamivudine vs. peginterferon alfa 2b[78]	52/0	1/307	**0.09 (0.04; 0.14)** (RD)	Low. Peginterferon alfa 2b+lamivudine vs. peginterferon alfa-2b increased rates of mutation
Followup				
Adefovir dipivoxil for 96 vs. 48 weeks[98]	96/18	1/140	Random differences in all mutations and duration of treatment	Low. No differences in mutations after adefovir dipivoxil for 96 vs. 48 weeks
Adefovir dipivoxil vs. placebo[98]	96/18	1/140	Random differences in all mutations and duration of treatment	Low. Adefovir dipivoxil vs. placebo did not increase rates of mutation
Interferon alfa 2b+lamivudine vs. interferon alfa 2b[67]	24/28	1/144	0.00 (-0.03; 0.03) (RD)	Low. No difference between Interferon alfa 2b+lamivudine vs. interferon alfa 2b on mutations at followup
Interferon alfa 2b+lamivudine vs. lamivudine[67]	24/28	1/157	**-0.23 (-0.32; -0.14)** (RD)	Low. Interferon alfa 2b+lamivudine vs. lamivudine reduced mutation at followup
Interferon alfa 2b+placebo vs. lamivudine[67]	24/28	1/151	**-0.23 (-0.33; -0.14)** (RD)	Low. Interferon alfa 2b+ placebo vs. lamivudine reduced mutations at followup

Appendix E. Figure 5. Effects of active treatments compared to placebo on HBsAg loss *at the end of the treatment* (results from individual RCTs[47,84,89,96,98,103])



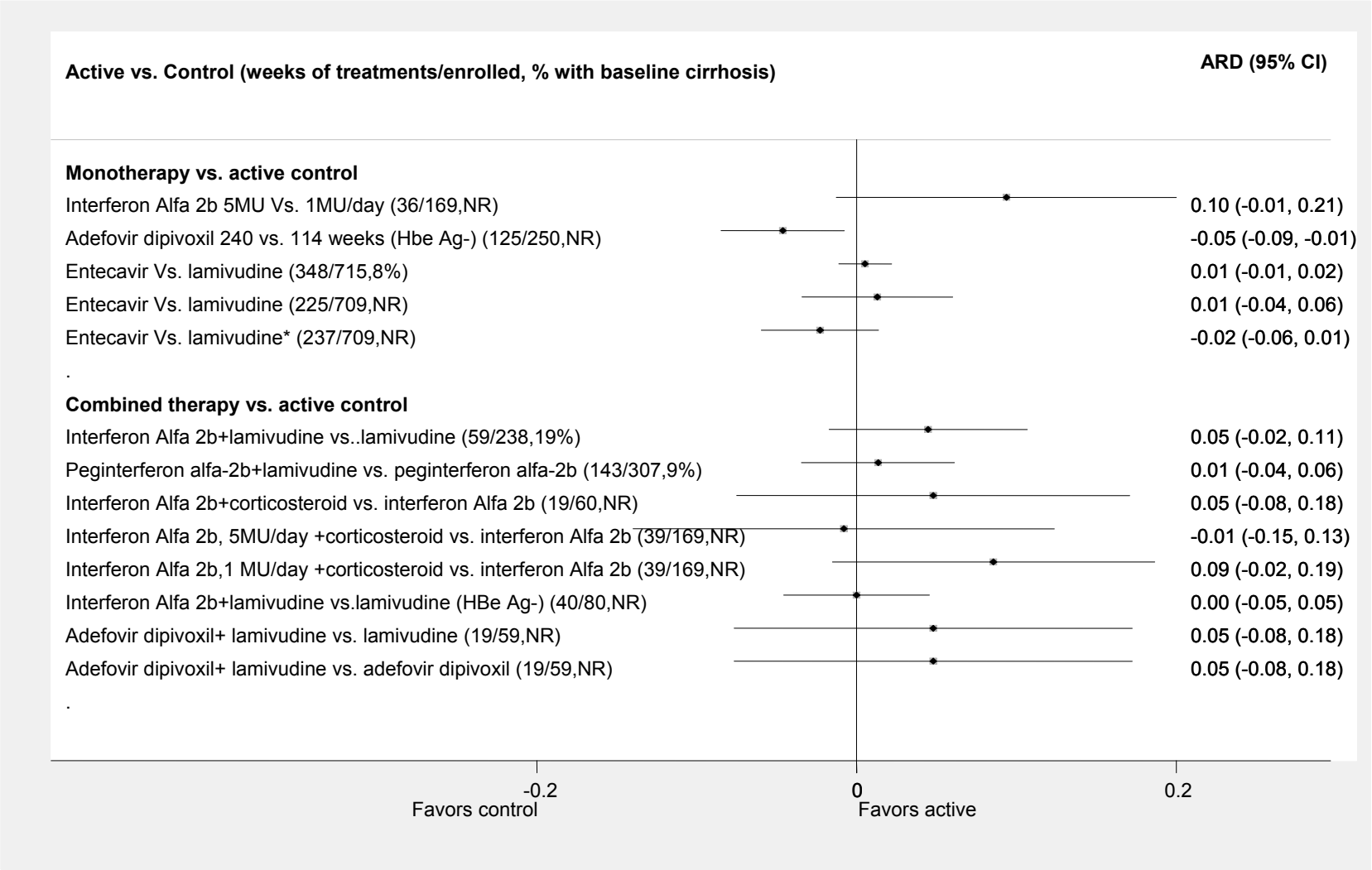
* HBsAg seroconversion

Appendix E. Figure 6. Effects of active treatments compared to placebo on HBsAg loss *at followup off the treatment* (results from individual RCTs)[46-48,83,84,86,89]



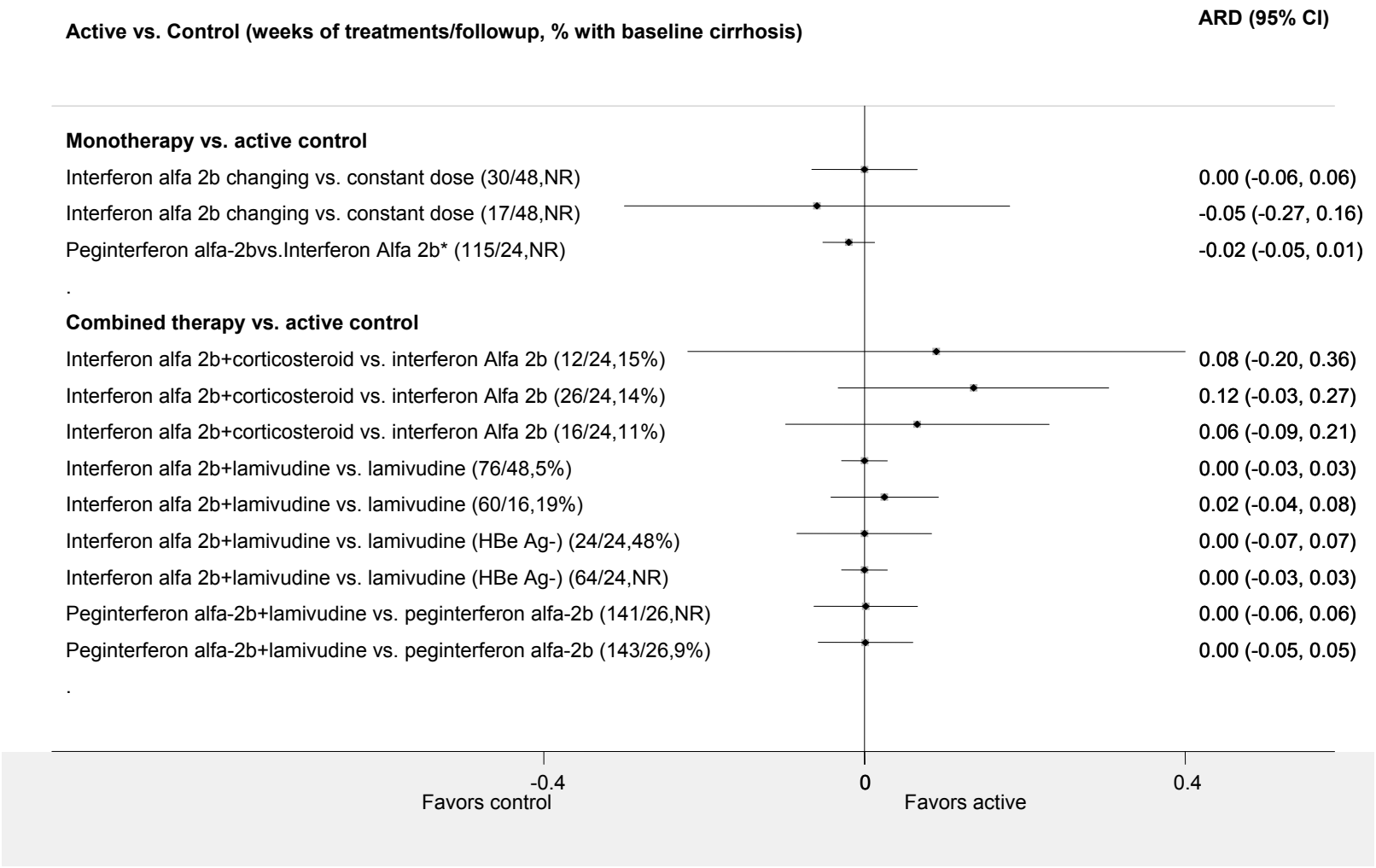
*HBs Ag seroconversion

Appendix E. Figure 7. Comparative effectiveness of active treatments on HBsAg loss *at the end of the treatments* (results from individual RCTs)[43,47,64,73,78,94,96,97,101]

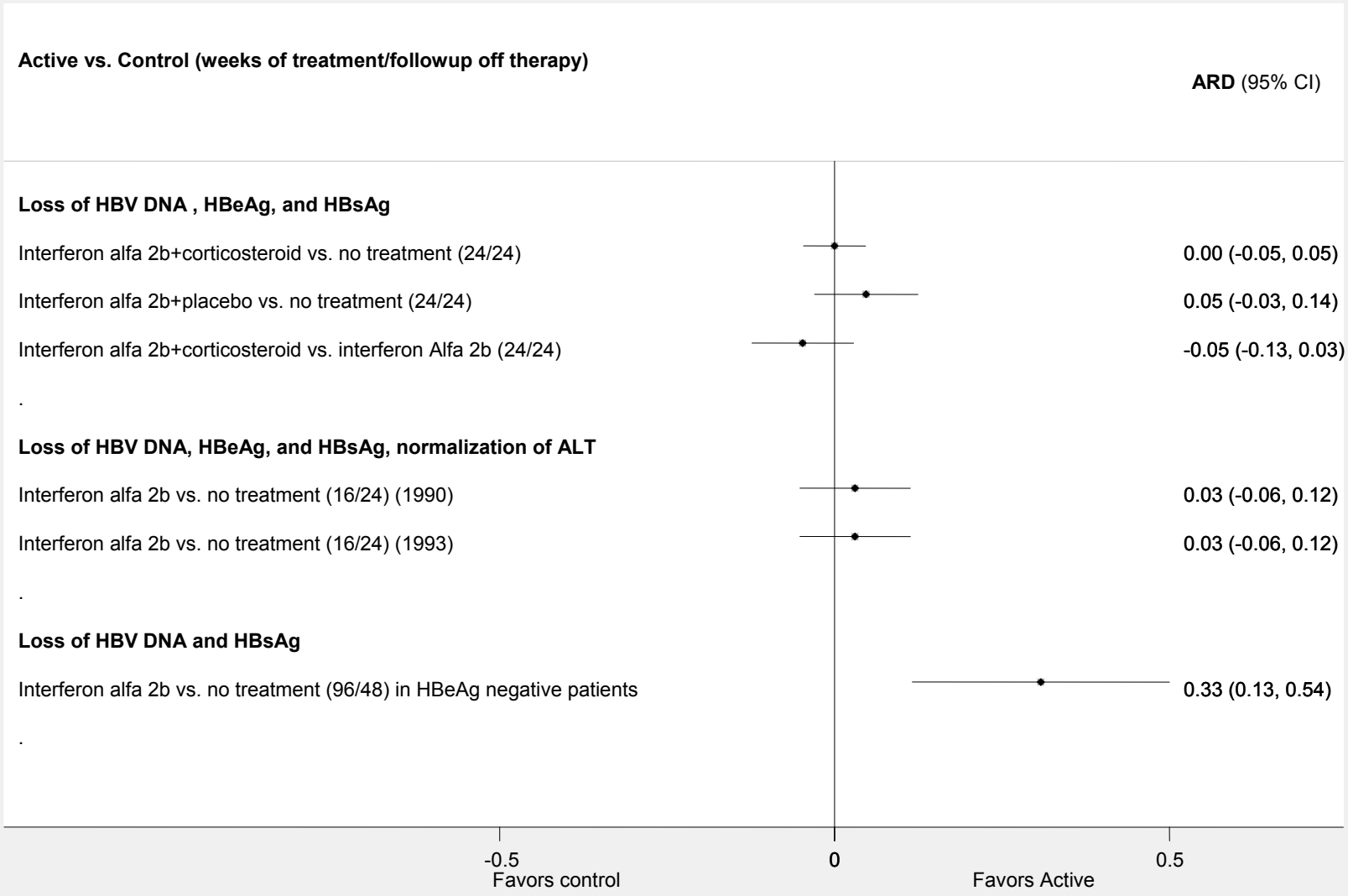


*-HBs Ag seroconversion

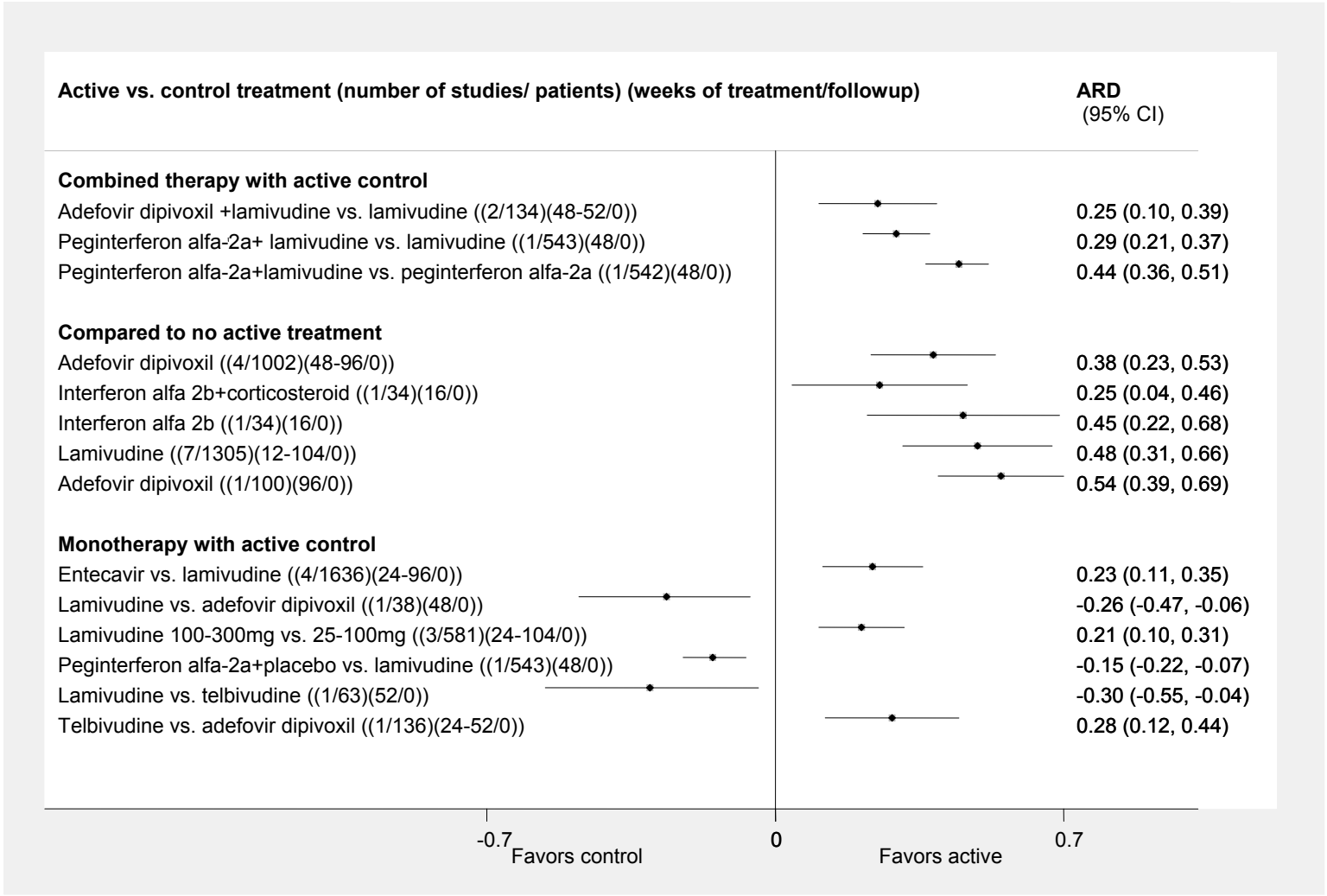
Appendix E. Figure 8. Comparative effectiveness of active treatments on HBsAg loss *at followup off the treatments* (results from individual RCTs)[47,62,63,66,78,81,82,85,91,92,95,122]



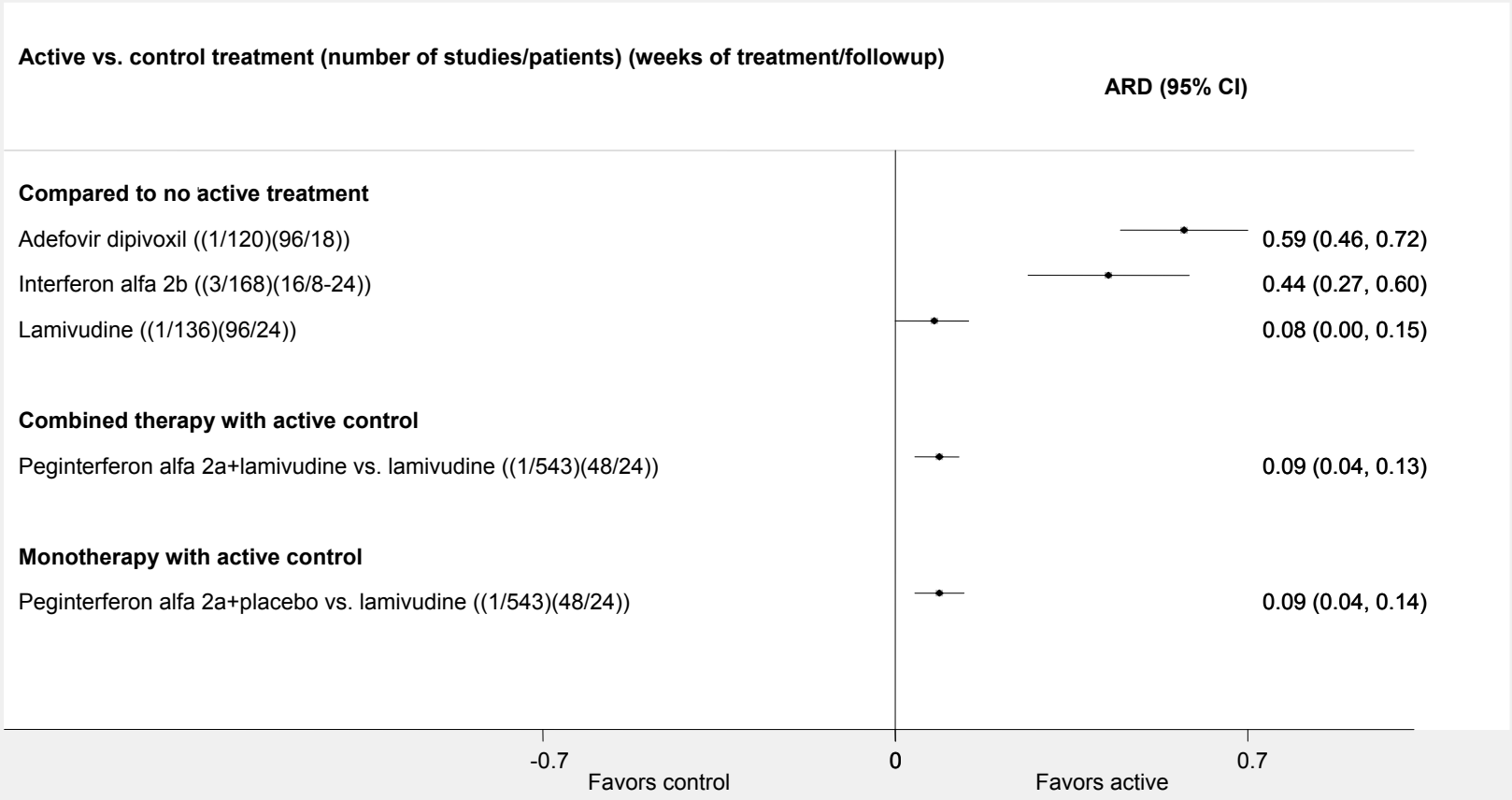
Appendix E. Figure 9. HBsAg loss combined with other criteria of resolved hepatitis B at followup off the therapy (results from individual RCTs [84,87,93,105]



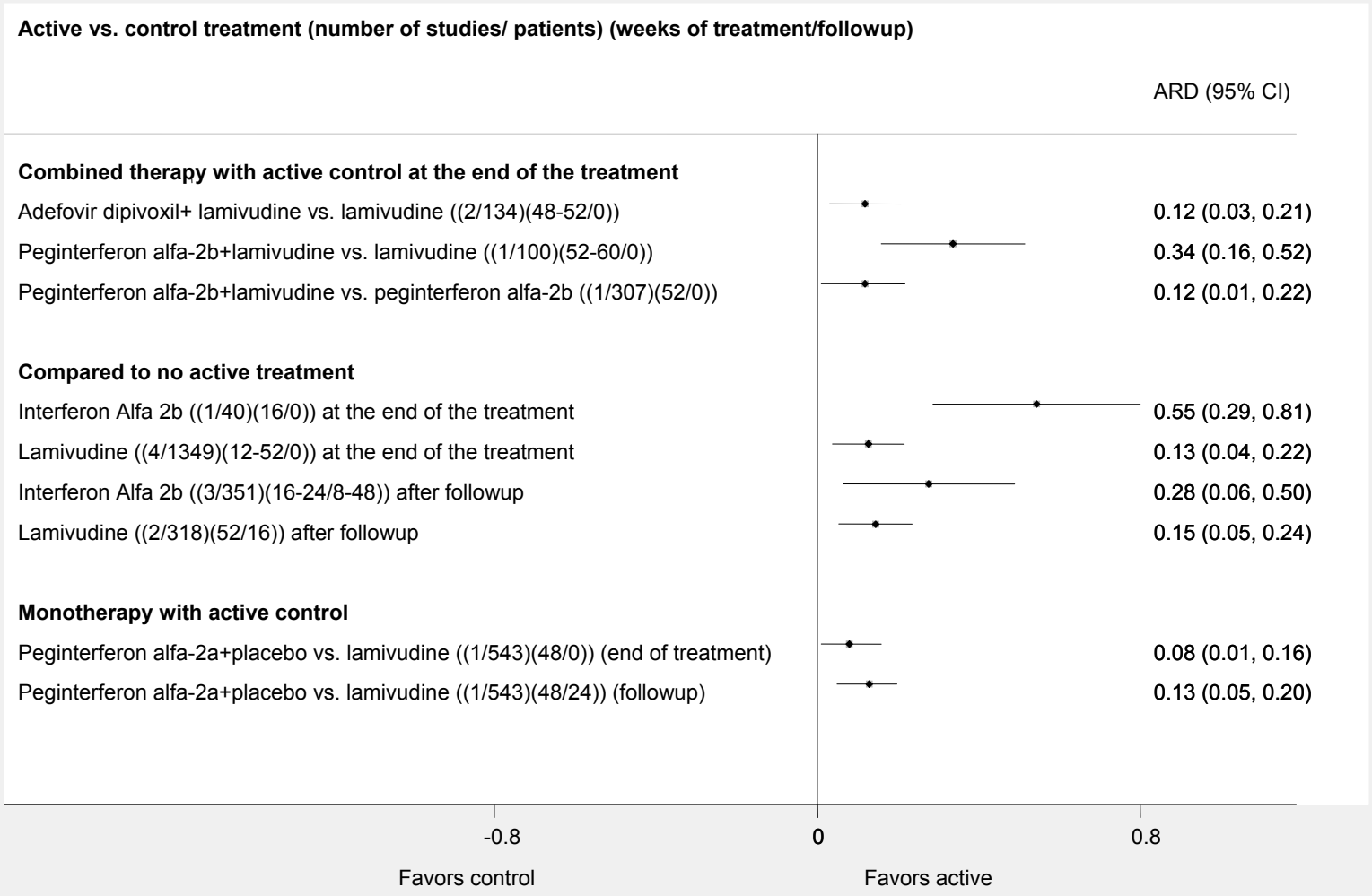
Appendix E. Figure 10. HBV DNA loss *at the end* of the drug therapies for chronic hepatitis B (significant risk differences from individual RCTs and pooled with random effects model)



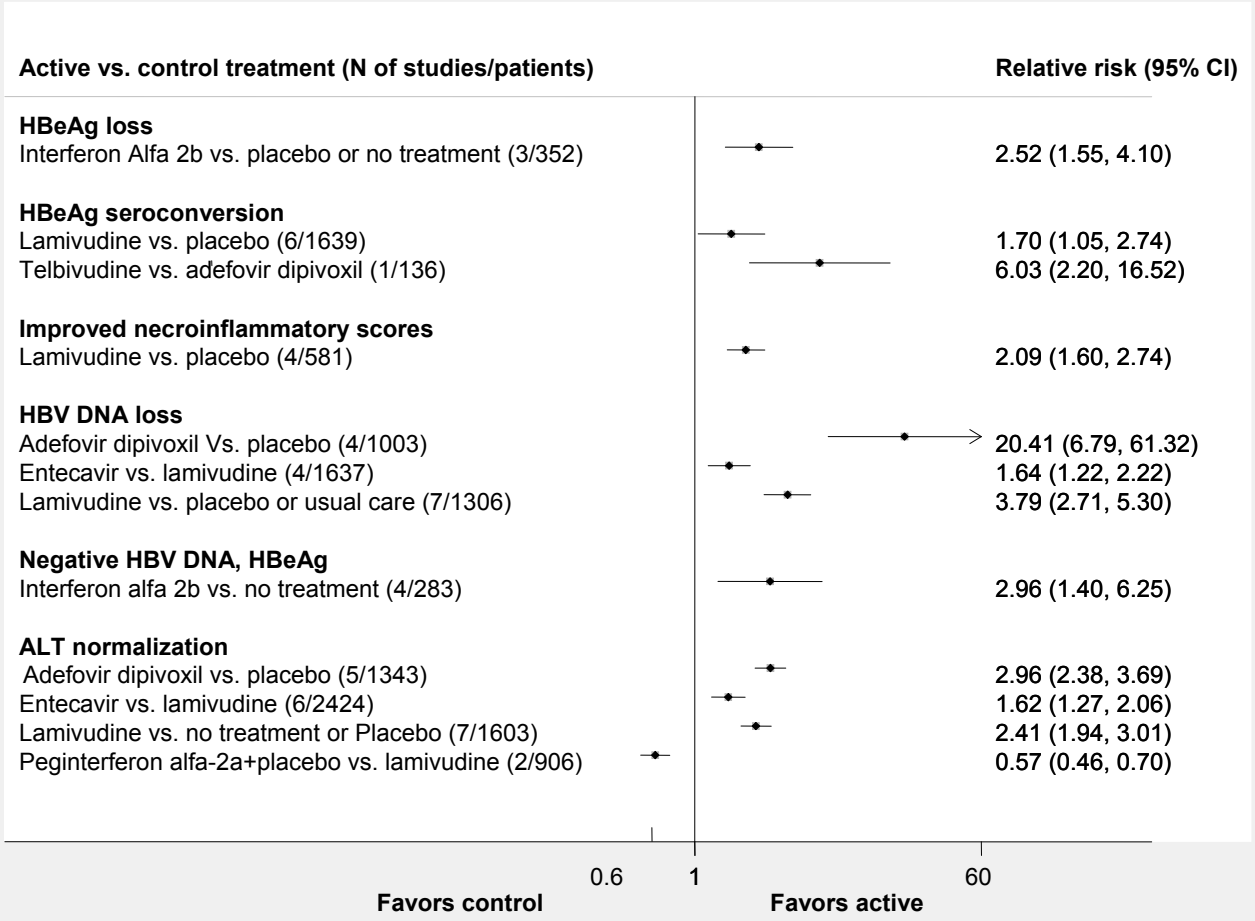
Appendix E. Figure 11. HBV DNA loss *at followup off* the drug therapies for chronic hepatitis B (significant risk differences from individual RCTs and pooled with random effects model)



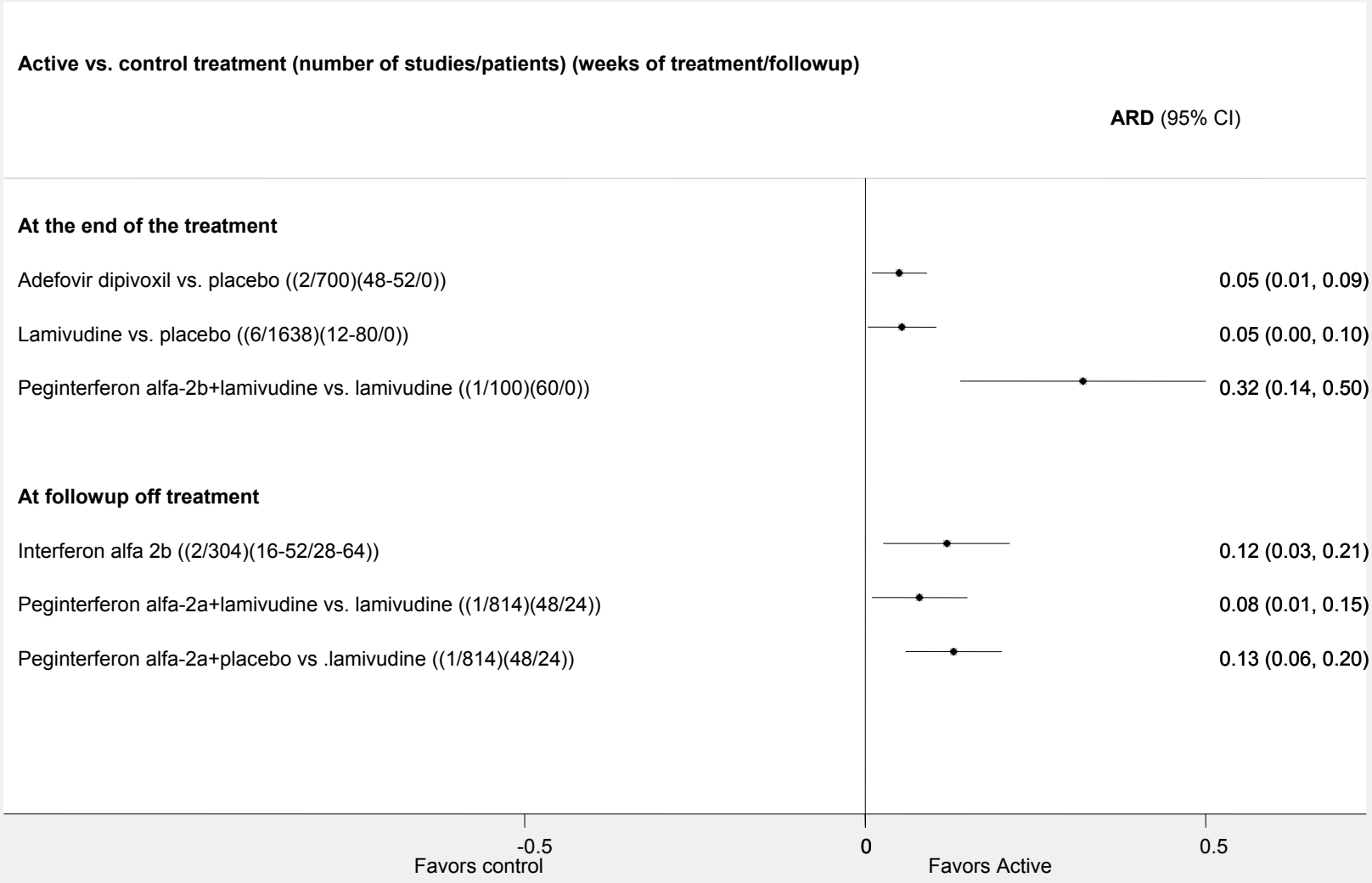
Appendix E. Figure 12. Significant effects on HBeAg loss for chronic hepatitis B (significant risk differences from individual RCTs and pooled with random effects model)



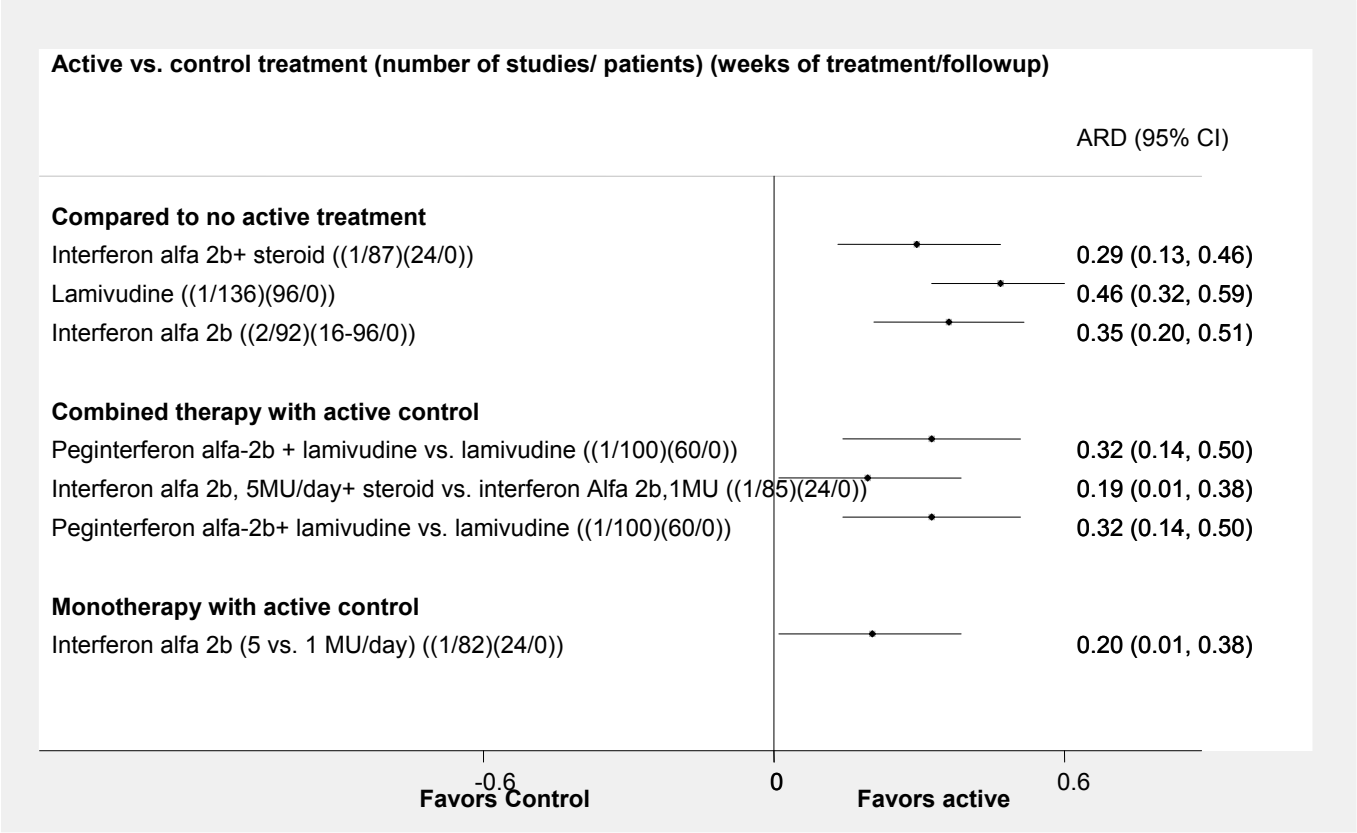
Appendix E. Figure 13. Significant relative risk of virological, histological and biochemical outcomes after drug therapies for chronic hepatitis B (results from individual RCT and pooled consistent results using random effects model)



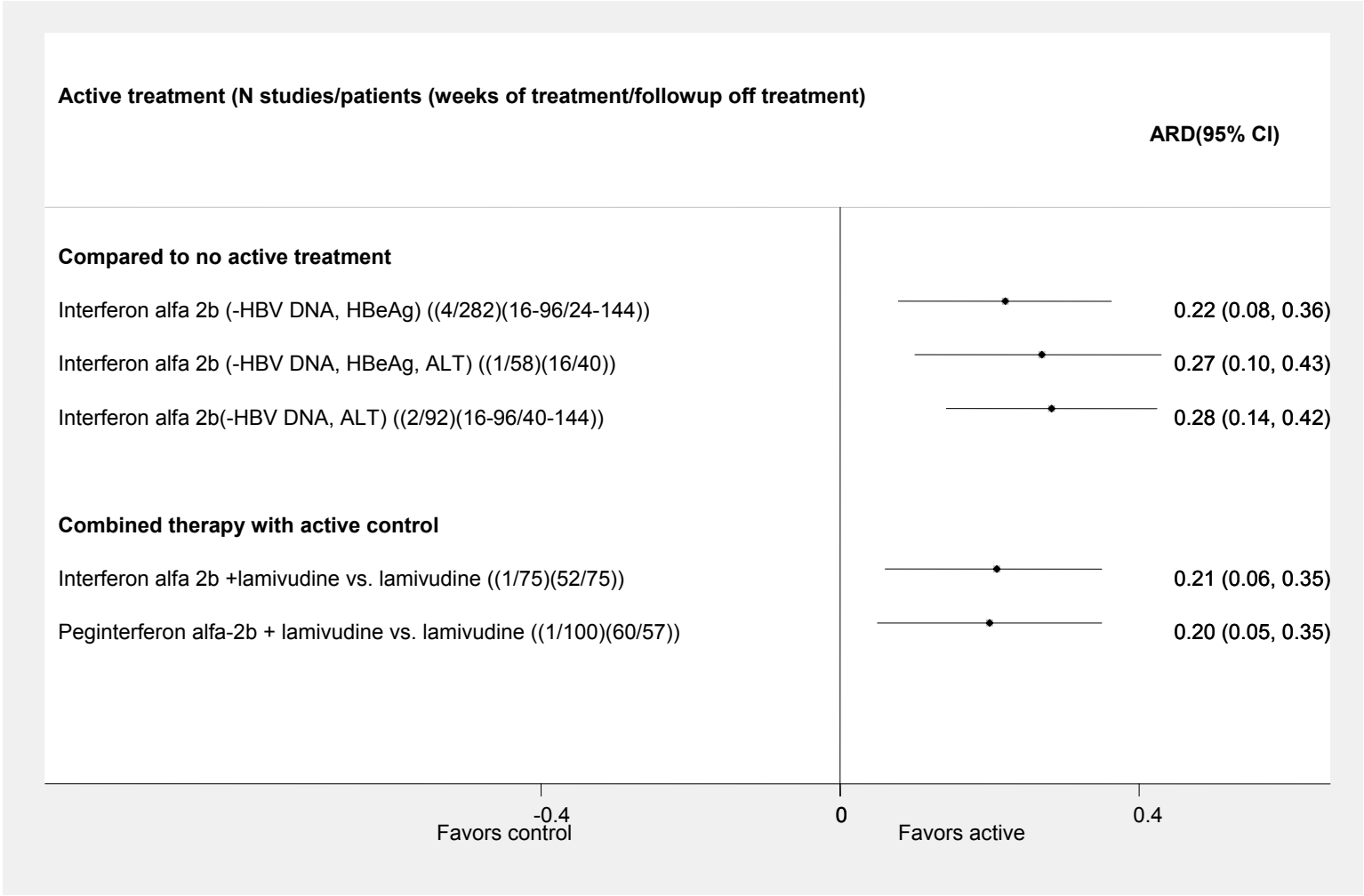
Appendix E. Figure 14. Significant effects on HBeAg seroconversion for chronic hepatitis B (significant risk differences from individual RCTs and pooled with random effects model)



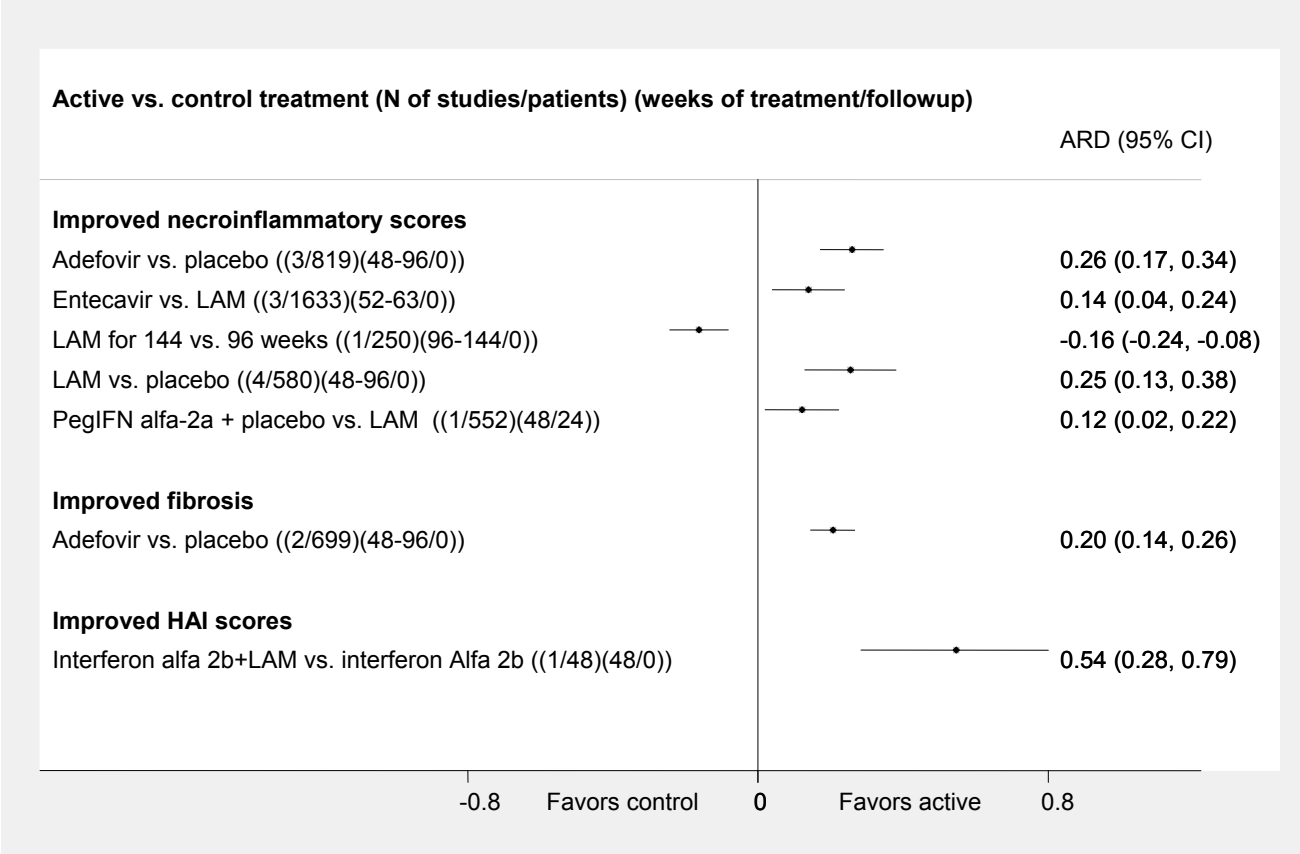
Appendix E. Figure 15. Significant effects on combined virological and biochemical outcomes *at the end* of the drug therapies for chronic hepatitis B (significant risk differences from individual RCTs and pooled with random effects model)



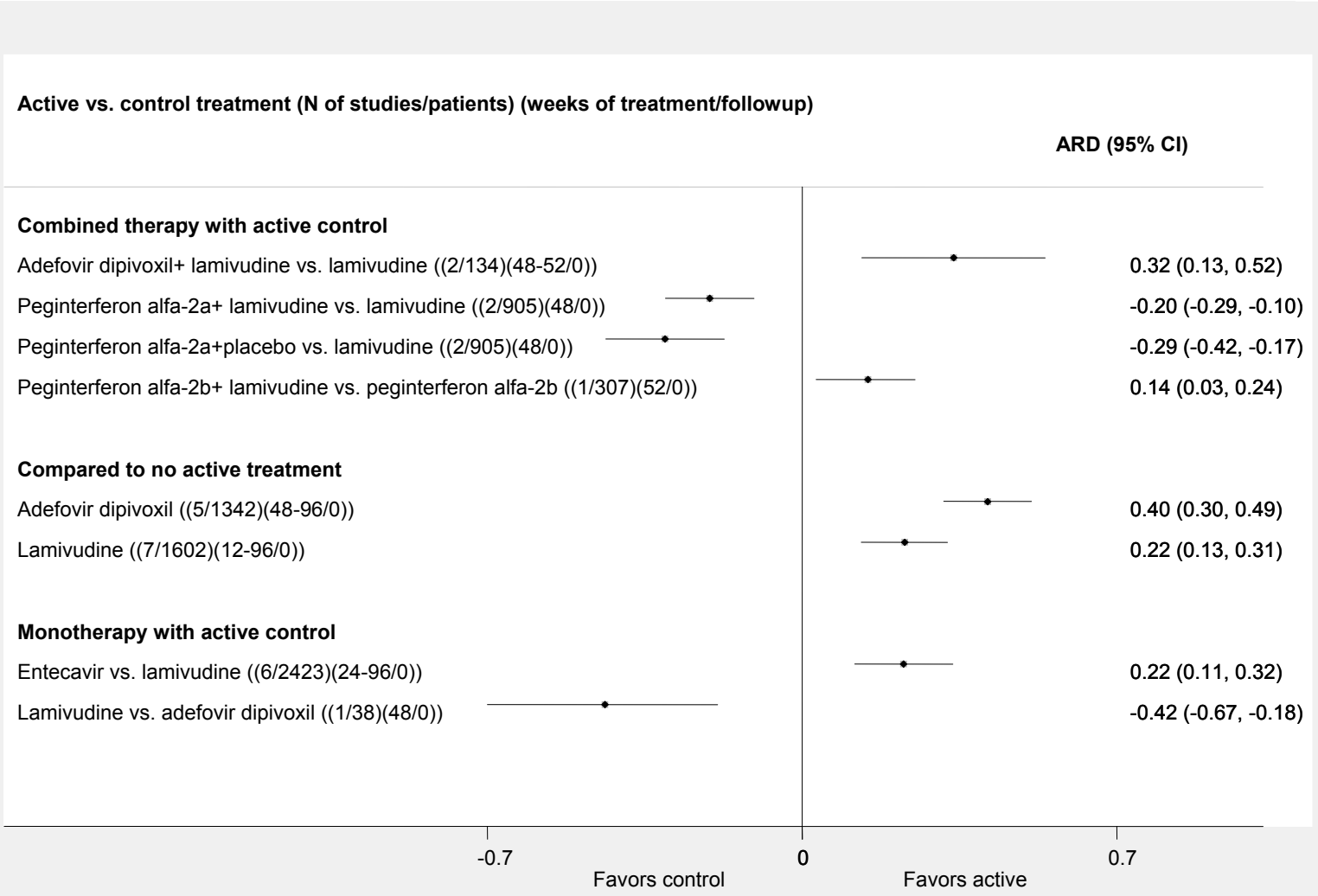
Appendix E. Figure 16. Significant effects on combined virological and biochemical outcomes *at follow up* after drug therapies for chronic hepatitis B (significant risk differences from individual RCTs and pooled with random effects model)



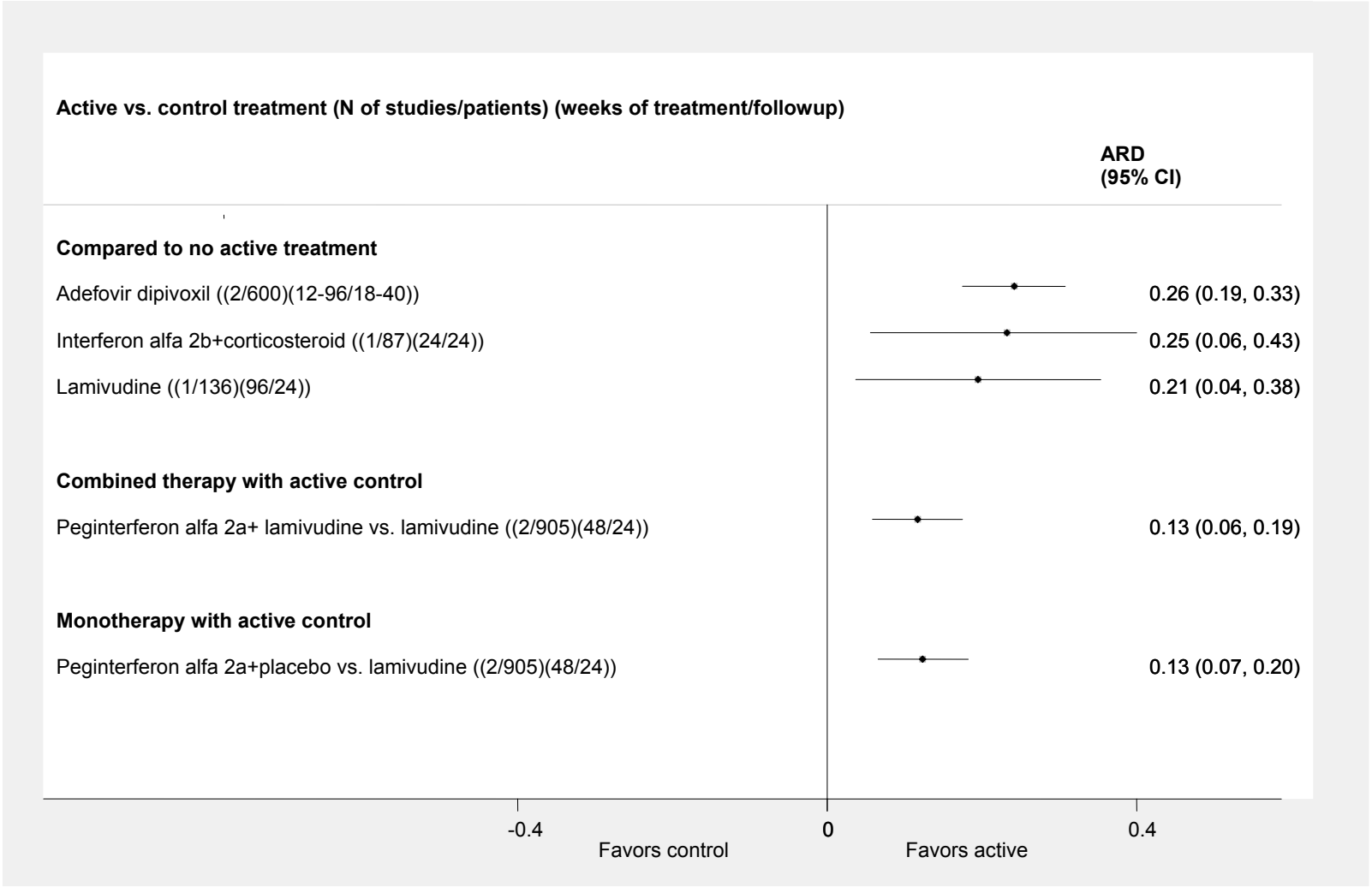
Appendix E. Figure 17. Histological outcomes *at the end* of the drug therapies for chronic hepatitis B (significant risk differences from individual RCTs and pooled with random effects model)



Appendix E. Figure 18. ALT normalization at *the end of* the drug therapies for chronic hepatitis B (significant risk differences from individual RCTs and pooled with random effects model)



Appendix E. Figure 19. ALT normalization *at followup off the drug* therapies for chronic hepatitis B (significant risk differences from individual RCTs and pooled with random effects model)



Appendix E. Table 6. Levels of viral load, biochemical, or histologic outcomes after antiviral drugs in adults with chronic hepatitis B

Author Active Drug, Daily/Weekly Dose Combined Active Drug, Daily/Weekly Dose, Length of Active Treatment in Weeks	Control Intervention, Daily/Weekly Dose Length of Control Intervention	Patients in Active/Control Group	Time to Measure Outcomes from Randomization (Weeks) After Active/Control Treatments	Outcome	Mean± Standard Deviation After Active Treatment	Mean± Standard Deviation After Control Treatment	Mean Difference (95% CI)
Barbaro, 2001[66] Recombinant interferon alpha-2b (Intron A, Schering Plough, Kenilworth, NJ), 4 9 million units 3 times per week Lamivudine (Glaxo-Wellcome Inc, Research Triangle Park, NC), 100mg/day, 24 weeks	lamivudine (Glaxo-Wellcome Inc, Research Triangle Park, NC), 100 mg/day, 52 weeks	76/75	24/52	Median reduction in the histological inflammation score	4±2	3±1	**0.63 (0.30; 0.96)**
Yalcin, 2003[79] IFN-a-2b, 4 10 MU 3 times per week Lamivudine, 100mg daily, 48 weeks	IFN-a-2b, 4 10 MU 3 times per week, 48 weeks	33/16	48/48	Mean of HAI score	4±3	8±3	**-1.35 (-2.00; -0.69)**
Robson, 1992[103] Interferon alpha-2b (Intron A; Scherag), 4 10MI 3 times/week after 6 weeks of prednisone and 2 weeks without treatment prednisone, 4060mg/day for 2 weeks then 40mg/day for 2 weeks, and then 20mg/day for 2 weeks, 24 weeks	Symptomatic treatment, , 24 weeks	10/10	24/24	WCCX10 in 9 degree	5±2	7±2	**-1.20 (-2.16; -0.24)**
		10/10	24/24	Platelets	111±74	149±69	-0.53 (-1.42; 0.36)
		10/10	24/24	AST U/L	96±82	156±106	-0.63 (-1.53; 0.27)
		10/10	24/24	ALT U/L	112±107	159±87	-0.48 (-1.37; 0.41)
		10/10	24/24	Albumin g/L	40±5	35±12	0.50 (-0.39; 1.39)
Akarca, 2004[64] Interferon Alfa, 4 10 MU 3 times per week for 24 weeks Lamivudine, 150mg daily, 96 weeks	Lamivudine, 150 mg/day, 96 weeks	40/40	24/24	ALT levels	58±37	36±21	**0.73 (0.28; 1.18)**
		40/40	96/96	ALT levels	28±15	29±26	-0.05 (-0.49; 0.39)
		40/40	96/96	Necroinflammatory activity scores	4±3	3±2	**0.70 (0.25; 1.15)**
		40/40	96/96	Fibrosis scores	1±1	1±1	**0.52 (0.07; 0.96)**
Sarin, 2005[69] IFN-α, 5 MU daily 16 weeks added after the first 8 weeks Lamivudine , 100mg/day, 52 weeks	Lamivudine , 100 mg/day, 52 weeks	38/37	52/52	ALT Levels (IU/L)	39±11	44±16	-0.35 (-0.81; 0.10)
		38/37	76/76	ALT Levels (IU/L)	77±156	58±24	0.17 (-0.28; 0.62)
		38/37	52/52	HBV DNA (copies/mL)	51±29	120±380	-0.26 (-0.71; 0.20)
		38/37	76/76	HBV DNA (copies/mL)	227±517	105±405	0.26 (-0.19; 0.72)

Appendix E. Table 6. Levels of viral load, biochemical, or histologic outcomes after antiviral drugs in adults with chronic hepatitis B

Author Active Drug, Daily/Weekly Dose Combined Active Drug, Daily/Weekly Dose, Length of Active Treatment in Weeks	Control Intervention, Daily/Weekly Dose Length of Control Intervention	Patients in Active/Control Group	Time to Measure Outcomes from Randomization (Weeks) After Active/Control Treatments	Outcome	Mean± Standard Deviation After Active Treatment	Mean± Standard Deviation After Control Treatment	Mean Difference (95% CI)
Akyuz, 2007[60] Interferon Alfa 2b, 4 10MU 3 times per week for 24 weeks Lamivudine, 100mg/day for 96 weeks	lamivudine, 100 mg/day for 96 weeks,	21/24	96/96	HAI scores	6±16	3±11	0.18 (-0.41; 0.77)
Zarski, 1994[91] interferon alpha-2b (INTRON A, Schering-Plough Corporation), 2 5 MU three times a week Prednisone, 40decreasing doses of 60, 40, 20 mg for 6 weeks, 24 weeks	interferon alpha-2b (INTRON A, Schering-Plough Corporation), 2 5 MU 3 times per week, 24 weeks	31/25	48/48	Knodell score	7±4	6±2	0.16 (-0.37; 0.69)
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1 1.5 MU 3 times per week Prednisone, 3750mg for 2 weeks, 25 mg for 2 weeks, then 2 weeks drug free interval, 24 weeks	Recombinant interferon alpha 2b (Intron), 1 placebo withdrawal followed 1.5 MU 3 times per week, 24 weeks	18/19	48/48	ALT level	116±95	211±280	-0.45 (-1.10; 0.20)
	Recombinant interferon alpha 2b (Intron), 2 placebo withdrawal followed 5 MU 3 times per week, 24 weeks	18/19	48/48	ALT level	116±95	155±242	-0.21 (-0.86; 0.44)
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1 placebo withdrawal followed 1.5 MU three times per week, 24 weeks	Recombinant interferon alpha 2b (Intron), 2 placebo withdrawal followed 5 MU 3 times per week, 24 weeks	19/19	48/48	ALT level	211±280	155±242	0.21 (-0.42; 0.85)
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1 1.5 MU 3 times per week prednisone, 3750mg for 2 weeks, 25 mg for two weeks, then 2 weeks drug free interval, 24 weeks	Recombinant interferon alpha 2b (Intron), 1 placebo withdrawal followed 1.5 MU 3 times per week, 24 weeks	18/19	48/48	Inflammation scores	7±4	9±5	-0.47 (-1.13; 0.18)
	Recombinant interferon	18/19	48/48	Inflammation scores	7±4	8±5	-0.24 (-0.88; 0.41)

Appendix E. Table 6. Levels of viral load, biochemical, or histologic outcomes after antiviral drugs in adults with chronic hepatitis B

Author Active Drug, Daily/Weekly Dose Combined Active Drug, Daily/Weekly Dose, Length of Active Treatment in Weeks	Control Intervention, Daily/Weekly Dose Length of Control Intervention	Patients in Active/Control Group	Time to Measure Outcomes from Randomization (Weeks) After Active/Control Treatments	Outcome	Mean± Standard Deviation After Active Treatment	Mean± Standard Deviation After Control Treatment	Mean Difference (95% CI)
	alpha 2b (Intron), 2 placebo withdrawal followed 5 MU 3 times per week, 24 weeks						
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1 placebo withdrawal followed 1.5 MU three times per week, 24 weeks	Recombinant interferon alpha 2b (Intron), 2 placebo withdrawal followed 5 MU 3 times per week, 24 weeks	19/19	48/48	Inflammation scores	9±5	8±5	0.21 (-0.43; 0.85)
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1 1.5 MU 3 times per week Prednisone, 3750mg for 2 weeks, 25 mg for 2 weeks, then 2 weeks drug free interval, 24 weeks	Recombinant interferon alpha 2b (Intron), 1 placebo withdrawal followed 1.5 MU 3 times per week, 24 weeks	18/19	48/48	Fibrosis scores	4±1	4±1	0.17 (-0.48; 0.81)
	Recombinant interferon alpha 2b (Intron), 2 placebo withdrawal followed 5 MU 3 times per week, 24 weeks	18/19	48/48	Fibrosis scores	4±1	3±2	0.56 (-0.10; 1.21)
Reichen, 1994[90] Recombinant interferon alpha 2b (Intron), 1 placebo withdrawal followed 1.5 MU 3 times per week, 24 weeks	Recombinant interferon alpha 2b (Intron), 2 placebo withdrawal followed 5 MU 3 times per week, 24 weeks	19/19	48/48	Fibrosis scores	4±1	3±2	0.40 (-0.25; 1.04)
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Baseline, 48 weeks	271/271	48/48	Reduction in HBV DNA log copies/ml			**-7.20 (-6.90; -7.50)**
Marcellin, 2004[57] Peginterferon alfa-2a (Pegasys, Roche), 26 180 mg once weekly, 48 weeks	48 weeks	181/181	48/48	Change in HBV DNA from baseline after Interferon+ LAM in log copies/ml			**-5.00 (-5.30; -4.70)**

Appendix E. Table 6. Levels of viral load, biochemical, or histologic outcomes after antiviral drugs in adults with chronic hepatitis B

Author Active Drug, Daily/Weekly Dose Combined Active Drug, Daily/Weekly Dose, Length of Active Treatment in Weeks	Control Intervention, Daily/Weekly Dose Length of Control Intervention	Patients in Active/Control Group	Time to Measure Outcomes from Randomization (Weeks) After Active/Control Treatments	Outcome	Mean± Standard Deviation After Active Treatment	Mean± Standard Deviation After Control Treatment	Mean Difference (95% CI)
		181/181	48/48	Change in HBV DNA from baseline after Interferon in log copies/ml			**-4.10 (-4.50; -3.80)**
		181/181	72/72	Change in HBV DNA in log copies/ml from baseline after Interferon			**-2.30 (-1.90; -2.70)**
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26 180 mg weekly Placebo, 48 weeks	Baseline, 48 weeks	271/272	48/48	Reduction in HBV DNA log copies/ml			**-4.50 (-4.10; -4.90)**
Lau, 2005[56] Peginterferon alfa-2a (Pegasys, Roche, 26 180 mg weekly Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100mg/day, 48 weeks	Baseline, 48 weeks	271/271	72/72	Reduction in HBV DNA log copies/ml			**-2.70 (-2.20; -3.10)**
Lau, 2005[56] peginterferon alfa-2a (Pegasys, Roche, 26 180 mg weekly Placebo, 48 weeks	Baseline, 48 weeks	271/272	72/72	Reduction in HBV DNA log copies/ml			**-2.40 (-2.00; -2.80)**
Van Zonneveld, 2006[125] Peg-interferon α-2b, 14 100 microg/week until week 32, then 50mg/week Lamivudine, 100mg/daily, 52 weeks	Peg-interferon α-2b+Placebo, 14/ 100 microg/week, 52 weeks	152/155	52/52	Change in fibrosis score	0±1	0±2	-0.14 (-0.36; 0.09)
		152/155	52/52	Necroinflammatory score	4±2	4±2	-0.21 (-0.43; 0.01)
		152/155	52/52	Fibrosis score	3±2	3±2	0.06 (-0.17; 0.28)
		152/155	52/52	Change in Necroinflammatory score	-2±3	-2±2	-0.08 (-0.31; 0.14)
		152/155	52/52	HBV DNA decline in log	5±2	2±2	**1.36 (1.11; 1.61)**

Appendix E. Table 6. Levels of viral load, biochemical, or histologic outcomes after antiviral drugs in adults with chronic hepatitis B

Author Active Drug, Daily/Weekly Dose Combined Active Drug, Daily/Weekly Dose, Length of Active Treatment in Weeks	Control Intervention, Daily/Weekly Dose Length of Control Intervention	Patients in Active/Control Group	Time to Measure Outcomes from Randomization (Weeks) After Active/Control Treatments	Outcome	Mean± Standard Deviation After Active Treatment	Mean± Standard Deviation After Control Treatment	Mean Difference (95% CI)
Hadziyannis, 2005[98] Placebo, 0 placebo after 48 weeks of adefovir therapy, 96 weeks	Adefovir dipivoxil, 10 mg daily after 48 weeks of placebo therapy, 96 weeks	40/60	96/96	Change in serum ALT, IU/liter	-63±131	-130±213	0.36 (-0.04; 0.77)
		40/60	96/96	Change in Knodell inflammatory scores	-1±2	-2±4	**0.43 (0.02; 0.83)**
		40/60	96/96	Change in total Knodell scores	-1±2	-2±5	0.26 (-0.15; 0.66)
		40/60	96/96	Change in Knodell fibrosis scores	0±1	0±1	-0.31 (-0.71; 0.10)
		40/60	96/96	Change in serum HBV DNA level in log copies/ml	-1±1	-4±1	**2.10 (1.60; 2.59)**
Leung, 2001 [106] Lamivudine , 100 mg/day, 156 weeks	Baseline, 0 weeks	58/58	156/0	Median ALT (range) X ULN	1±2	2±3	-0.36 (-0.72; 0.01)
		58/58	156/0	Median HBV DNA (range) in pg/mL	1±58	59±149	**-0.52 (-0.89; -0.15)**
Kweon, 2001[113] lamivudine, 100 mg/day, 52 weeks	Placebo, 52 weeks	47/33	52/52	ALT (IU/l)	61±55	104±109	**-0.53 (-0.98; -0.07)**
		47/33	52/52	HAI score: Portal inflammation	2±1	3±1	**-0.65 (-1.11; -0.19)**
		47/33	52/52	HAI score: Periportal inflammation	2±1	3±1	**-0.64 (-1.10; -0.19)**
		47/33	52/52	Population of activated hepatic stellate cells and collagen synthesis as measured by immunohistochemistry for a-SMA	1±0	1±0	**-4.66 (-5.51; -3.80)**
		47/33	52/52	HAI score: lobular necrosis	1±1	2±1	**-0.46 (-0.91; -0.01)**
		47/33	52/52	Total Knodell score	7±3	10±3	**-0.81 (-1.27; -0.34)**
		47/33	52/52	HAI score: fibrosis	2±1	2±1	-0.39 (-0.84; 0.06)
		47/33	52/52	HBV DNA (pg/ml)	33±120	71±111	-0.32 (-0.77; 0.12)
Hadziyannis, 2003[41] Adefovir dipivoxil, 10 mg daily, 48 weeks	Placebo, 48 weeks	123/61	48/48	Change in Knodell necroinflammatory score	-3±3	0±3	**-1.23 (-1.56; -0.90)**

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		123/61	48/48	Change in total Knodell score	-4±3	0±4	**-1.24 (-1.57; -0.91)**
		123/61	48/48	Change in Knodell fibrosis score	0±1	0±1	**-0.52 (-0.83; -0.21)**
Marcellin, 2003[42] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	171/173	48/48	Change in ALT	-92±167	-74±128	-0.12 (-0.33; 0.09)
	Placebo, 48 weeks	171/167	48/48	Change in ALT	-92±167	-23±141	**-0.45 (-0.66; -0.23)**
Marcellin, 2003[42] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo,, 48 weeks	173/167	48/48	Change in ALT	-74±128	-23±141	**-0.38 (-0.60; -0.17)**
Marcellin, 2003[42] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	171/173	48/48	Change in Knodell necroinflammatory activity scores	-3±3	-3±3	0.18 (-0.03; 0.39)
	Placebo, 48 weeks	171/167	48/48	Change in Knodell necroinflammatory activity scores	-3±3	0±3	**-0.77 (-0.99; -0.55)**
Marcellin, 2003[42] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	173/167	48/48	Change in Knodell necroinflammatory activity scores	-3±3	0±3	**-0.95 (-1.17; -0.72)**
Marcellin, 2003[42] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	171/173	48/48	Change in Knodell fibrosis scores	0±1	0±1	0.17 (-0.04; 0.38)
	Placebo, 48 weeks	171/167	48/48	Change in Knodell fibrosis scores	0±1	0±1	-0.20 (-0.41; 0.01)
Marcellin, 2003[42] Adefovir dipivoxil, 30 mg/day, 48 weeks	Placebo, 48 weeks	173/167	48/48	Change in Knodell fibrosis scores	0±1	0±1	**-0.37 (-0.59; -0.16**)
Marcellin, 2003[42] Adefovir dipivoxil, 10 mg/day, 48 weeks	Adefovir dipivoxil, 30 mg/day, 48 weeks	171/173	48/48	Change in serum HBV DNA log copies/ml	-4±2	-4±2	**0.54 (0.32; 0.76)**
	Placebo, 48 weeks	171/167	48/48	Change in serum HBV DNA log copies/ml	-4±2	-1±1	**-1.74 (-1.99; -1.49)**
Marcellin, 2003[42] Adefovir dipivoxil, 30 mg/day , 48 weeks	Placebo, 48 weeks	173/167	48/48	Change in serum HBV DNA log copies/ml	-4±2	-1±1	**-2.34 (-2.62; -2.07)**

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Perrillo, 2004[58] Adefovir dipivoxil, 10 mg/day for 52 weeks Lamivudine, 100mg/day for at least 6 months, 52 weeks	Lamivudine, 100 mg/day, 52 weeks	46/49	52/52	Change from baseline in ALT level (IU/L)	-90±160	-44±132	-0.31 (-0.72; 0.09)
		46/49	52/52	Median HBV DNA level at baseline, log10 copies/mL	9±1	9±1	0.38 (-0.02; 0.79)
		46/49	52/52	Median change from baseline in HBV DNA level	-5±2	0±4	**-1.63 (-2.10; -1.17)**
Peters, 2004[43] Adefovir dipivoxil, 10 mg/day Lamivudine, 100mg/day, 48 weeks	Lamivudine, 100 mg/day, 48 weeks	20/19	48/48	Change in serum ALT level	-49±82	0±31	**-0.78 (-1.43; -0.12)**
	Adefovir dipivoxil, 10 mg/day, 48 weeks	20/19	48/48	Change in serum ALT level	-49±82	-88±122	0.38 (-0.26; 1.01)
Peters, 2004[43] Lamivudine, 100 mg/day, 48 weeks	Adefovir dipivoxil, 10 mg/day, 48 weeks	19/19	48/48	Change in serum ALT level	0±31	-88±122	**0.99 (0.31; 1.66)**
Peters, 2004[43] Adefovir dipivoxil, 10 mg/day Lamivudine, 100mg/day, 48 weeks	Lamivudine, 100 mg/day, 48 weeks	20/19	16/16	Time-weighted average change from baseline in serum HBV DNA level	-2±1		**-5.51 (-6.91; -4.11)**
	Adefovir dipivoxil, 10 mg/day, 48 weeks	20/19	16/16	Time-weighted average change from baseline in serum HBV DNA level	-2±1	-3±1	0.24 (-0.39; 0.87)
Peters, 2004[43] Lamivudine, 100 mg/day, 48 weeks	Adefovir dipivoxil, 10 mg/day, 48 weeks	19/19	16/16	Time-weighted average change from baseline in serum HBV DNA level		-3±1	**4.33 (3.14; 5.51)**
Peters, 2004[43] Adefovir dipivoxil, 10 mg/day Lamivudine, 100mg/day, 48 weeks	Lamivudine, 100 mg/day, 48 weeks	20/19	48/48	Time-weighted average change from baseline in serum HBV DNA level	-3±1		**-5.42 (-6.80; -4.03**)
	Adefovir dipivoxil, 10 mg/day, 48 weeks	20/19	48/48	Time-weighted average change from baseline in serum HBV DNA level	-3±1	-3±1	0.33 (-0.30; 0.96)

Appendix E. Table 6. Levels of viral load, biochemical, or histologic outcomes after antiviral drugs in adults with chronic hepatitis B

Author Active Drug, Daily/Weekly Dose Combined Active Drug, Daily/Weekly Dose, Length of Active Treatment in Weeks	Control Intervention, Daily/Weekly Dose Length of Control Intervention	Patients in Active/Control Group	Time to Measure Outcomes from Randomization (Weeks) After Active/Control Treatments	Outcome	Mean± Standard Deviation After Active Treatment	Mean± Standard Deviation After Control Treatment	Mean Difference (95% CI)
Peters, 2004[43] Lamivudine, 100 mg/day, 48 weeks	Adefovir dipivoxil, 10 mg/day, 48 weeks	19/19	48/48	Time-weighted average change from baseline in serum HBV DNA level		-3±1	**4.14 (2.99; 5.29)**
Peters, 2004[43] Adefovir dipivoxil, 10 mg/day Lamivudine, 100mg/day, 48 weeks	lamivudine, 100 mg/day, 48 weeks	20/19	16/16	Change in serum HBV DNA log10 copies	-3±1	0±0	**-5.92 (-7.41; -4.43)**
	Adefovir dipivoxil, 10 mg/day, 48 weeks	20/19	16/16	Change in serum HBV DNA log10 copies	-3±1	-3±1	0.20 (-0.43; 0.83)
Peters, 2004[43] Lamivudine, 100 mg/day, 48 weeks	Adefovir dipivoxil, 10 mg/day, 48 weeks	19/19	16/16	Change in serum HBV DNA log10 copies		-3±1	**4.48 (3.27; 5.70)**
Peters, 2004[43] Adefovir dipivoxil, 10 mg/day Lamivudine, 100mg/day, 48 weeks	Lamivudine, 100 mg/day, 48 weeks	20/19	48/48	Change in serum HBV DNA log 10 copies	-3±1	0±1	**-3.09 (-4.03; -2.14)**
	Adefovir dipivoxil, 10 mg/day, 48 weeks	20/19	48/48	Change in serum HBV DNA log 10 copies	-3±1	-4±1	0.43 (-0.21; 1.06)
Peters, 2004[43] Lamivudine, 100 mg/day, 48 weeks	Adefovir dipivoxil, 10 mg/day, 48 weeks	19/19	48/48	Change in serum HBV DNA log10 copies	0±1	-4±1	**3.09 (2.13; 4.05)**
Marcellin, 2004[57] Lamivudine (Epivir-HBV or Zeffix, GlaxoSmithKline), 100 mg once daily, 48 weeks	48 weeks	181/181	48/48	Change from baseline in HBV DNA after LAM log copies/ml			**-4.20 (-4.50; -3.90)**
	48 weeks	181/181	72/72	Change in HBV DNA in log copies/ml from baseline after LAM			**-1.60 (-1.20; -2.00)**
Hadziyannis, 2005[98] Adefovir dipivoxil, 10 mg daily continued-adefovir therapy for the previous treatment for 48 weeks, 96 weeks	Placebo after 48 weeks of adefovir therapy, 96 weeks	80/40	96/96	Change in serum ALT, IU/liter	-98±118	-63±131	-0.29 (-0.67; 0.10)
	Adefovir dipivoxil, 10 mg daily after 48 weeks of placebo therapy , 96 weeks	80/60	96/96	Change in serum ALT, IU/liter	-98±118	-130±213	0.19 (-0.14; 0.53)
	Placebo after 48 weeks of adefovir therapy, 96 weeks	80/40	114/96	Change in serum ALT, IU/liter	-97±120	-63±131	-0.27 (-0.66; 0.11)
	Adefovir dipivoxil, 10	80/60	114/96	Change in serum	-97±120	-130±213	0.20 (-0.14; 0.53)

Appendix E. Table 6. Levels of viral load, biochemical, or histologic outcomes after antiviral drugs in adults with chronic hepatitis B

Author Active Drug, Daily/Weekly Dose Combined Active Drug, Daily/Weekly Dose, Length of Active Treatment in Weeks	Control Intervention, Daily/Weekly Dose Length of Control Intervention	Patients in Active/Control Group	Time to Measure Outcomes from Randomization (Weeks) After Active/Control Treatments	Outcome	Mean± Standard Deviation After Active Treatment	Mean± Standard Deviation After Control Treatment	Mean Difference (95% CI)
	mg daily after 48 weeks of placebo therapy, 96 weeks			ALT, IU/liter			
	Placebo after 48 weeks of adefovir therapy, 96 weeks	80/40	96/96	Change in Knodell inflammatory scores	-4±3	-1±2	**-1.37 (-1.78; -0.95)**
	Adefovir dipivoxil, 10 mg daily after 48 weeks of placebo therapy , 96 weeks	80/60	96/96	Change in Knodell inflammatory scores	-4±3	-2±4	**-0.61 (-0.95; -0.27)**
	Placebo after 48 weeks of adefovir therapy, 96 weeks	80/40	96/96	Change in Knodell scores	-5±3	-1±2	**-1.34 (-1.75; -0.92)**
	Adefovir dipivoxil, 10 mg daily after 48 weeks of placebo therapy, 96 weeks	80/60	96/96	Change in Knodell scores	-5±3	-2±5	**-0.62 (-0.96; -0.27)**
	Placebo after 48 weeks of adefovir therapy, 96 weeks	80/40	96/96	Change in Knodell fibrosis scores	0±1	0±1	0.09 (-0.29; 0.47)
	Adefovir dipivoxil, 10 mg daily after 48 weeks of placebo therapy, 96 weeks	80/60	96/96	Change in Knodell fibrosis scores	0±1	0±1	-0.21 (-0.55; 0.12)
	Placebo after 48 weeks of adefovir therapy, 96 weeks	80/40	96/96	Change in serum HBV DNA level in log copies/ml	-3±1	-1±1	**-1.67 (-2.11; -1.24)**
	Adefovir dipivoxil, 10 mg daily after 48 weeks of placebo therapy, 96 weeks	80/60	96/96	Change in serum HBV DNA level in log copies/ml	-3±1	-4±1	0.32 (-0.02; 0.66)
	Placebo after 48 weeks of adefovir therapy, 96 weeks	80/40	114/96	Change in serum HBV DNA level— log copies/ml	-3±1	-1±1	**-1.65 (-2.08; -1.22)**
	Adefovir dipivoxil, 10	80/60	114/96	Change in serum HBV	-3±1	-4±1	0.25 (-0.09; 0.58)

Appendix E. Table 6. Levels of viral load, biochemical, or histologic outcomes after antiviral drugs in adults with chronic hepatitis B

Author Active Drug, Daily/Weekly Dose Combined Active Drug, Daily/Weekly Dose, Length of Active Treatment in Weeks	Control Intervention, Daily/Weekly Dose Length of Control Intervention	Patients in Active/Control Group	Time to Measure Outcomes from Randomization (Weeks) After Active/Control Treatments	Outcome	Mean± Standard Deviation After Active Treatment	Mean± Standard Deviation After Control Treatment	Mean Difference (95% CI)
	mg daily after 48 weeks of placebo therapy, 96 weeks			DNA level in log copies/ml			
Lau, 2005[56] Lamivudine (Epivir-HBV or Zeffix, Glaxo-SmithKline), 100 mg/day, 48 weeks	Baseline, baseline, 48 weeks	271/272	48/48	Reduction in HBV DNA log copies/ml			**-5.80 (-5.40; -6.10)**
		271/272	72/72	Reduction in HBV DNA log copies/ml			**-1.90 (-1.50; -2.30)**
Lai, 2005[72] Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 500 mg/day (both 400mg or 600 mg/day) Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100mg/day, 52 weeks	Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100 mg/day, 52 weeks	41/19	52/52	Mean change in HBV DNA levels from baseline (log 10 copies/mL)	-6±2	-5±3	**-0.59 (-1.14; -0.03)**
	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 500 mg/day, 52 weeks	41/44	52/52	Mean change in HBV DNA levels from baseline (log 10 copies/mL)	-6±2	-6±2	0.01 (-0.42; 0.43)
Lai, 2005 [72] Lamivudine GlaxoSmithKline (Research Triangle Park, NC), 100 mg/day, 52 weeks	Telbivudine Idenix Pharmaceuticals Inc (Cambridge, MA), 500 mg/day, 52 weeks	19/44	52/52	Mean change in HBV DNA levels from baseline (log 10 copies/mL)	-5±3	-6±2	**0.62 (0.07; 1.17)**
Chang, 2005[76] Entecavir, 1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, total 48 weeks	42/47	24/24	Reduction in HBV DNA by Roche PCR assay, (log 10 copies/mL	-4±2	-4±2	-0.24 (-0.66; 0.17)
	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	42/47	24/24	Reduction in HBV DNA by Roche PCR assay, (log 10 copies/mL	-4±2	-2±2	**-1.39 (-1.86; -0.93)**
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, 48 weeks	42/45	24/24	Reduction in HBV DNA by Roche PCR assay, (log 10 copies/mL	-4±2	-1±2	**-1.94 (-2.45; -1.43)**
Chang, 2005[76] Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine,	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, 48	47/47	24/24	Reduction in HBV DNA by Roche PCR assay, (log 10	-4±2	-2±2	**-1.00 (-1.43; -0.57)**

Appendix E. Table 6. Levels of viral load, biochemical, or histologic outcomes after antiviral drugs in adults with chronic hepatitis B

Author Active Drug, Daily/Weekly Dose Combined Active Drug, Daily/Weekly Dose, Length of Active Treatment in Weeks	Control Intervention, Daily/Weekly Dose Length of Control Intervention	Patients in Active/Control Group	Time to Measure Outcomes from Randomization (Weeks) After Active/Control Treatments	Outcome	Mean± Standard Deviation After Active Treatment	Mean± Standard Deviation After Control Treatment	Mean Difference (95% CI)
total 48 weeks	weeks			copies/mL			
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, 48 weeks	47/45	24/24	Reduction in HBV DNA by Roche PCR assay, (log 10 copies/mL	-4±2	-1±2	**-1.49 (-1.95; -1.03)**
Chang, 2005[76] Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, 48 weeks	47/45	24/24	Reduction in HBV DNA by Roche PCR assay, (log 10 copies/mL	-2±2	-1±2	**-0.57 (-0.98; -0.15)**
Chang, 2005[76] Entecavir, 1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, 48 weeks	42/47	48/48	Reduction in HBV DNA by Roche PCR assay, (log 10 copies/mL	-5±2	-4±2	-0.31 (-0.73; 0.11)
	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, 48 weeks	42/47	48/48	Reduction in HBV DNA by Roche PCR assay, (log 10 copies/mL	-5±2	-3±2	**-1.24 (-1.69; -0.78)**
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, 48 weeks	42/45	48/48	Reduction in HBV DNA by Roche PCR assay, (log10 copies/mL	-5±2	-1±3	**-1.59 (-2.08; -1.11)**
Chang, 2005[76] Entecavir, 0.5 mg/day after at least 24 weeks of lamivudine, 48 weeks	Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, total 48 weeks	47/47	48/48	Reduction in HBV DNA by Roche PCR assay,(log10 copies/mL	-4±2	-3±2	**-0.78 (-1.20; -0.36)**
	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, 48 weeks	47/45	48/48	Reduction in HBV DNA by Roche PCR assay, (log 10 copies/mL	-4±2	-1±3	**-1.23 (-1.67; -0.78)**
Chang, 2005[76] Entecavir, 0.1 mg/day after at least 24 weeks of lamivudine, 48 weeks	Lamivudine, 100 mg/day after at least 24 weeks of lamivudine, 48 weeks	47/45	48/48	Reduction in HBV DNA by Roche PCR assay, (log 10 copies/mL	-3±2	-1±3	**-0.62 (-1.04; -0.20)**

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Author Active Drug, Daily/Weekly Dose Combined Active Drug, Daily/Weekly Dose, Length of Active Treatment in Weeks	Control Intervention, Daily/Weekly Dose Length of Control Intervention	Patients in Active/Control Group	Time to Measure Outcomes from Randomization (Weeks) After Active/Control Treatments	Outcome	Mean± Standard Deviation After Active Treatment	Mean± Standard Deviation After Control Treatment	Mean Difference (95% CI)
Chang, 2006[73] Entecavir (Baraclude, Bristol-Myers Squibb), 0.5 mg/day, 52 weeks	Lamivudine (Epivir-HBV, GlaxoSmithKline), 100 mg/day, 52 weeks	354/355	52/52	Mean change in HBV DNA from baseline by PCR assay in log copies/ml	-7±2	-5±3	**-0.65 (-0.80; -0.50)**
Lai, 2006[74] Entecavir (Baraclude, Bristol-Myers Squibb), 0.5 mg/day, 52 weeks	Lamivudine (Epivir-HBV, GlaxoSmithKline), 100 mg/day, 52 weeks	325/313	52/52	Mean change in HBV DNA level from baseline by PCR assay in log copies/ml	-5±2	-4±2	**-0.28 (-0.43; -0.12)**
Sherman, 2006[75] Entecavir, 1 mg/day, 63 weeks	Lamivudine, 100 , 52 weeks	141/145	63/52	Mean change HBV DNA from baseline by PCR assay, log10 copies/mL	-5±2	0±2	**-2.20 (-2.49; -1.91)**
Chan, 2007[44] telbivudine Idenix Pharmaceuticals, Cambridge, MA, 600 mg/day in 3 tablets, 24 weeks	Adefovir (Hepsera, Gilead Sciences, Foster City, CA), 10 mg/day, 24 weeks	45/91	52/52	Adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site) Mean HBV DNA, log 10 copies/mL			**-0.84 (-1.49; -0.19)**
		45/91	24/24	Change from baseline in mean HBV DNA, log 10 copies/mL	-6±1	-5±2	**-0.73 (-1.09; -0.36)**
		45/91	24/24	Change from baseline in mean HBV DNA, log 10 copies/mL adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site)			**-1.46 (-2.01; -0.91)**
		45/91	52/52	Adjusted for baseline covariates (baseline HBV DNA level, age, body mass index, sex, and study site)			**-0.84 (-1.49; -0.19)**

Appendix E. Table 6. Levels of viral load, biochemical, or histologic outcomes after antiviral drugs in adults with chronic hepatitis B

Author Active Drug, Daily/Weekly Dose Combined Active Drug, Daily/Weekly Dose, Length of Active Treatment in Weeks	Control Intervention, Daily/Weekly Dose Length of Control Intervention	Patients in Active/Control Group	Time to Measure Outcomes from Randomization (Weeks) After Active/Control Treatments	Outcome	Mean± Standard Deviation After Active Treatment	Mean± Standard Deviation After Control Treatment	Mean Difference (95% CI)
				Change from baseline in mean HBV DNA, log10 copies/mL			
Lai, 1998[50] Lamivudine , 25 mg/day, 48 weeks	Lamivudine , 100 mg/day, 48 weeks	142/143	48/48	Knodell score	6±3	5±3	**0.33 (0.10; 0.57)**
	Placebo, 48 weeks	142/73	48/48	Knodell score	6±3	8±4	**-0.59 (-0.88; -0.31)**
Lai, 1998[50] Lamivudine , 100 mg/day, 48 weeks	Placebo, 48 weeks	143/73	48/48	Knodell score	5±3	8±4	**-0.89 (-1.18; -0.60)**

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

(A) Adefovir monotherapy (L-nucleotide analogue)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus placebo [41,42]						
Subjects not completing study/treatment	`	26 / 345* (7.5) (10 and 30 mg)	13 / 170* (7.6)	0 [-5; 5]	0.99 [0.52; 1.87]	48 weeks
Any adverse event	1	94 / 123 (76.4)	45 / 61 (73.7)	3 [-11; 16]	1.04 [0.87; 1.24]	
Severe adverse event (grade III or IV)	2	24 / 294 (8.2)	19 / 228 (8.3)	0 [-6; 6]	0.95 [0.45; 2.01]	
AE leading to discontinuation of study drug	2	4 / 294 (1.4)	1 / 228 (<1)	1 [-1; 3]	2.34 [0.37; 14.75]	
Treatment-related adverse events for 10 mg dose (Gilead Sciences package insert)						
Asthenia	2	38 / 294 (12.9)	32 / 228 (14.0)	-1 [-7; 5]	0.92 [0.59; 1.43]	48 weeks
Headache	2	26 / 294 (8.8)	23 / 228 (10.1)	-1 [-6; 4]	0.88 [0.51; 1.49]	
Abdominal pain	2	26 / 294 (8.8)	25 / 228 (11.0)	-2 [-7; 3]	0.81 [0.48; 1.36]	
Nausea	2	15 / 294 (5.1)	18 / 228 (7.9)	-3 [-7; 2]	0.65 [0.33; 1.25]	
Flatulence	2	12 / 294 (4.1)	9 / 228 (3.9)	0 [-3; 4]	1.03 [0.44; 2.41]	
Diarrhea	2	9 / 294 (3.1)	9 / 228 (3.9)	-1 [-4; 2]	0.78 [0.31; 1.92]	
Dyspepsia	2	12 / 294 (4.1)	5 / 228 (2.2)	1 [-2; 4]	1.40 [0.47; 4.11]	
Other adverse events						
Pharyngitis	2	67 / 294 (22.8)	68 / 228 (29.8)	-6 [-13; 2]	0.80 [0.60; 1.07]	48 weeks
Flu-like syndrome	2	41 / 294 (13.9)	44 / 228 (19.3)	-5 [-14; 3]	0.70 [0.41; 1.22]	
Back pain	2	23 / 294 (7.8)	15 / 228 (6.6)	1 [-4; 5]	1.13 [0.59; 2.17]	
Versus lamivudine, subjects with lamivudine resistance [43]						
Subjects not completing study/treatment	1	1 / 20** (5)	1 / 19 (5.3)	0 [-14; 14]	0.95 [0.06; 14.13]	48 weeks
Any adverse event	1	18 / 19 (94.7)	19 / 19 (100)	-5 [-19; 8]	0.95 [0.82; 1.09]	
Serious adverse event	1	3 / 19 (15.8)	1 / 19 (5.3)	11 [-9; 30]	3.0 [0.34; 26.3]	
AE leading to discontinuation of study drug	1	0 / 19	0 / 19	0	-	
Asthenia	1	9 / 19 (47.4)	6 / 19 (31.6)	16 [-15; 46]	1.50 [0.66; 3.39]	
Headache	1	5 / 19 (26.3)	5 / 19 (26.3)	0	1.00 [0.35; 2.90]	
Abdominal pain	1	4 / 19 (21)	5 / 19 (26.3)	-5 [-32; 22]	0.80 [0.25; 2.53]	
Diarrhea	1	2 / 19 (10.5)	6 / 19 (31.6)	-21 [-46; 4]	0.33 [0.08; 1.45]	
Pharyngitis		5 / 19 (26.3)	6 / 19 (31.6)	-5 [-34; 24]	0.83 [0.31; 2.27]	
Versus telbivudine [44]						
Subjects not completing study/treatment	1	2 / 45 (4.4)	2 / 45 (4.4)	0 [-9; 9]	1.00 [0.13; 7.43]	52 weeks
Any adverse event	1	27 / 44 (61.4)	34 / 45 (75.6)	-14 [-33; 5]	0.81 [0.61; 1.08]	
Serious adverse event	1	NR	NR	-	-	
AE leading to discontinuation of study drug	1	0 / 44	0 / 45	0	-	
Upper respiratory tract infection	1	5 / 44 (11.4)	5 / 45 (11.1)	0 [-13; 13]	1.02 [0.32; 3.29]	
Headache	1	3 / 44 (6.8)	5 / 45 (11.1)	-4 [-16; 8]	0.61 [0.16; 2.41]	
Diarrhea	1	1 / 44 (2.3)	6 / 45 (13.3)	-11 [-22; 0]	0.17 [0.02; 1.36]	
Pharyngitis	1	5 / 44 (11.4)	1 / 45 (2.2)	9 [-1; 19]	5.11 [0.62; 42.03]	
Influenza	1	3 / 44 (6.8)	5 / 45 (11.1)	-4 [-16; 8]	0.61 [0.16; 2.41]	

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Back pain		3 / 44 (6.8)	6 / 45 (13.3)	-7 [-19; 6]	0.51 [0.14; 1.92]	
Versus adefovir, then switched to telbivudine[44]						
Subjects not completing study/treatment	1	2 / 45 (4.4)	0 / 46	4 [-3; 12]	5.34 [0.25; 114.49]	52 weeks
Any adverse event	1	27 / 44 (61.4)	31 / 46 (67.4)	-6 [-26; 14]	0.91 [0.67; 1.24]	
Serious adverse event	1	NR	NR			
AE leading to discontinuation of study drug	1	0 / 44	0 / 46	0	-	
Upper respiratory tract infection	1	5 / 44 (11.4)	6 / 46 (13)	-2 [-15; 12]	0.87 [0.29; 2.65]	
Headache	1	3 / 44 (6.8)	6 / 46 (13)	-6 [-18; 6]	0.52 [0.14; 1.96]	
Diarrhea	1	1 / 44 (2.3)	5 / 46 (10.9)	-9 [-19; 1]	0.21 [0.03; 1.72]	
Pharyngitis	1	5 / 44 (11.4)	2 / 46 (4.3)	7 [-4; 18]	2.61 [0.53; 12.78]	
Influenza	1	3 / 44 (6.8)	4 / 46 (8.7)	-2 [-13; 9]	0.78 [0.19; 3.31]	
Back pain	1	3 / 44 (6.8)	3 / 46 (6.5)	0 [-10; 11]	1.05 [0.22; 4.91]	

* Includes subjects not receiving any study medication
** Includes 1 subject not receiving any study medication

(B) Adefovir versus combination therapy

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus combined lamivudine and adefovir[43]						
Subjects not completing study/ treatment	1	1 / 20* (5)	0 / 20	5 [-8; 18]	3.00 [0.13; 69.52]	48 weeks
Any adverse event	1	18 / 19 (94.7)	18 / 20 (90)	5 [-12; 21]	1.05 [0.88; 1.26]	
Serious adverse event	1	3 / 19 (15.8)	0 / 20	16 [-2; 34]	7.35 [0.40; 133.48}	
AE leading to discontinuation of study drug	1	0 / 19	0 / 20	-	-	
Asthenia	1	9 / 19 (47.4)	10 / 20 (50)	-3 [-34; 29]	0.95 [0.50; 1.81]	
Headache	1	5 / 19 (26.3)	6 / 20 (30)	-4 [-32; 25]	0.88 [0.32; 2.40]	
Abdominal pain	1	4 / 19 (21)	6 / 20 (30)	-9 [-36; 18]	0.70 [0.23; 2.10]	
Diarrhea	1	2 / 19 (10.5)	2 / 20 (10)	1 [-19; 20]	1.05 [0.16; 6.74]	
Pharyngitis	1	5 / 19 (26.3)	1 / 20 (5)	21 [-1; 43]	5.26 [0.68; 41.01]	

* Includes 1 subject not receiving any study medication

(C) Lamivudine monotherapy (L-nucleoside analog)

Adverse Event	Number of studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus placebo [46,48,50]						
Subjects not completing study/treatment	2	33 / 374 (8.8)	16 / 120 (13.3)	-1 [-7; 4]	0.87 [0.51; 1.49]	52-104 weeks
Any adverse event	1	224 / 285 (78.6)	56 / 73 (76.7)	2 [-9; 13]	1.02 [0.89; 1.18]	52 weeks
Serious adverse event	2	18 / 374 (4.8)	6 / 120 (5)	2 [-1; 4]	1.24 [0.53; 2.93]	52-104 weeks

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

Adverse Event	Number of studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Upper respiratory tract infection	1	100 / 285 (35.1)	21 / 73 (28.8)	6 [-5; 18]	1.22 [0.82; 1.81]	52 weeks
Upper respiratory tract symptoms	1	29 / 89 (32.6)	15 / 47 (31.9)	1 [-16; 17]	1.02 [0.28; 1.81]	104 weeks
Asthenia	2	49 / 355 (13.8)	28 / 144 (19.4)	-5 [-12; 3]	0.76 [0.49; 1.17]	52-68 weeks
Headache	3	57 / 444 (12.8)	23 / 191 (12)	-1 [-6; 5]	0.88 [0.56; 1.39]	52-104 weeks
Abdominal pain	1	45 / 285 (15.8)	9 / 73 (12.3)	3 [-5; 12]	0.95 [0.71; 1.28]	52 weeks
Diarrhea	1	44 / 285 (15.4)	7 / 73 (9.6)	6 [-2; 14]	1.61 [0.76; 3.43]	52 weeks
Nausea	2	21 / 355 (5.9)	12 / 144 (8.3)	-1 [-15; 13]	1.20 [0.17; 8.32]	52-68 weeks
Pyrexia	1	18 / 285 (6.3)	2 / 73 (2.7)	4 [-1; 8]	2.31 [0.55; 9.71]	52 weeks
Myalgia	1	0 / 71	6 / 70 (8.6)	-9 [-16; -2]	0.08 [0.00; 1.32]	68 weeks
Versus placebo, subjects refractory interferon therapy[47]						
Subjects not completing study/treatment	1	9 / 119 (7.6)	10 / 56 (17.9)	-10 [-21; 1]	0.42 [0.18; 0.98]	68 weeks
AE leading to discontinuation of study drug	1	1 / 119 (<1)	4 / 56 (7.1)	-6 [-13; 1]	0.12 [0.01; 1.03]	
Asthenia	1	18 / 119 (15.1)	10 / 56 (17.9)	-3 [-15; 9]	0.85 [0.42; 1.71]	
Headache	1	10 / 119 (8.4)	7 / 56 (12.5)	-4 [-14; 6]	0.67 [0.27; 1.67]	
Diarrhea	1	8 / 119 (6.7)	0 / 56	7 [2; 12]	8.08 [0.47; 137.48]	
Nausea	1	12 / 119 (10.1)	6 / 56 (10.7)	-1 [-10; 9]	0.94 [0.37; 2.38]	
Pyrexia	1	6 / 119 (5)	0 / 56	5 [0; 10]	6.18 [0.35; 107.73]	
Myalgia	1	13 / 119 (10.9)	3 / 56 (5.4)	6 [-3; 14]	2.04 [0.61; 6.87]	
Versus placebo, subjects with advanced liver disease[51]						
Any adverse event	1	335 / 436 (76.8)	178 / 215 (82.8)	-6 [-12; 0]	0.93 [0.86; 1.01]	32 months (median)
Serious adverse event	1	54 / 436 (12.4)	38 / 215 (17.7)	-5 [-11; 1]	0.70 [0.48; 1.03]	
AE leading to discontinuation of study drug		NR	NR	-	-	
Ear, nose, throat infections	1	97 / 436 (22.2)	44 / 215 (20.5)	2 [-5; 8]	1.09 [0.79; 1.49]	
Asthenia	1	65 / 436 (14.9)	42 / 215 (19.5)	-5 [-11; 2]	0.76 [0.54; 1.09]	
Headache	1	64 / 436 (14.7)	21 / 215 (9.8)	5 [0; 10]	1.50 [0.94; 2.39]	
Abdominal pain	1	77 / 436 (17.7)	43 / 215 (20.0)	-2 [-9; 4]	0.88 [0.63; 1.24]	
Diarrhea	1	33 / 436 (7.6)	29 / 215 (13.5)	-6 [-11; -1]	0.56 [0.35; 0.90]	
Cough	1	62 / 436 (14.2)	15 / 215 (7.0)	7 [3; 12]	2.04 [1.19; 3.50]	
Versus placebo, HBV antigen-negative/ pHBV DNA-positive (precore mutant) patient[49]						
Any adverse event	1	40 / 65 (61.5)	28 / 60 (46.7)	15 [-2 to 32]	1.32 [0.95 to 1.84]	26 weeks
Headache	1	12 / 65 (18.5)	10 / 60 (16.7)	2 [-12 to 15]	1.11 [0.52 to 2.37]	
Asthenia	1	8 / 65 (12.3)	8 / 60 (13.3)	-1 [-13 to 11]	0.92 [0.37 to 2.30]	
Abdominal pain	1	8 / 65 (12.3)	4 / 60 (6.7)	6 [-5 to 16]	1.85 [0.59 to 5.82]	
Versus entecavir (see below)						
Versus telbivudine (see below)						
Versus pegylated interferon-α-2a monotherapy[56,57]						
Subjects not completing treatment/study	2	71 / 456* (15.6)	45 / 453* (9.9)	6 [1; 10]	1.57 [1.10; 2.22]	72 weeks
Any adverse event	2	238 / 453 (52.5)	395 / 448 (88.2)	-36 [-43; -29]	0.59 [0.51; 0.69]	
Serious adverse event	2	10 / 453 (2.2)	21 / 448 (4.7)	-2 [-5; 0]	0.47 [0.22; 0.99]	

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

Adverse Event	Number of studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
AE leading to discontinuation of study drug	2	2 / 453 (<1)	21 / 448 (4.7)	-5 [-10; 1]	0.13 [0.20; 0.90]	
Dose modification due to AE	2	0 / 453	33 / 448 (7.4)	-7 [-10; -5]	0.03 [0.00; 0.22]	
Pyrexia	2	20 / 453 (4.4)	238 / 448 (53.1)	-50 [-60; -40]	0.08 [0.05; 0.13]	
Fatigue	2	70 / 453 (15.5)	182 / 448 (40.6)	-25 [-31; -20]	0.38 [0.30; 0.49]	
Myalgia	2	19 / 453 (4.2)	117 / 448 (26.1)	-22 [-26; -18]	0.16 [0.08; 0.33]	
Headache	2	41 / 453 (9.1)	118 / 448 (26.3)	-17 [-22; -12]	0.34 [0.25; 0.48]	
Alopecia	2	7 / 453 (1.5)	79 / 448 (17.6)	-16 [-21; -10]	0.09 [0.04; 0.20]	
Decreased appetite	2	11 / 453 (2.4)	71 / 448 (15.8)	-13 [-17; -10]	0.16 [0.08; 0.29]	
Dizziness	2	19 / 453 (4.2)	40 / 448 (8.9)	-5 [-8; -2]	0.47 [0.28; 0.80]	
Diarrhea	2	14 / 453 (3.1)	45 / 448 (10.0)	-7 [-10; -4]	0.31 [0.17; 0.56]	
Pruritus	2	9 / 453 (2.0)	35 / 448 (7.8)	-5 [-10; 0]	0.27 [0.12; 0.59]	
Nausea	2	15 / 453 (3.3)	38 / 448 (8.5)	-5 [-9; -2]	0.40 [0.16; 1.00]	
Arthralgia	2	13 / 453 (2.9)	51 / 448 (11.4)	-9 [-14; -3]	0.25 [0.14; 0.46]	
Rigors	2	0 / 453	29 / 448 (6.5)	-6 [-9; -4]	0.03 [0.00; 0.25]	
Injection-site reaction	2	0 / 453	34 / 448 (7.6)	-7 [-10; -4]	0.03 [0.00; 0.22]	
Gingival bleeding	1	1 / 272 (<1)	15 / 271 (5.5)	-5 [-8; -2]	0.07 [0.01; 0.50]	
Depression	1	4 / 272 (1.5)	13 / 271 (4.8)	-3 [-6; 0]	0.31 [0.10; 0.93]	

* Includes subjects not receiving any study medication

(D) Lamivudine versus combination therapy

Adverse Event	Number of studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus combined lamivudine and adefovir[58]						
Any adverse event	1	40 / 48 (83.3)	36 / 44 (81.8)	2 [-14; 17]	1.02 [0.84; 1.23]	52 weeks
Versus combined pegylated interferon-α-2a and lamivudine[56,57]						
Subjects not completing treatment / study	2	71 / 456* (15.6)	49 / 457* (10.7)	5 [1; 9]	1.45 [1.03; 2.03]	72 weeks
Any adverse event	2	238 / 453 (52.5)	395 / 450 (87.8)	-35 [-41; -29]	0.60 [0.52; 0.68]	
Serious adverse event	2	10 / 453 (2.2)	28 / 450 (6.2)	-4 [-7; -1]	0.36 [0.18; 0.73]	
AE leading to discontinuation of study drug	2	2 / 453 (<1)	19 / 450 (4.2)	-4 [-6; -2]	0.13 [0.03; 0.47]	
Dose modification due to AE	2	0 / 453	48 / 450 (10.7)	-10 [-15; -6]	0.02 [0.00; 0.15]	
Pyrexia	2	20 / 453 (4.4)	246 / 450 (54.7)	-50 [-55; -45]	0.08 [0.05; 0.12]	
Fatigue	2	70 / 453 (15.5)	176 / 450 (39.1)	-24 [-29; -18]	0.40 [0.31; 0.51]	
Myalgia	2	19 / 453 (4.2)	126 / 450 (28.0)	-24 [-28; -19]	0.15 [0.07; 0.33]	
Headache	2	41 / 453 (9.1)	115 / 450 (25.6)	-16 [-24; -7]	0.35 [0.25; 0.49]	
Alopecia	2	7 / 453 (1.5)	98 / 450 (21.8)	-19 [-35; -2]	0.07 [0.03; 0.15]	
Decreased appetite	2	11 / 453 (2.4)	60 / 450 (13.3)	-11 [-14; -7]	0.19 [0.10; 0.35]	
Dizziness	2	19 / 453 (4.2)	44 / 450 (9.8)	-5[-11; 0]	0.45[0.24; 0.84]	
Diarrhea	2	14 / 453 (3.1)	36 / 450 (8.0)	-5 [-8; -1]	0.39 [0.21; 0.71]	

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

Adverse Event	Number of studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Pruritus	2	9 / 453 (2.0)	37 / 450 (8.2)	-6 [-10; -2]	0.25 [0.12; 0.51]	
Nausea	2	15 / 453 (3.3)	40 / 450 (8.9)	-5 [-11; 0]	0.39 [0.13; 1.20]	
Arthralgia	2	13 / 453 (2.9)	51 / 450 (11.3)	-9 [-14; -3]	0.25 [0.14; 0.46]	
Rigors	2	0 / 453	32 / 450 (7.1)	-6 [-14; 2]	0.04 [0.01; 0.29]	
Injection-site reaction	2	0 / 453	36 / 450 (8.0)	-8 [-15; -2]	0.03 [0.00; 0.20]	
Gingival bleeding	1	1 / 272 (<1)	15 / 271 (5.5)	-5 [-8; -2]	0.07 [0.01; 0.50]	
Depression	1	4 / 272 (1.5)	16 / 450 (5.9)	-4 [-8; -1]	0.25 [0.08; 0.74]	
Versus combined pegylated interferon-α-2b and lamivudine see below[59]						
Subjects not completing treatment/study	1	2 / 50	2 / 50 (4)	0 [-8; 8]	1.00 [0.15; 6.82]	52 weeks
Subjects not completing post-treatment followup	1	13 / 50	7 / 50 (14)	12 [-4; 28]	1.86 [0.81; 4.26]	76 weeks
Serious adverse event	1	0 / 50	4 / 50 (8)	-8 [-16; 0]	0.11 [0.01; 2.01]	
AE leading to discontinuation of study drug	1	0 / 50	4 / 50 (8)	-8 [-16; 0]	0.11 [0.01; 2.01]	
Upper respiratory tract symptoms	1	19 / 50 (38)	37 / 50 (74)	-36 [-54; -18]	0.51 [0.35; 0.75]	
Pyrexia	1	2 / 50 (4)	36 / 50 (72)	-68 [-82; -54]	0.06 [0.01; 0.22]	
Alopecia	1	2 / 50 (4)	24 / 50 (48)	-44 [-59; -29]	0.08 [0.02; 0.33]	
Abdominal discomfort	1	13 / 50 (26)	22 / 50 (44)	-18 [-36; 0]	0.59 [0.34; 1.04]	
Malaise	1	7 / 50 (14)	22 / 50 (44)	-30 [-47; -13]	0.32 [0.15; 0.68]	
Headache	1	2 / 50 (4)	21 / 50 (42)	-38 [-53; -23]	0.10 [0.02; 0.38]	
Myalgia	1	2 / 50 (4)	13 / 50 (26)	-22 [-35; -9]	0.15[0.04; 0.65]	
Arthralgia	1	2 / 50 (4)	12 / 50 (24)	-20 [-33; -7]	0.17 [0.04; 0.71]	
Decreased appetite	1	0 / 50	12 / 50 (24)	-24 [-36; -12]	0.04 [0.00; 0.66]	
Injection-site reaction	1	0 / 50	12 / 50 (24)	-24 [-36; -12]	0.04 [0.00; 0.66]	
Allergic rashes	1	1 / 50 (2)	9 / 50 (18)	-16 [-27; -5]	0.11 [0.01; 0.84]	
Dizziness	1	1 / 50 (2)	8 / 50 (16)	-14 [-25; -3]	0.13 [0.02; 0.96]	
Nausea/diarrhea	1	3 / 50 (6)	7 / 50 (14)	-8 [-20; 4]	0.43 [0.12; 1.56]	
Weight loss >10%	1	1 / 50 (2)	7 / 50 (14)	-12 [-22; -2]	0.14 [0.02; 1.12]	
Versus combined interferon-α-2b and lamivudine[63 64-67]						
Subjects not completing treatment/study	5	21 / 267 (7.9)	18 / 257 (7)	0 [-6; 6]	0.98 [0.37; 2.64]	24-208 weeks
AE leading to discontinuation of study drug	4	3 / 192 (1.6)	8 / 181 (4.4)	-2 [-8; 3]	0.42 [0.08; 2.28]	52-208 weeks
Influenza-like symptoms[66]	1	12 / 75 (16)	47 / 76 (61.8)	-46 [-60; -32]	0.26 [0.15; 0.45]	100 weeks
Pyrexia[67]	1	6 / 84 (7.1)	46 / 76 (48.7)	-53 [-66; -41]	0.12 [0.05; 0.26]	24-52 weeks
Fatigue [67]	1	35 / 84 (41.7)	66 / 76 (86.8)	-45 [-58; -32]	0.48 [0.37; 0.63]	
Fatigue[66]	1	8 / 75 (10.7)	8 / 76 (10.5)	0 [-10; 10]	1.01 [0.40; 2.56]	100 weeks
Myalgia[67]	1	11 / 84 (13.1)	36 / 76 (47.4)	-34 [-48; -21]	0.28 [0.15; 0.50]	24-52 weeks
Arthralgia[67]	1	4 / 84 (4.8)	9 / 76 (11.8)	-7 [-16; 1]	0.40 [0.13; 1.25]	
Headache[67]	1	27 / 84 (32.1)	71 / 76 (93.4)	-61 [-73; -50]	0.34 [0.27; 0.47]	
Headache[66]	1	7 / 75 (9.3)	8 / 76 (10.5)	-1 [-11; 8]	0.89 [0.34; 2.32]	100 weeks
Nausea[67]	1	19 / 84 (22.6)	33 / 76 (43.4)	-21 [-35; -7]	0.52 [0.33; 0.83]	24-52 weeks

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

Adverse Event	Number of studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Nausea[66]	1	5 / 75 (6.7)	7 / 76 (9.2)	-3 [-11; 6]	0.72 [0.24; 2.18]	100 weeks
Alopecia[67]	1	8 / 84 (9.5)	30 / 76 (39.5)	-30 [-43; -17]	0.24 [0.12; 0.49]	24-52 weeks
Feeding problems / anorexia[67]	1	4 / 84 (4.8)	30 / 76 (39.5)	-35 [-47; -23]	0.12 [0.04; 0.33]	
Viral respiratory infections[67]	1	25 / 84 (29.8)	32 / 76 (42.1)	-12 [-27; 2]	0.71 [0.46; 1.08]	
Versus combined interferon-α-2b and lamivudine, subjects refractory interferon therapy[47]						
Subjects not completing treatment / study	1	9 / 119 (7.6)	10 / 63 (15.9)	-8 [-19; 2]	0.48 [0.20; 1.11]	68 weeks
AE leading; discontinuation of study drug	1	1 / 119 (<1)	1 / 63 (1.6)	-1 [-4; 3]	0.53 [0.03; 8.32]	
Pyrexia	1	6 / 119 (5)	38 / 63 (60.3)	-55 [-68; -43]	0.08 [0.04; 0.19]	
Fatigue	1	18 / 119 (15.1)	38 / 63 (60.3)	-45 [-59; -32]	0.25 [0.16; 0.40]	
Myalgia	1	13 / 119 (10.9)	18 / 63 (28.6)	-18 [-30; -5]	0.38 [0.20; 0.73]	
Headache	1	10 / 119 (8.4)	30 / 63 (47.6)	-39 [-53; -26]	0.18 [0.09; 0.34]	
Nausea	1	12 / 119 (10.1)	23 / 63 (36.5)	-26 [-39; -13]	0.28 [0.15; 0.52]	
Alopecia	1	1 / 119 (<1)	19 / 63 (30.2)	-29 [-41; -18]	0.03 [0.00; 0.20]	
Feeding problems / anorexia	1	1 / 119 (<1)	12 / 63 (19)	-18 [-28; -8]	0.04 [0.01; 0.33]	
Viral respiratory infections or	1	2 / 119 (1.7)	14 / 63 (22.2)	-21 [-31; -10]	0.08 [0.02; 0.32]	
Depression	1	3 /119 (2.5)	11 / 63 (17.5)	-15 [-25; -5]	0.14 [0.04; 0.50]	
Shi, 2006[62]						
Any adverse event	1	0 / 98	NR			72 weeks
Serious adverse event	1	0 / 98	6 / 64 (9.4) *Pyrexia, fatigue, myalgia, headache*	-9 [-17; -2]	0.05 [0.00; 0.88]	

(E) Telbivudine (L-nucleoside analog)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus adefovir (see above)						
Versus lamivudine, attributed to study drug (SEBIVO INSERT – 007 GLOBE)[71]						
Subjects not completing treatment/study	1	18 / 680 (2.6)	32 / 687 (4.7)	-2 [-4; 0]	0.57[0.32; 1.00]	52 weeks
Any adverse event		NR	NR			
Serious adverse event	1	18 / 680 (2.6)	33 / 687 (4.8)	-2 [-4; 0]	0.55 [0.31; 0.97]	
AE leading to discontinuation of study drug	1	2 / 680 (<1)	5 / 687 (<1)	0 [-1; 0]	0.40 [0.08; 2.08]	
AE leading to discontinuation, possibly related to study drug	1	1 / 680 *myopathy*	1 / 687 *urticaria*	0 [0; 0]	1.01 [0.06; 16.12	
Fatigue	1	29 / 680 (4.3)	18 / 687 (2.6)	2 [0; 4]	1.63 [0.91; 2.90]	
Nausea	1	19 / 680 (2.8)	15 / 687 (2.2)	1 [-1; 2]	1.28 [0.66; 2.50]	
Diarrhea	1	10 / 680 (1.5)	4 / 687 (<1)	1 [0; 2]	2.53 [0.80; 8.01]	
Abdominal pain	1	7 / 680 (1.0)	1 / 687 (<1)	1 [0; 2]	7.07 [0.87; 57.33]	
Headache	1	22 / 680 (3.2)	27 / 687 (3.9)	-1 [-3; 1]	0.82 [0.47; 1.43]	

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Dizziness	1	10 / 680 (1.5)	5 / 687 (<1)	1 [0; 2]	2.02 [0.69; 5.88]	
Rash	1	9 / 680 (1.3)	7 / 687 (1.0)	0 [-1; 1]	1.30 [0.49; 3.47]	
Nasopharyngitis	1	7 / 680 (1.0)	4 / 687 (<1)	0 [-1; 1]	1.77 [0.52; 6.01]	
Cough	1	7 / 680 (1.0)	3 / 687 (<1)	1 [0; 1]	2.36 [0.61; 9.08]	
Versus lamivudine (SEBIVO INSERT – 007 GLOBE)[71]						
Upper respiratory tract infection	1	82 / 680 (12.1)	82 / 687 (11.9)	0 [-3; 4]	1.01 [0.76; 1.35]	52 weeks
Nasopharyngitis	1	68 / 680 (10)	69 / 687 (10)	0 [-3; 3]	1.00 [0.72; 1.37]	
Fatigue	1	68 / 680 (10)	62 / 687 (9.0)	1 [-2; 4]	1.11 [0.80; 1.54]	
Headache	1	68 / 680 (10)	82 / 687 (11.9)	-2 [-5; 1]	0.84 [0.62; 1.13]	
Dizziness	1	27 / 680 (4.0)	34 / 687 (4.9)	-1 [-3; 1]	0.80 [0.49; 1.31]	
Myalgia	1	20 / 680 (2.9)	14 / 687 (2.0)	1 [-1; 3]	1.44 [0.74; 2.83]	

(F) Entecavir monotherapy (Acyclic guanosine derivative)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
0.5 mg dose versus lamivudine[73,74]						
Subjects not completing study/treatment	2	37 / 688* (5.4)	58 / 675 (8.6)	-3 [-8; 2]	0.64 [0.33; 1.26]	E=56-75 weeks
Any adverse event	2	552 / 679 (80.3)	545 / 668 (81.1)	0 [-6; 6]	1.00 [0.92; 1.08]	L=56-65 weeks
Serious adverse event	2	48 / 679 (7.1)	54 / 668 (8.1)	-1 [-4; 2]	0.88 [0.60; 1.27]	
AE leading to discontinuation of study drug	2	7 / 679 (1.0)	18 / 668 (2.7)	-2 [-3; 0]	0.33 [0.06; 1.86]	
Lai 2005 0.5 mg dose versus lamivudine [77]						
Any adverse event	1	30 / 46 (65.2)	30 / 41 (73.1)	-8 [-27; 11]	0.89 [0.67; 1.18]	24 weeks
AE leading to discontinuation of study drug	1	0 / 46	1 / 41 (2.4)	-2 [-9; 4]	0.30 [0.01; 7.12]	
Headache	1	14 / 46 (30.4)	8 / 41 (19.5)	11 [-7; 29]	1.56 [0.73; 3.33]	
Abdominal pain	1	12 / 46 (26.1)	7 / 41 (17.1)	9 [-8; 26]	1.53 [0.67; 3.51]	
Rhinitis	1	5 / 46 (10.9)	8 / 41 (19.5)	-9 [-24; 6]	0.56 [0.20; 1.57]	
Fatigue	1	8 / 46 (17.4)	7 / 41 (17.1)	0 [-16; 16]	1.02 [0.40; 2.56]	
Pyrexia	1	2 / 46 (4.3)	6 / 41 (14.6)	-10 [-23; 2]	0.30 [0.06; 1.39]	
Diarrhea	1	5 / 46 (10.9)	4 / 41 (9.8)	1 [-12; 14]	1.11 [0.32; 3.87]	
Nausea	1	5 / 46 (10.9)	3 / 41 (7.3)	4 [-8; 16]	1.49 [0.38; 5.83]	
Dizziness	1	5 / 46 (10.9)	2 / 41 (4.9)	6 [-5; 17]	2.23 [0.46; 10.87]	
Cough	1	2 / 46 (4.3)	2 / 41 (4.9)	-1 [-9; 8]	0.89 [0.13; 6.04]	
Myalgia	1	0 / 46	4 / 41 (9.8)	-10 [-20; 0]	0.10 [0.01; 1.79]	
1 mg dose versus lamivudine in lamivudine-refractory subjects patient information sheet (Bristol Myers Squibb)						
Any Grade II to IV adverse event	2	40 / 183 (21.9)	44 / 190 (23.2)	-1 [-10; 7]	0.94 [0.87; 1.14]	Through 2 years
Fatigue	2	5 / 183 (2.7)	6 / 190 (3.2)	0 [-4; 3]	0.87 [0.27; 2.79]	
Headache	2	7 / 183 (3.8)	2 / 190 (1.1)	3 [0; 6]	3.63 [0.76; 17.26]	

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus lamivudine in lamivudine-refractory subjects Chang, 2005 #52}[75]						
Subjects not completing study/treatment (24 weeks)	1	7 / 136 (5.1) *All doses***	2 / 45 (4.4)	1 [-6; 8]	1.16 [0.25; 5.37]	24 weeks
Subjects not completing study / treatment (48 weeks)	2	39 / 283* (13.9)	38 / 191* (19.9)	-12 [-30; 6]	0.54 [0.36; 0.81]	48 weeks
Any adverse event	2	225 / 277 (81.2)	155 / 190 (81.6)	0 [-12; 11]	0.99 [0.87; 1.14]	
Serious adverse event	2	22 / 277 (7.9)	14 / 190 (7.4)	1 [-4; 6]	1.18 [0.62; 2.27]	
Severe (grade III or IV) AE	1	32 / 136 (23.5)	9 / 45 (20)	4 [-10; 17]	1.18 [0.61; 2.27]	
AE leading to discontinuation of study drug	2	11 / 277 (4.0)	14 / 190 (7.4)	-5 [-9; 1]	0.43 [0.12; 1.54]	
Headache	1	35 / 136 (25.7)	10 / 45 (22.2)	4 [-11; 18]	1.16 [0.63; 2.15]	
Fatigue	1	23 / 136 (16.9)	6 / 45 (13.3)	4 [-8; 15]	1.27 [0.55; 2.92]	
Pyrexia	1	15 / 136 (11)	3 / 45 (6.7)	4 [-5; 13]	1.65 [0.50; 5.45]	
Upper respiratory tract infection	1	10 / 136 (7.4)	6 / 45 (13.3)	-6 [-17; 5]	0.55 [0.21; 1.43]	
Diarrhea	1	14 / 136 (10.3)	3 / 45 (6.7)	4 [-5; 13]	1.54 [0.46; 5.13]	
Upper abdominal pain	1	8 / 136 (5.9)	5 / 45 (11.1)	-5 [-15; 5]	0.53 [0.18; 1.54]	
Back pain	1	13 / 136 (9.6)	3 / 45 (6.7)	3 [-6; 12]	1.43 [0.43; 4.80]	
Arthralgia	1	12 / 136 (8.8)	2 / 45 (4.4)	4 [-3; 12]	1.99 [0.46; 8.54]	
Nasopharyngitis	1	11 / 136 (8.1)	5 / 45 (11.1)	-3 [-13; 7]	0.73 [0.27; 1.98]	

* Includes subjects not receiving any study medication
** 0.1, 0.5, and 1 mg arms

(G) Combination pegylated interferon-α-2a and lamivudine therapy (interferon)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus lamivudine (see above)[56,57]						
Versus pegylated interferon-α-2a monotherapy[56,57]						
Subjects not completing treatment / study	2	49 / 457* (10.7)	45 / 453* (9.9)	1 [-4; 5]	1.08 [0.71; 1.66]	72 weeks
Any adverse event	2	395 / 450 (87.8)	395 / 448 (88.2)	0 [-58; 4]	1.00 [0.95; 1.05]	
Serious adverse event	2	28 / 450 (6.2)	21 / 448 (4.7)	2 [-1; 4]	1.33 [0.77; 2.30]	
AE leading to discontinuation of study drug	2	19 / 450 (4.2)	21 / 448 (4.7)	-1 [-6; 4]	0.90 [0.33; 2.48]	
Pyrexia	2	246 / 450 (54.7)	238 / 448 (53.1)	1 [-9; 11]	1.02 [0.85; 1.22]	
Fatigue	2	176 / 450 (39.1)	182 / 448 (40.6)	-2 [-8; 5]	0.96 [0.82; 1.13]	
Myalgia	2	126 / 450 (28.0)	117 / 448 (26.1)	2 [-4; 8]	1.07 [0.86; 1.33]	
Headache	2	115 / 450 (25.6)	118 / 448 (26.3)	-1 [-8; 5]	0.96 [0.74; 1.26]	
Alopecia	2	98 / 450 (21.8)	79 / 448 (17.6)	3 [-8; 14]	1.14 [0.68; 1.92]	
Decreased appetite	2	60 / 450 (13.3)	71 / 448 (15.8)	-2 [-7; 2]	0.84 [0.61; 1.16]	
Dizziness	2	44 / 450 (9.8)	40 / 448 (8.9)	1 [-4; 5]	1.09 [0.70; 1.70]	
Diarrhea	2	36 / 450 (8.0)	45 / 448 (10.0)	-2 [-8; 3]	0.75 [0.36; 1.55]	

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Pruritus	2	37 / 450 (8.2)	35 / 448 (7.8)	1 [-3; 4]	1.05 [0.68; 1.64]	
Nausea	2	40 / 450 (8.9)	38 / 448 (8.5)	0 [-3; 4]	1.05 [0.69; 1.60]	
Arthralgia	2	51 / 450 (11.3)	51 / 448 (11.4)	0 [-4; 4]	0.99 [0.69; 1.43]	
Rigors	2	32 / 450 (7.1)	29 / 448 (6.5)	0 [-6; 6]	0.92 [0.33; 2.56]	
Injection-site reaction	2	36 / 450 (8.0)	34 / 448 (7.6)	1 [-8; 10]	1.12 [0.35; 3.64]	
Gingival bleeding	1	15 / 271 (5.5)	15 / 271 (5.5)	0 [-4; 4]	1.00 [0.50; 2.00]	
Depression	1	16 / 271 (5.9)	13 / 271 (4.8)	1 [-3; 5]	1.23 [0.60; 2.51]	

(H) Combination pegylated interferon-α-2b and lamivudine therapy (interferon)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus pegylated interferon-α-2b monotherapy[78]						
Subjects not completing treatment/study	1	38 / 152* (25)	37 / 155* (23.9)	1 [-8; 11]	1.05 [0.71; 1.55]	78 weeks
Serious adverse event	1	32 total, 17 probably related to therapy (including hepatitis flare (4), depression (3), severe neutropenia (3), and one case each of psychosis, seizures, pancreatitis, anxiety, dizziness, diarrhea, and syncope. All serious AE were reversible after treatment was stopped.				
AE leading to discontinuation of study drug	1	12 / 152 (7.9)	11 / 155 (7.1)	1 [-5; 7]	1.11 [0.51; 2.44]	
Flu-like syndrome	1	96 / 130 (73.8)	84 / 136 (61.8)	12 [1; 23]	1.20 [1.01; 1.41]	
Headache	1	59 / 130 (45.4)	55 / 136 (40.4)	5 [-7; 17]	1.12 [0.85; 1.48]	
Fatigue	1	54 / 130 (41.5)	59 / 136 (43.4)	-2 [-14; 10]	0.96 [0.72; 1.27]	
Myalgia	1	42 / 130 (32.3)	41 / 136 (30.1)	2 [-9; 13]	1.07 [0.75; 1.53]	
Injection-site reaction	1	38 / 130 (29.2)	36 / 136 (26.5)	3 [-8; 14]	1.10 [0.75; 1.63]	
Alopecia	1	35 / 130 (26.9)	26 / 136 (19.1)	8 [-2; 18]	1.41 [0.90; 2.20]	
Depression	1	28 / 130 (21.5)	29 / 136 (21.3)	0 [-10; 10]	1.01 [0.64; 1.60]	
Abdominal pain	1	25 / 130 (19.2)	26 / 136 (19.1)	0 [-9; 10]	1.01 [0.61; 1.65]	
Weight loss > 10%	1	25 / 130 (19.2)	28 / 136 (20.6)	-1 [-11; 8]	0.93 [0.58; 1.51]	
Decreased appetite	1	21 / 130 (16.2)	22 / 136 (16.2)	0 [-9; 9]	1.00 [0.58; 1.73]	
Insomnia	1	20 / 130 (15.4)	11 / 136 (8.1)	7 [0; 15]	1.90 [0.95; 3.81]	
Arthralgia	1	20 / 130 (15.4)	22 / 136 (16.2)	-1 [-10; 8]	0.95 [0.55; 1.66]	
Pruritus	1	18 / 130 (13.8)	14 / 136 (10.3)	4 [-4; 11]	1.35 [0.70; 2.59]	
Diarrhea	1	14 / 130 (10.8)	15 / 136 (11)	0 [-8; 7]	0.98 [0.49; 1.94]	
Nausea	1	14 / 130 (10.8)	25 / 136 (18.4)	-8 [-16; 1]	0.59 [0.32; 1.08]	

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

(I) Pegylated interferon-α-2b versus Interferon-α-2b (interferon)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Zhao 2007[81]						
Subjects not completing treatment/study	1	7 / 115 (6.1)	20 / 115 (17.4)	-11 [-19; -3]	0.35 [0.15; 0.80]	72 weeks
AE leading to discontinuation of study drug	1	0 / 115	4 / 115 (3.5)	-3 [-7; 0]	0.11 [0.01; 2.04]	
Any adverse event	75% of patients in each treatment group experienced various clinical forms of drug-related adverse effects, mainly flulike symptoms and fever. Two patients with an increased ALT level experienced nausea and vomiting and discontinued treatment. Only 1 patient who received pegylated IFN-a-2b experienced nausea and vomiting but discontinuation of treatment was not required.					

(J) Interferon-α-2b and Lamivudine (Interferon)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus placebo, subjects refractory interferon therapy[47]						
Subjects not completing treatment/study	1	10 / 63 (15.9)	10 / 56 (17.9)	-2 [-15; 12]	0.89 [0.40; 1.98]	68 weeks
Any adverse event	1	NR	NR	-	-	
Serious adverse event	1	NR	NR	-	-	
AE leading to discontinuation of study drug	1	1 / 63 (1.6)	4 / 56 (7.1)	-6 [-13; 2]	0.22 [0.03; 1.93]	
Pyrexia	1	38 / 63 (60.3)	0 / 56	60 [48; 73]	68.58 [4.31; >1000]	
Fatigue	1	38 / 63 (60.3)	10 / 56 (17.9)	42 [27; 58]	3.38 [1.86; 6.13]	
Myalgia	1	18 / 63 (28.6)	3 / 56(5.4)	23 [11; 36]	5.33 [1.66; 17.15]	
Headache	1	30 / 63 (47.6)	7 / 56 (12.5)	35 [20; 50]	3.81 [1.82; 7.98]	
Nausea	1	23 / 63 (36.5)	6 / 56 (10.7)	26 [11; 40]	3.41 [1.50; 7.76]	
Alopecia	1	19 / 63 (30.2)	1 / 56 (1.8)	28 [17; 40]	16.89 [2.34; 122.13]	
Feeding problems	1	12 / 63 (19.0)	1 / 56 (1.8)	17 [7; 28]	10.67 [1.43; 79.45]	
Viral respiratory infections	1	14 / 63 (22.2)	0 / 56	22 [12; 33]	25.83 [1.58; 423.25]	
Depression	1	11 / 63 (17.5)	1 / 56 (1.8)	16 [6; 26]	9.78 [1.30; 73.36]	
Versus IFN monotherapy[67]						
Subjects not completing treatment / study	1	6 / 76 (7.9)	6 / 70 (8.6)	-1 [-10; 8]	0.92 [0.31; 2.72]	24-52 weeks
Pyrexia	1	46 / 76 (60.5)	43 / 70 (61.4)	-1 [-17; 15]	0.99 [0.76; 1.28]	
Fatigue	1	66 / 76 (86.8)	70 / 70 (100)	-13 [-21; -5]	0.87 [0.79; 0.95]	
Myalgia	1	36 / 76 (47.4)	40 / 70 (57.1)	-10 [-26; 6]	0.83 [0.61; 1.13]	
Arthralgia	1	9 / 76 (11.8)	23 / 70 (32.9)	-21 [-34; -8]	0.36 [0.18; 0.72]	
Headache	1	71 / 76 (93.4)	47 / 70 (67.1)	26 [14; 39]	1.39 [1.17; 1.66]	
Nausea	1	33 / 76 (43.4)	34 / 70 (48.6)	-5 [-21; 11]	0.89 [0.63; 1.27]	
Alopecia	1	30 / 76 (39.5)	21 / 70 (30)	9 [-6; 25]	1.32 [0.84; 1.27]	

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Feeding problems / anorexia	1	30 / 76 (39.5)	33 / 70 (47.1)	-8 [-24; 8]	0.84 [0.58; 1.22]	
Viral respiratory infections	1	32 / 76 (42.1)	37 / 70 (52.9)	-11 [-27; 5]	0.80 [0.56; 1.12]	
Versus IFN monotherapy[79]						
Subjects not completing treatment/study	1	0 / 33	1 subject	-	-	52 weeks
Serious adverse event	1	0 / 33	0 / 16	0	-	
Mouth dryness	1	25 / 33 (75.6)	3 / 16 (33.3)	57 [33; 81]	4.04 [1.43; 11.41]	
Malaise	73% all patients combined					
Alopecia	64% all patients combined					
Myalgia	61% all patients combined					
Pyrexia	50% all patients combined					
Weight loss	50% all patients combined					
Anorexia	47% all patients combined					
12 versus 16 week, subjects refractory interferon therapy[80]						
	1	Dose reduction was required in one subject (20 total) for malaise and fatigue, and symptoms responded to dose reduction. For another subject, treatment was stopped after 15 weeks of treatment.				32 weeks

(K) Interferon-α-2b monotherapy (Interferon)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) duration
Chung, 2003[82] Prolonged individualized versus 6 months treatment (N=65, all subjects combined). Flu-like symptoms 51/65 (90.8); anorexia/nausea 14/65 (21.5); weight loss >10% 7/65 (10.8); oral ulcer 1/65 (1.5); emotional liability 2/65 (3.1)						
Janssen, 1999[83] Prolonged (32 weeks) versus standard (16 weeks) duration						
Hair loss	Significant difference (P < 0.05) between the two groups					
Dose reduction due to AE	11.5% (7/61) in the prolonged group. Due to depression, fatigue, hair loss, and headache. Not reported in standard group.					
AE leading to discontinuation of study drug	4.9% (3/61) in the prolonged group. Not reported in standard group.					
Phase A – all subjects prior to randomization (n=162)	Dose modification due to AE: 16/162 (10%). 11 stopped treatment prior to randomization due to flu-like symptoms (3), psychosis/depression (3), dizziness (2), fatigue (1) thrombocytopenia (1), and exacerbation of HBV (1). AE in ≥20% of subjects included fatigue, asthenia, anorexia, arthralgia, and depression/irritability.					
Lampertico, 1997[84] IFN (n=21) versus no treatment (n=21). Study duration was 104 weeks. 5/21 (23.8%) IFN subjects withdrew from study due to persistent headache (1) persistent myalgias, arthralgias or headache (3), and depression (1). Dose in reduction in two subjects due to mild depression (1) and myalgias (1).						
Di Bisceglie, 1993[86] IFN (n=25) versus no treatment (n=22). Study duration was 6 months. IFN AE included flu-like syndrome, headache, fatigue, and muscle aches. Treatment stopped in three subjects due to severe fatigue (1), thrombocytopenia (1), and exacerbation of osteoarthritis. Dose in reduction in 16 subjects due to (could be multiple reasons) fatigue (12), nausea (3), marrow suppression (2), arthralgia (2), infections (2), jaundice (1), and depression (1).						

Appendix E. Table 7. Number of subjects experiencing adverse events from RCTs

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) duration
Versus no treatment						
Lopez-Alcorocho, 1997[85] 6 months (n=19) versus 12 months (n=19). "Treatment was well tolerated by all subjects who finished the study, and no dose modification was needed."						
Waked, 1990[89]. IFN (n=20) versus no treatment (n=20). Study duration was 68 weeks. 4 (3 deaths) IFN and 5 (2 deaths) did not complete study. All subjects developed flu-like symptoms (pyrexia, myalgia, chills, and occasionally arthralgias). Other AE were mild and transient and did not lead to study withdrawal.						
Muller ,1990[87] IFN (n=30) versus no treatment (n=28). Study duration was 10 months. "Treatment generally well tolerated." All patients treated with IFN showed mild flu-like symptoms which disappeared in the majority of patients. One subject with a pre-existing depressive state converted to overt depression. This subject was taken off treatment.						
Hadziyannis, 1990[88] IFN (n=25) versus no treatment (n=25). Study duration was 52 weeks. IFN therapy well tolerated, no serious AE observed. Fever, fatigue, and headache were commonly associated with treatment.						

Appendix E. Table 8. Number of subjects with laboratory abnormalities from RCTS

(A) Adefovir monotherapy (L-nucleotide analog)

Laboratory Abnormality	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus placebo [From Gilead Sciences package insert]						
ALT: >5 x ULN	2	59 / 294 (20.1)	93 / 228 (40.8)	-21 [-29; -13]	0.49 [0.37; 0.65]	48 weeks
Hematuria: ≥ 3+	2	32 / 294 (10.9)	23 / 228 (10.1)	1 [-4; 6]	1.08 [0.65; 1.79]	
AST: >5 x ULN	2	24 / 294 (8.2)	52 / 228 (22.8)	-15 [-21; -8]	0.36 [0.23; 0.56]	
Creatine kinase: > 4 x ULN	2	21 / 294 (7.1)	16 / 228 (7.0)	0 [-4; 5]	1.02 [0.54; 1.91]	
Amylase: <2 x ULN	2	12 / 294 (4.1)	9 / 228 (3.9)	0 [-3; 4]	1.03 [0.44; 2.41]	
Glycosuria: ≥3+	2	3 / 294 (1.0)	7 / 228 (3.1)	-2 [-5; 0]	0.33 [0.09; 1.27]	
Versus lamivudine*, *subjects with lamivudine resistance: Grade 3 and 4 laboratory toxicity[43]						
ALT: >5 x ULN	1	7 / 19 (36.8)	3 / 19 (15.8)	21 [-6; 48]	2.33 [0.71; 7.70]	48 weeks
AST: >5 x ULN	1	1 / 19 (5.3)	3 / 19 (15.8)	-11 [-30; 9]	0.33 [0.04; 2.93]	
Amylase	1	0 / 19	3 / 19 (15.8)	-16 [-34; 2]	0.14 [0.01; 2.59]	
Serum glucose	1	2 / 19 (10.5)	3 / 19 (15.8)	-5 [-27; 16]	0.67 [0.13; 3.55]	
Glycosuria	1	2 / 19 (10.5)	4 / 19 (21.1)	-11 [-33; 12]	0.50 [0.10; 2.41]	
Versus telbivudine [44]						
Neutropenia	1	Two cases of Grade 3 and 4 neutropenia were observed in one telbivudine subject and one adefovir; telbivudine subject. Both cases resolved without dose reduction/treatment interruption.				52 weeks

(B) Adefovir versus combination therapy

Laboratory Abnormality	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus combined lamivudine and adefovir, subjects refractory; lamivudine: Grade 3 and 4 laboratory toxicity[43]						
ALT: >5 x ULN	1	7 / 19 (36.8)	2 / 20 (10)	27 [1; 52]	3.68 [0.87; 15.56]	48 weeks
AST: >5 x ULN	1	1 / 19 (5.3)	0 / 20	5 [-8; 19]	3.15 [0.14; 72.88]	
Amylase	1	0 / 19	2 / 20 (10)	-10 [-25; 5]	0.21 [0.01; 4.11]	
Serum glucose	1	2 / 19 (10.5)	1 / 20 (5)	6 [-11; 22]	2.11 [0.21; 21.36]	
Glycosuria	1	2 / 19 (10.5)	1 / 20 (5)	6 [-11; 22]	2.11 [0.21; 21.36]	

(C) Lamivudine monotherapy (L-nucleoside analog)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus placebo, 100 and 25 mg doses combined[50]						
Abnormal liver-function tests	1	9 / 285 (3.2)	6 / 73 (8.3)	-5 [-12; 2]	0.38 [0.14; 1.04]	52 weeks
Abnormal liver-function tests	1	5 / 285	5 / 73 (6.9)	-5 [-11; 1]	0.26 [0.08; 0.86]	

Appendix E. Table 8. Number of subjects with laboratory abnormalities from RCTS

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
deemed; be of major clinical concern		(1.8) (*25 mg=1; 100 mg=4*)				
Abnormal ALT or ASP	1	3 / 285 (1.1)	3 / 73 (4.1)	-3 [-8; 2]	0.26 [0.05; 1.24]	
Versus placebo[48]						
ALT: ≥2 x baseline level	1	18 / 70 (25.7)	19 / 71 (26.8)	-1 [-16; 13]	0.96 [0.55; 1.67]	52 weeks (during therapy)
ALT: ≥3 x baseline level	1	7 / 70 (10)	9 / 71 (12.7)	-3 [-13; 8]	0.79 [0.31; 2.00]	
ALT: ≥2 x baseline level and >500 U/liter	1	1 / 70 (1.4)	7 / 71 (9.9)	-8 [-16; -1]	0.14 [0.02; 1.15]	
ALT: Grade III or IV abnormality	1	7 / 70 (10)	9 / 71 (12.7)	-3 [-13; 8]	0.79 [0.31; 2.00]	
Albumin: Grade III or IV abnormality	1	0 / 70 (0)	2 / 71 (2.8)	-3 [-7; 2]	0.20 [0.01; 4.15]	68 weeks
Amylase: Grade III or IV abnormality	1	0 / 70 (0)	1 / 71 (1.4)	-1 [-5; 2]	0.34 [0.01; 8.16]	
Lipase: Grade III or IV abnormality	1	6 / 70 (8.6)	5 / 71 (7.0)	2 [-7; 10]	1.22 [0.39; 3.81]	
Creatine kinase: Grade III or IV abnormality	1	6 / 70 (8.6)	3 / 71 (4.2)	4 [-4; 12]	2.03 [0.53; 7.79]	
Platelets: Grade III or IV abnormality	1	0 / 70 (0)	2 / 71 (2.8)	-3 [-7; 2]	0.20 [0.01; 4.15]	
Versus placebo following treatment[48]						
ALT: Grade III abnormality	1	14 / 65 (21.5)	4 / 66 (6.1)	15 [4; 27]	3.55 [1.23; 10.23]	16 weeks post-treatment (after 52 weeks therapy)
ALT: Grade IV abnormality	1	2 / 65 (3.1)	1 / 66 (1.5)	2 [-4; 7]	2.03 [0.19; 21.85]	
ALT: ≥2 x baseline level	1	19 / 65 (29.2)	13 / 66 (19.7)	10 [-5; 24]	1.48 [0.80; 2.75]	
ALT: ≥3 x baseline level	1	16 / 65 (24.6)	5 / 66 (7.6)	17 [5; 29]	3.25 [1.26; 8.35]	
ALT: ≥2 x baseline level and >500 U/liter	1	12 / 65 (18.5)	6 / 66 (9.1)			
ALT: ≥2 x baseline levels and bilirubin ≥2 x baseline levels	1	1 subject	1 subject			
Versus placebo[46]						
ALT: Grade III or IV abnormality	1	17 / 89 (19.1)	19 / 47 (40.4)	-21 [-38; -5]	0.47 [0.27; 0.82]	78 weeks
Increased ALT	1	11 / 89 (12.4)	6 / 47 (12.8)	0 [-12; 11]	0.97 [0.38; 2.45]	
Hyperbilirubinemia	1	1 subject	1 subject			
Increased creatine kinase	1	3 / 89 (3.4)	3 / 47 (6.4)	-3 [-11; 5]	0.53 [0.11; 2.52]	
Increased amylase	1	3 / 89 (3.4)	0 / 47	3 [-2; 8]	3.73 [0.20; 70.79]	
Prolonged prothrombin time	1	1 / 89 (1.1)	3 / 47 (6.4)	-5 [-13; 2]	0.18 [0.02; 1.65]	
Low neutrophil count	1	0	1 subject			
Thrombocytopenia	1	7 / 89 (7.9)	3 / 47 (6.4)	1 [-7; 10]	1.23 [0.33; 4.55]	

Appendix E. Table 8. Number of subjects with laboratory abnormalities from RCTS

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus placebo, subjects refractory interferon therapy[47]						
Abnormal ALT or ASP	1	13 / 119 (10.9)	5 / 56 (8.9)	2 [-7; 11]	1.22 [0.46; 3.26]	68 weeks
Abnormal enzymes (amylase/CPK)	1	11 / 119 (9.2)	2 / 56 (3.6)	6 [-1; 13]	2.59 [0.59; 11.29]	
Versus placebo, during treatment (0; week 52), subjects refractory interferon therapy[47]						
ALT: ≥2 x baseline level	1	31 / 119 (26.1)	11 / 56 (19.6)	6 [-7; 19]	1.33 [0.72; 2.44]	52 weeks
ALT: ≥3 x baseline level	1	20 / 119 (16.8)	7 / 56 (12.5)	4 [-7; 15]	1.34 [0.60; 2.99]	
ALT: ≥2 x baseline level and >500 U/liter	1	9 / 119 (7.6)	4 / 56 (7.1)	0 [-8; 9]	1.06 [0.34; 3.29]	
Versus placebo post-treatment, subjects refractory interferon therapy[47]						
ALT: ≥2 x baseline level	1	17 / 67 (25.4)	7 / 47 (14.9)	10 [-4; 25]	1.70 [0.77; 3.78]	16 weeks post-treatment
ALT: ≥3 x baseline level	1	13 / 67 (19.4)	4 / 47 (8.5)	11 [-1; 23]	2.28 [0.79; 6.56]	
ALT: ≥2 x baseline level and >500 U/liter	1	9 / 67 (13.4)	2 / 47 (4.3)	9 [-1; 19]	3.16 [0.71; 13.95]	
Lamivudine maintained during followup period versus placebo, subjects refractory interferon therapy[47]						
ALT: ≥2 x baseline level	1	6 / 44 (13.6)	7 / 47 (14.9)	-1 [-16; 13]	0.92 [0.33; 2.51]	16 weeks post-treatment
ALT: ≥3 x baseline level	1	3 / 44 (6.8)	4 / 47 (8.5)	-2 [-13; 9]	0.80 [0.19; 3.38]	
ALT: ≥2 x baseline level and >500 U/liter	1	3 / 44 (6.8)	2 / 47 (4.3)	3 [-7; 12]	1.60 [0.28; 9.14]	
Versus placebo, subjects with advanced liver disease[51]						
ALT: ≥3 x baseline	1	52 / 436 (11.9)	54 / 215 (25.1)	-13 [-20; -7]	0.47 [0.34; 0.67]	32 months (median)
Versus adefovir (see above)						
Versus telbivudine(see below)						
Versus entecavir (see below)						
Versus pegylated interferon-α-2a [56,57]						
Dose modification	2	0 / 453	207 / 448 (46.2)	-46 [-51; -42]	0.00 [0.00; 0.03]	72 weeks
Dose modification due; lab abnormality	2	0 / 453	164 / 448 (36.6)	-37 [-41; -32]	0.01 [0.00; 0.04]	
ALT elevation	1	0 / 181	15 / 177 (8.5)	-8 [-13; -4]	0.03 [0.00; 0.52]	
Neutropenia	1	0 / 181	30 / 177 (16.9)	-17 [-23; -11]	0.02 [0.00; 0.26]	
Thrombocytopenia	1	0 / 181	34 / 177 (19.2)	-19 [-25; -13]	0.01 [0.00; 0.23]	

(D) Lamivudine versus combination therapy

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus combined lamivudine and adefovir[58]						
Creatinine increase ≥0.5 mg/dL	1	0 / 48	0 / 46	-	-	52 weeks

Appendix E. Table 8. Number of subjects with laboratory abnormalities from RCTS

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus combined pegylated interferon-α-2a and lamivudine[56,57]						
Dose modification	2	0 / 453	213 / 450 (47.3)	-47 [-52; -43]	0.00 [0.00; 0.03]	72 weeks
Dose modification due; lab abnormality	2	0 / 453	166 / 450 (36.9)	-37 [-41; -32]	0.01 [0.00; 0.04	
ALT elevation	1	0 / 181	6 / 179 (3.4)	-3 [-6; -1]	0.08 [0.00; 1.34]	
Neutropenia	1	0 / 181	44 / 179 (24.6)	-25 [-31; -18]	0.01 [0.00; 0.18]	
Thrombocytopenia	1	0 / 181	22 / 179 (12.3)	-12 [-17; -7]	0.02 [0.00; 0.36]	
Versus combined pegylated Interferon-α-2b and lamivudine see below[59]						
Dose modification due; lab abnormality	1	0 / 50	5 / 50 (10)	-10 [-19; -1]	0.09 [0.01; 1.60]	76 weeks
Increased ALT level	1	12 / 50 (24)	8 / 50 (16)	8 [-8; 24]	1.50 [0.67; 3.35]	
Decreased phosphate level	1	1 / 50 (2)	2 / 50 (4)	-2 [-9; 5]	0.50 [0.05; 5.34]	
Decreased neutrophil count	1	0	1 subject			
Increased creatine kinase level	1	1 subject	0			
Versus combined interferon-α-2b and lamivudine, Grade 3 and 4 laboratory abnormalities[66]						
ALT	1	9 / 75 (12)	15 / 76 (19.7)	-8 [-19; 4]	0.61 [0.28; 1.30]	100 weeks
Albumin	1	2 / 75 (2.7)	2 / 76 (2.6)	0 [-5; 5]	1.01 [0.15; 7.01]	
Amylase	1	1 / 75 (1.3)	2 / 76 (2.6)	-1 [-6; 3]	0.51 [0.05; 5.47]	
Lipase	1	2 / 75 (2.7)	4 / 76 (5.3)	-3 [-9; 4]	0.51 [0.10; 2.68]	
Creatine kinase	1	5 /75 (6.7)	6 / 76 (1.3)	-1 [-10; 7]	0.84 [0.27; 2.65]	
Platelets	1	2 / 75 (2.7)	2 / 76 (2.6)	0 [-5; 5]	1.01 [0.15; 7.01]	
Versus combined interferon-α-2b and lamivudine, subjects refractory interferon therapy[47]						
Abnormal ALT/AST	1	13 / 119 (10.9)	6 / 63 (9.5)	1 [-8; 11]	1.15 [0.46; 2.87]	68 weeks
Abnormal enzymes (amylase/CPK)	1	11 / 119 (9.2)	5 / 63 (7.9)	1 [-7; 10]	1.16 [0.42; 3.20]	
Decreased WBCs	1	1 / 119 (<1)	10 / 63 (15.9)	-15 [-24; -6]	0.05 [0.01; 0.40]	
Versus combined interferon-α-2b and lamivudine, during treatment (0; week 52), subjects refractory interferon therapy[47]						
ALT ≥2 x baseline level	1	31 / 119 (26.1)	30 / 63 (47.6)	-22 [-36; -7]	0.55 [0.37; 0.81]	52 weeks
ALT ≥ 3 x baseline level	1	20 / 119 (16.8)	13 / 63 (20.6)	-4 [-16; 8]	0.81 [0.43; 1.53]	
ALT ≥2 x baseline level and 500U/l	1	9 / 119 (7.6)	8 / 63 (12.7)	-5 [-15; 4]	0.60 [0.24; 1.47]	
Versus combined interferon-α-2b and lamivudine, post-treatment, subjects refractory interferon therapy[47]						
ALT ≥2 x baseline level	1	17 / 67 (25.4)	4 / 53 (7.5)	18 [5; 30]	3.36 [1.20; 9.40]	16 weeks post-treatment
ALT ≥3 x baseline level	1	13 / 67 (19.4)	2 / 53 (3.8)	16 [5; 26]	5.14 [1.21; 21.80]	
ALT ≥2 x baseline level and 500 U/l	1	9 / 67 (13.4)	1 / 53 (1.9)	12 [3; 20]	7.12 [0.93; 54.44]	
Lamivudine maintained during post-treatment period versus combined interferon-α-2b and lamivudine, subjects refractory interferon therapy Schiff, 2003 #109}						
ALT ≥2 x baseline level	1	6 / 44 (13.6)	4 / 53 (7.5)	6 [-6; 18]	1.81 [0.54; 6.00]	16 weeks post-treatment
ALT ≥3 x baseline level	1	3 / 44 (6.8)	2 / 53 (3.8)	3 [-6; 12]	1.81 [0.32; 10.34]	

Appendix E. Table 8. Number of subjects with laboratory abnormalities from RCTS

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
ALT ≥2 x baseline level and 500 U/l	1	3 / 44 (6.8)	1 / 53 (1.9)	5 [-3; 13]	3.61 [0.39; 33.53]	
Versus combined interferon-α-2b and lamivudine[64]						
Dose modification	1	none	*Possibly 12 subjects, 2 permanent*			96 weeks
ALT flare	1	1 / 40 (2.5)	3 / 40 (7.5)	-5 [-14; 4]	0.33 [0.04; 3.07]	
Thrombocytopenia	1	3 / 40 (7.5)	11 / 40 (27.5)	-20 [-36; -4]	0.27 [0.08; 0.90]	
Leucopenia	1	0 / 40	4 / 40 (10)	-10 [-20; 0]	0.11 [0.01; 2.00]	
Versus combined interferon-α-2b and lamivudine, during treatment[67]						
Dose modification	1	none	*Approx. 20%*			24-52 weeks
Hepatic flares (ALT ≥500 IU/l and >2 x baseline	1	10 / 82 (12.2)	0 / 75	12 [5; 20]	19.23 [1.15; 322.57]	
Versus combined interferon-α-2b and lamivudine, post-treatment[67]						
Hepatic flares (ALT ≥500 IU/l and >2 x baseline	1	10 / 78 (12.8)	5 / 74 (6.8)	6 [-3; 20]	1.90 [0.68; 5.29]	12 weeks post-treatment
Hepatic flares associated with bilirubin >2 ULN	1	2 subjects	0			

(E) Telbivudine (L-nucleoside analog)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus adefovir (see above)						
Versus lamivudine [SEBIVO Insert- Novartis]						
Elevated creatine kinase (CK) leading; study interruption or withdrawal	1	5 / 680 (<1) *3 withdrew*	0 / 687 (0)	1 [0; 1]	11.1 [0.62; 200.59]	52 weeks
Grade 1 CK 1; 3 ULN	1	287 / 680 (42.2)	203 / 687 (29.5)	13 [8; 18]	1.43 [1.24; 1.65]	
Grade 2 CK >3; 7 ULN	1	123 / 680 (18.1)	45 / 687 (6.6)	12 [8; 15]	2.76 [2.00; 3.82]	
Grade 3 CK >7; 10 ULN	1	28 / 680 (4.1)	7 / 687 (1.0)	3 [1; 5]	4.04 [1.78; 9.19]	
Grade 4 CK >10 ULN	1	23 / 680 (3.4)	14 / 687 (2.0)	1 [0; 3]	1.66 [0.86; 3.82]	
All Grades	1	461 / 680 (67.8)	269 / 687 (39.2)	29 [24; 34]	1.73 [1.56; 1.93]	
ALT: ≥3 x baseline level	1	25 / 680 (3.7)	43 / 687 (6.3)	-3 [-5; 0]	0.59 [0.36; 0.95]	
AST: ≥3 x baseline level	1	18 / 680 (2.6)	32 / 687 (4.7)	-2 [-4; 0]	0.57 [0.32; 1.00]	
Lipase >2.5 x ULN	1	12 / 680 (1.8)	22 / 687 (3.2)	-1 [-3; 0]	0.55 [0.72; 1.10]	
Amylase >3.0 x ULN	1	1 / 680 (<1)	2 / 687 (<1)	0 [-1; 0]	0.55 [0.72; 1.10]	
Total bilirubin >5.0 x ULN	1	0	2 subjects	-	-	
Neutropenia	1	0	1 subject	-	-	
Thrombocytopenia	1	0	1 subject	-	-	

Appendix E. Table 8. Number of subjects with laboratory abnormalities from RCTS

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus lamivudine, Grade 3-4 laboratory abnormalities from Lai 2007 (Globe Study)[71]						
Creatine kinase	1	51 / 680 (7.5)	21 / 687 (3.1)	4 [2; 7]	2.45 [1.49; 4.03]	52 weeks
Absolute neutrophil count	1	13 / 680 (1.9)	9 / 687 (1.3)	1 [-1; 2]	1.46 [0.63; 3.39]	
Platelet count	1	5 / 680 (<1)	4 / 687 (<1)	1 [-1; 1]	1.26 [0.34; 4.68]	

(F) Entecavir (Acyclic guanosine derivative)

Laboratory Abnormality	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus lamivudine, nucleoside-naïve subjects, during treatment[73,74]						
ALT: >2 x baseline level and > 0 x ULN	2	15 / 679 (2.2)	28 / 668 (4.2)	-2 [-4; 1]	0.53 [0.29; 0.99]	52-75 weeks
ALT: >2 x baseline level and >5 x ULN	2	43 / 679 (6.3)	69 / 668 (10.3)	-3 [-10; 3]	0.62 [0.43; 0.89]	
Versus lamivudine, post-treatment [73 74]						
ALT: >2 x baseline level and >10 x ULN	2	25 / 431 (5.8)	38 / 392 (9.7)	-4 [-8; -1]	0.48 [0.16; 1.44]	24 weeks post-treatment
ALT: >2 x baseline level and >5 x ULN	2	39 / 431 (9)	93 / 392 (23.7)	-14 [-21; -6]	0.34 [0.16; 0.69]	
Versus lamivudine, nucleoside-naïve subjects. Patient information sheet (trials Bristol Myers Squibb)						
Any Grade 3 or 4 Lab abnormality	2	238 / 679 (35.1)	240 / 668 (35.9)	-1 [-6; 4]	0.98 [0.84; 1.13]	Through 104 weeks
AST >5 x ULN	2	34 / 679 (5)	53 / 668 (7.9)	-3 [-6; 0]	0.63 [0.42; 0.96]	
Total bilirubin > 2.5 x ULN	2	14 / 679 (2.1)	13 / 668 (1.9)	0 [-1; 2]	1.06 [0.50; 2.24]	
Amylase ≥2.1 x ULN	2	14 / 679 (2.1)	13 / 668 (1.9)	0 [-1; 2]	1.06 [0.50; 2.24]	
Lipase ≥2.1 x ULN	2	48 / 679 (7.1)	40 / 668 (6)	1 [-2; 4]	1.18 [0.79; 1.77]	
Creatinine ≥3.0 x ULN	2	0 / 679	0 / 668			
Creatinine increase ≥0.5 mg/dL	2	7 / 679 (1.0)	7 / 668 (1)	0 [-1; 1]	0.98 [0.35; 2.79]	
Hyperglycemia, fasting >250 mg/dL	2	14 / 679 (2.1)	7 / 668 (1)	1 [0; 2]	1.97 [0.80; 4.84]	
Glycosuria	2	28 / 679 (4.1)	20 / 668 (3)	1 [-1; 3]	1.38 [0.78; 2.42]	
Hematuria	2	61 / 679 (9)	67 / 668 (10)	-1 [-4; 2]	0.90 [0.64; 1.25]	
Platelets <50,000/mm^3	2	<1%	<1%			

Appendix E. Table 8. Number of subjects with laboratory abnormalities from RCTS

Laboratory Abnormality	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
1 mg dose versus lamivudine in lamivudine-refractory subjects. Patient information sheet (trials Bristol Myers Squibb)						
ALT: >2 x baseline level and >10 x ULN	2	4 / 183 (2.2)	21 / 190 (11.1)	-9 [-14; -4]	0.20 [0.07; 0.57]	Through 104 weeks
ALT: >5 x ULN	2	22 / 183 (12)	46 / 190 (24.2)	-12 [-20; -4]	0.50 [0.31; 0.79]	
Any Grade 3 or 4 Lab abnormality	2	68 / 183 (37.2)	86 / 190 (45.3)	-8 [-18; 2]	0.82 [0.64; 1.05]	
AST >5 x ULN	2	9 / 183 (4.9)	32 / 190 (16.8)	-12 [-18; -6]	0.29 [0.14; 0.59]	
Total bilirubin > 2.5 x ULN	2	5 / 183 (2.7)	4 / 190 (2.1)	1 [-2; 4]	1.30 [0.35; 4.76]	
Amylase ≥ 2.1 x ULN	2	5 / 183 (2.7)	6 / 190 (3.2)	0 [-4; 3]	0.87 [0.27; 2.79]	
Lipase ≥2.1 x ULN	2	13 / 183 (7.1)	13 / 190 (6.8)	0 [-5; 5]	1.04 [0.49; 2.18]	
Creatinine ≥3.0 x ULN	2	0 / 183	0 / 190	-	-	
Creatinine increase ≥0.5 mg/dL	2	4 / 183 (2.2)	2 / 190 (1.1)	1 [-1; 4]	2.08 [0.39; 11.20]	
Hyperglycemia, fasting >250 mg/dL	2	5 / 183 (2.7)	2 / 190 (1.1)	2 [-1; 4]	2.60 [0.51; 13.21]	
Glycosuria	2	7 / 183 (3.8)	11 / 190 (5.8)	-2 [-6; 2]	0.66 [0.26; 1.67]	
Hematuria	2	16 / 183 (8.7)	11 / 190 (5.8)	3 [-2; 8]	1.51 [0.72; 3.17]	
Platelets <50,000/mm^3	2	<1%	<1%	-	-	
Lai 2002 [77] One entecavir 0.01-mg subject had an increase in ALT level; 1.9 times the baseline level and the bilirubin level increased; 6.2 mg/dL (grade 4 toxicity) leading; drug discontinuation. One lamivudine subject had a grade 4 elevation of ALT level at baseline and was withdrawn from the trial.						

(G) Combination pegylated interferon alfa-2a and lamivudine therapy (*see under lamivudine*)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus lamivudine (see above)[56,57]						
Versus pegylated Interferon alfa-2a monotherapy[56,57]						
Dose modification	2	213 / 450 (47.3)	207 / 448 (46.2)	1 [-5; 8]	1.02 [0.89; 1.18]	72 weeks
Dose modification due; lab abnormality	2	166 / 450 (36.9)	164 / 448 (36.6)	0 [-6; 7]	1.01 [0.85; 1.20]	
ALT elevation[57]	1	6 / 179 (3.4)	15 / 177 (8.5)	-5 [-10; 0]	0.40 [0.16; 1.00]	
Neutropenia[57]	1	44 / 179 (24.6)	30 / 177 (16.9)	8 [-1; 16]	1.45 [0.96; 2.20]	
Thrombocytopenia[57]	1	22 / 179 (12.3)	34 / 177 (19.2)	-7 [-14; 1]	0.64 [0.39; 1.05]	

Appendix E. Table 8. Number of subjects with laboratory abnormalities from RCTS

(H) Combined pegylated interferon alfa-2b and lamivudine

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus pegylated interferon-α-2b monotherapy [78]						
Neutropenia (<1.5 x 10^9/L)	1	34 / 130 (26.2)	26 / 136 (21.3)	7 [-3; 17]	1.37 [0.87; 2.15]	78 weeks
Thrombocytopenia (<75 x 10^9/L)	1	14 / 130 (10.8)	17 / 136 (12.5)	-2 [-9; 6]	0.86 [0.44; 1.86]	

(I) Pegylated interferon alfa-2b versus Interferon alfa-2b (Interferon)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Zhao 2007[81]						
Subjects with elevated ALT and/or bilirubin discontinuing treatment	1	0 / 115	4 / 115 (6.1)	-3 [-7; 0]	0.11 [0.01; 2.04]	72 weeks

(J) Combined interferon alfa-2b and lamivudine

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus placebo, subjects refractory; interferon therapy[47]						
Abnormal ALT/AST	1	6 / 63 (9.5)	5 / 56 (8.9)	1 [-10; 11]	1.07 [0.34; 3.31]	68 weeks
Abnormal enzymes	1	5 / 63 (7.9)	2 / 56 (3.6)	4 [-4; 13]	2.22 [0.45; 11.0]	
Decreased WBCs	1	10 / 63 (15.9)	5 / 56 (8.9)	7 [-5; 19]	1.78 [0.65; 4.89]	
Versus placebo, during treatment (0; week 52), subjects refractory; interferon therapy[47]						
ALT: ≥2 x baseline level	1	30 / 63 (47.6)	11 / 56 (19.6)	28 [12; 44]	2.42 [1.34; 4.37]	52 weeks
ALT: ≥3 x baseline level	1	13 / 63 (20.6)	7 / 56 (12.5)	8 [-5; 21]	1.65 [0.71; 3.84]	
ALT: ≥2 x baseline level and 500 U/l	1	8 / 63 (12.7)	4 / 56 (7.1)	6 [-5; 16]	1.78 [0.57; 5.59]	
Versus placebo, post-treatment, subjects refractory; interferon therapy[47]						
ALT: ≥2 x baseline level	1	4 / 53 (7.5)	7 / 47 (14.9)	-7 [-20; 5]	0.51 [0.16; 1.62]	16 weeks post-treatment
ALT: ≥3 x baseline level	1	2 / 53 (3.8)	4 / 47 (8.5)	-5 [-14; 5]	0.44 [0.09; 2.31]	
ALT: ≥2 x baseline level and 500 U/l	1	1 / 53 (1.9)	2 / 47 (4.3)	-2 [-9; 4]	0.44 [0.04; 4.73]	
Versus IFN monotherapy, during treatment [67]						
Dose modification	1	*Approx. 20%*	*Approx. 20%*			16; 24 weeks
Hepatic flares (ALT ≥500 IU/l and > 2 x baseline	1	0 / 75	8 / 70 (11.4)	-11 [-19; -4]	0.05 [0.00; 0.93]	

Appendix E. Table 8. Number of subjects with laboratory abnormalities from RCTS

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Versus IFN monotherapy, post- treatment [67]						
Hepatic flares (ALT ≥500 IU/l and > 2 x baseline	1	5 / 74 (6.8)	6 / 68 (8.8)	-2 [-11; 7]	0.77 [0.24; 2.39]	40 weeks post-treatment
Hepatic flares associated with bilirubin >2 ULN	1	0	1 subject			
Yalcin 2003[79] No elevations of serum amylase or creatinine phosphokinase levels observed. No patient required dose reduction or interruption of therapy						
Mutimer 1998[80]***, 16 weeks interferon plus 12 or 16 weeks lamivudine, subjects refractory interferon therapy***						
ALT > 10 ULN	1	1 / 20 (5)	During treatment (weeks 6-16), both groups combined			
	1	2 / 20 (10)	4-16 weeks post-treatment, both groups combined			
Creatinine phosphokinase (CPK) elevation	1	8 / 20 (40)	During treatment (weeks 6-16), both groups combined			
	1	12 / 20 (60)	4-16 weeks post-treatment, both groups combined			
CPK > 3 ULN	1	0 / 20	During treatment (weeks 6-16), both groups combined			
	1	2 / 20 (10)	4-16 weeks post-treatment, both groups combined			
Amylase elevation	1	5 / 20 (25)	During treatment (weeks 6-16), both groups combined			
	1	6 / 20 (30)	4-16 weeks post-treatment, both groups combined			

(K) Interferon alfa-2b monotherapy (interferon)

Adverse Event	Number of Studies	Treatment n / N (%)	Control n / N (%)	Absolute Risk Difference [95% CI]	Relative Risk Ratio [95% CI]	Trial(s) Duration
Chung 2003[82] Prolonged individualized versus 6 months treatment (*all subjects combined, N=65*). Leucopenia 4 subjects (6.2%) and thrombocytopenia 4 subjects (6.2%).						
Janssen 1999[83] Prolonged (32 weeks) versus standard (16 weeks) duration. Phase A – all subjects prior; randomization (n=162), one case of thrombocytopenia occurred' leading; dose modification.						
Versus no treatment						
Lopez-Alcorocho 1997[85] 6 months (n=19) versus 12 months (n=19). No dose modification needed.						
Hadziyannis 1990[88] IFN (n=25) versus no treatment (n=25). Study duration was 52 weeks. Two subjects in the IFN group required temporary dose reduction due; thrombocytopenia and neutropenia.						

ALT = Alanine aminotranferase
AST= Aspartate aminotranferase
ULN= Upper limit of normal

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Age						
Jang,2004 [65] Interferon Alfa 2b, 2+Lamivudine, 100 vs. Lamivudine,100	176/174	Viral breakthrough as the reappearance of serum HBV-DNA by solution hybridization assay in at least 2 consecutive tests during lamivudine therapy following the disappearance of the serum HBV DNA	Age:1 year increase	1.00 (1.00; 1.00)		
Bonino, 2007[114] Peginterferon alfa-2a, 26 vs. Lamivudine,100	48/48	Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Age: 10 year decrease	1.30 (1.00; 1.70)		
		Adjusted odds ratios of sustained combined response at 1 year of followup	Age: 10 year increase	0.80 (0.63; 1.02)		
		Adjusted odds ratios of sustained combined response	Age: 10 year decrease	1.26 (1.00; 1.50)		
Bonino,2007[114] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	48/48	Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Age >40 years	1.61 (0.97; 2.68)	**0.13 (0.00; 0.25)**	8
			Age <40 years	1.66 (1.09; 2.52)	**0.17 (0.04; 0.31)**	6
Bonino, 2007[114] Peginterferon alfa-2a, 26 +Placebo vs. Lamivudine,100	48/48	Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Age >40 years	1.59 (0.96; 2.65)	0.12 (-0.01; 0.25)	8
			Age <40 years	1.50 (0.97; 2.31)	0.13 (-0.01; 0.26)	8
Zhao, 2007[81] Peginterferon alfa-2b, 11 vs. Interferon Alfa 2b, 1	24/24	Multivariate adjusted odds ratio of Sustained combined response: HBeAg negative, HBV DNA <5 log10 copies/mL, and normal ALT level	Age >25 years vs. <25 years	0.39 (0.16; 0.92)		
Baseline ALT level						
Jang, 2004[65] Interferon Alfa 2b, 2+Lamivudine, 100 vs. Lamivudine, 100	176/174	Viral breakthrough as the reappearance of serum HBV-DNA by solution hybridization assay in at least 2 consecutive tests during lamivudine therapy following the disappearance of the serum HBV DNA	Baseline ALT	1.00 (1.00; 1.00)		

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Zarski, 1994[91] Interferon Alfa 2b, 2+Prednisone, 40 vs. Interferon Alfa 2b, 2	24/24	Chronic active hepatitis	Baseline ALT<3ULN	0.81 (0.22; 2.91)	-0.03 (-0.22; 0.15)	-32
		Cirrhosis	Baseline ALT<3ULN	0.40 (0.04; 4.19)	-0.05 (-0.17; 0.08)	-21
		Sustained clearance of HBV DNA during therapy + HBeAg seroconversion during or after therapy	Baseline ALT<3ULN	1.34 (0.36; 5.09)	0.04 (-0.14; 0.22)	24
Zarski, 1994[91] Interferon Alfa 2b, 2+Prednisone, 40 vs. Interferon Alfa 2b, 2	24/24	Sustained clearance of HBV DNA during therapy	Baseline ALT<3ULN	2.42 (0.27; 21.86)	0.06 (-0.07; 0.19)	18
		HBsAg loss	Baseline ALT<3ULN	3.23 (0.38; 27.06)	0.09 (-0.05; 0.23)	11
Perrillo, 2002[104] Interferon Alfa 2b, 4 vs. Lamivudine, 100	24/24	HBeAg loss irrespective of HBV-DNA status at baseline or week 25	Baseline ALT >5ULN	0.68 (0.25; 1.86)	-0.03 (-0.09; 0.03)	-37
		HBeAg seroconversion and HBV DNA loss	Baseline ALT >5ULN	0.72 (0.22; 2.31)	-0.02 (-0.07; 0.04)	-57
		HBeAg loss irrespective of HBV-DNA status at baseline or week 34	Baseline ALT >2-≤5ULN	0.89 (0.42; 01.89)	-0.01 (-0.09; 0.07)	-78
		HBeAg seroconversion and HBV DNA loss	Baseline ALT >2-≤5ULN	1.12 (0.49; 2.58)	0.01 (-0.06; 0.08)	106
		HBeAg loss irrespective of HBV-DNA status	Baseline ALT >1-≤2ULN	1.00 (0.30; 3.29)	0.00 (-0.05; 0.05)	-4602
		HBeAg seroconversion and HBV DNA loss	Baseline ALT >1-≤2ULN	1.49 (0.32; 6.88)	0.01 (-0.03; 0.05)	103
		HBeAg loss irrespective of HBV-DNA status at baseline or week 52	Baseline ALT ≤1ULN	2.99 (0.27; 32.47)	0.01 (-0.02; 0.04)	102
		HBeAg seroconversion and HBV DNA loss	Baseline ALT ≤1ULN	5.97 (0.38; 94.32)	0.01 (-0.02; 0.04)	82
Schalm, 2000[67] Interferon Alfa 2b, 4 vs. Lamivudine, 100	24/52	HBeAg seroconversion and undetectable HBV DNA	Baseline ALT 5 ULN	0.85 (0.40; 1.79)	-0.03 (-0.14; 0.09)	-39
		HBeAg seroconversion and undetectable HBV DNA	Baseline ALT 2-5 ULN	1.02 (0.71; 1.47)	0.01 (-0.15; 0.17)	126
		HBeAg seroconversionand undetectable HBV DNA	Baseline ALT 2 ULN	0.92 (0.60; 1.41)	-0.03 (-0.18; 0.12)	-33
Perrillo, 2002[104] Interferon Alfa 2b, 4 +Lamivudine, 100 vs. Interferon Alfa	24/24	HBeAg loss irrespective of HBV-DNA status at baseline or week 25	Baseline ALT >5ULN	1.26 (0.41; 3.87)	0.02 (-0.06; 0.09)	66
		HBeAg seroconversion and	Baseline ALT >5ULN	1.51 (0.42; 5.40)	0.02 (-0.04; 0.09)	44

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
2b, 4		HBV DNA loss				
		HBeAg loss irrespective of HBV-DNA status at baseline or week 34	Baseline ALT >2-≤5ULN	1.30 (0.57; 2.95)	0.03 (-0.06; 0.12)	33
		HBeAg seroconversion and HBV DNA loss	Baseline ALT >2-≤5ULN	1.09 (0.43; 2.75)	0.01 (-0.08; 0.09)	124
		HBeAg loss irrespective of HBV-DNA status at baseline or week 43	Baseline ALT >1-≤2ULN	1.18 (0.31; 4.40)	0.01 (-0.05; 0.07)	129
		HBeAg seroconversion and HBV DNA loss	Baseline ALT >1-≤2ULN	1.26 (0.25; 6.32)	0.01 (-0.04; 0.06)	131
		HBeAg loss irrespective of HBV-DNA status at baseline or week 52	Baseline ALT ≤1ULN	0.17 (0.01; 4.10)	-0.01 (-0.05; 0.02)	-68
		HBeAg seroconversion and HBV DNA loss	Baseline ALT ≤1ULN	0.17 (0.01; 4.10)	-0.01 (-0.05; 0.02)	-68
Schalm, 2000[67] Interferon Alfa 2b, 4 +Lamivudine, 100 vs. Interferon Alfa 2b, 4	24/24	HBeAg seroconversionand undetectable HBV DNA	Baseline ALT >5 ULN	0.92 (0.41; 2.07)	-0.01 (-0.12; 0.10)	-86
			ALT 2-5 ULN	0.95 (0.65; 1.39)	-0.02 (-0.18; 0.14)	-47
			ALT <2 ULN	1.04 (0.67; 1.61)	0.01 (-0.14; 0.17)	82
Barbaro, 2001[66] Interferon Alfa 2b, 4 + Lamivudine, 100 vs. Lamivudine, 100	24/52	Odds Ratio of sustained virologic response (sustained suppression of serum levels of HBeAg and HBV DNA) in those with baseline ALT levels of 150 or more independent on gender and age	Baseline ALT	**3.12 (1.43; 6.82)**		
Perrillo, 2002[104] Interferon Alfa 2b, 4 +Lamivudine, 100 vs. Lamivudine, 100	24/52	HBeAg loss irrespective of HBV-DNA status at baseline or week 25	Baseline ALT >5ULN	0.86 (0.44; 1.69)	-0.01 (-0.06; 0.04)	-82
		HBeAg seroconversion and HBV DNA loss	Baseline ALT >5ULN	1.08 (0.52; 2.26)	0.01 (-0.04; 0.05)	196
		HBeAg loss irrespective of HBV-DNA status at baseline or week 34	Baseline ALT >2-≤5ULN	1.15 (0.69; 1.91)	0.02 (-0.05; 0.08)	57
		HBeAg seroconversion and HBV DNA loss	Baseline ALT >2-≤5ULN	1.22 (0.66; 2.26)	0.02 (-0.04; 0.07)	57
		HBeAg loss irrespective of HBV-DNA status at baseline or	Baseline ALT >1-≤2ULN	1.17 (0.50; 2.74)	0.01 (-0.03; 0.05)	133

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		week 43				
		HBeAg seroconversion and HBV DNA loss	Baseline ALT >1-≤2ULN	1.88 (0.63; 5.65)	0.02 (-0.02; 0.05)	58
		HBeAg loss irrespective of HBV-DNA status at baseline or week 52	Baseline ALT ≤1ULN	0.60 (0.03; 12.39)	0.00 (-0.02; 0.01)	-203
		HBeAg seroconversion and HBV DNA loss	Baseline ALT ≤1ULN	1.00 (0.04; 24.34)	0.00 (-0.01; 0.01)	-406
Schalm, 2000[67] Interferon Alfa 2b, 4 + Lamivudine, 100 vs. Lamivudine, 100	24/52	HBeAg seroconversionand undetectable HBV DNA	Baseline ALT >5 ULN	0.78 (0.37; 1.65)	-0.04 (-0.15; 0.07)	-27
			Baseline ALT 2-5 ULN	0.97 (0.67; 1.40)	-0.01 (-0.17; 0.14)	-74
			Baseline ALT <2 ULN	0.95 (0.63; 1.43)	-0.02 (-0.17; 0.13)	-55
Lok, 1992[93] Interferon Alfa 2b,4 + Prednisone,15 vs. placebo for 6 weeks + 2 weeks rest than Interferon Alfa 2b, 4	24/24	Partial antiviral response: sustained clearance of serum HBV DNA by direct spot hybridization (lower limit of detection of 10 pg/mL) and clearance of HBeAg but not HBsAg	Elevated baseline ALT	1.54 (0.63; 03.77)	0.15 (-0.15; 0.45)	7
		Complete antiviral response: sustained clearance of serum HBV DNA by direct spot hybridization (lower limit of detection of 10 pg/mL) and clearance of HBeAg and HBsAg	Elevated baseline ALT	0.29 (0.01; 6.66)	-0.06 (-0.19; 0.08)	-18
Wai, 2002[102] Interferon Alfa 2b, 4 +Prednisone,15 vs. placebo for 6weeks + 2 weeks rest than Interferon Alfa 2b, 4	24/24	Adjusted for age, gender, baseline ALT, HBV DNA, and histology, precore G1896A mutation, core promoter A1762T, G1764A, and treatment with Interferon with and without prednisone pretreatment odds ratios of antiviral response: as sustained clearance of serum HBV DNA	Elevated baseline ALT	**1.22 (1.05; 1.42)**		
Perrillo, 1990[96] Interferon Alfa 2b, 5 vs. Interferon Alfa 2b, 1	24/24	Loss of HBV DNA and HBeAg	Baseline ALT 100-200U/l	2.00 (0.54; 7.46)	0.07 (-0.06; 0.21)	14
		Loss of HBV DNA and HBeAg	Baseline ALT >200U/l	2.33 (0.65; 8.40)	0.10 (-0.04; 0.24)	10
		Loss of HBV DNA and HBeAg	Baseline ALT <100U/l	2.00 (0.19; 21.21)	0.02 (-0.06; 0.11)	41

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Perrillo, 1990[96] Interferon Alfa 2b, 5 + Prednisone,40 vs. Interferon Alfa 2b,1	24/24	Loss of HBV DNA and HBeAg	Baseline ALT 100-200U/l	1.24 (0.30; 5.22)	0.02 (-0.10; 0.13)	56
		Loss of HBV DNA and HBeAg	Baseline ALT >200U/l	1.24 (0.30; 5.22)	0.02 (-0.10; 0.13)	56
		Loss of HBV DNA and HBeAg	Baseline ALT <100U/l	7.45 (0.97; 57.04)	**0.16 (0.03; 0.28)**	6
Interferon Alfa 2b, 5 + Prednisone,40 vs. Interferon Alfa 2b,5		Loss of HBV DNA and HBeAg	Baseline ALT 100-200U/l	0.62 (0.19; 2.04)	-0.06 (-0.19; 0.08)	-18
		Loss of HBV DNA and HBeAg	Baseline ALT >200U/l	0.53 (0.17; 1.69)	-0.08 (-0.22; 0.06)	-13
		Loss of HBV DNA and HBeAg	Baseline ALT <100U/l	3.73 (0.84; 16.54)	**0.13 (0.00; 0.26)**	8
Lopez-Alcorocho , 1997[85] Interferon Alfa 2b, 6 vs. Interferon Alfa 2b, 2	24/48	Increase in ALT above normal	Baseline normal ALT	13.00 (0.78; 215.69)	**0.32 (0.10; 0.53)**	3
Kim, 2006[54] Lamivudine,100 vs. placebo	80/80	Odds ratio of hepatic decompensation change in the Child-Turcotte-Pugh score of 2 or more points adjusted for treatments, ALT, HBV DNA, sex, YMDD variant, platelet, bilirubin, albumin	Higher Baseline ALT	1.01 (01.00; 01.01)		
Liaw, 2004[51] Lamivudine,100 vs. placebo	130/130	Overall disease progression by the first occurrence of any of the following: an increase of at least 2 points in the Child–Pugh score (an assessment of the severity of liver disease [range, 5 to 15, where 5 indicates good and 15 - poor liver function]	Baseline ALT ≤2 times the upper limit of normal	0.53 (0.32; 0.89)	**-0.05 (-0.10; -0.01)**	-18
			Baseline ALT >2 times the upper limit of normal	0.27 (0.11; 0.66)	**-0.04 (-0.08; -0.01)**	-23
Liaw, 2000[110] Lamivudine, 100 vs. Lamivudine, 25	104/104	Sustained HBeAg Seroconversion	Baseline ALT > 5X ULN	1.09 (0.42; 02.78)	0.01 (-0.07; 0.08)	147
			Baseline ALT 2–5X ULN	1.09 (0.49; 02.39)	0.01 (-0.08; 0.10)	107
		HBeAg Seroconversion	Baseline ALT 2–5X ULN	1.09 (0.67; 01.75)	0.02 (-0.10; 0.14)	47
		Sustained HBeAg Seroconversion	Baseline ALT 1–2X ULN	0.87 (0.24; 03.14)	-0.01 (-0.07; 0.05)	-154
			Baseline ALT <3X ULN	2.17 (0.20; 23.56)	0.01 (-0.02; 0.05)	86
Bonino, 2007[114] Peginterferon alfa-2a, 26 vs. Lamivudine, 100	48/48	Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Baseline ALT: 1 log 10 unit (IU/l) increase	4.00 (2.00; 8.00)		
			Baseline ALT	1.00 (1.00; 1.00)		
Bonino, 2007[114] Peginterferon alfa-2a, 26 + Lamivudine,	48/48	Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Baseline ALT >5 ULN	1.40 (0.73; 2.70)	0.13 (-0.12; 0.39)	8
			Baseline ALT >2-5 ULN	1.43 (0.83; 2.45)	0.10 (-0.05; 0.24)	11
			Baseline ALT<2 ULN	1.84 (1.11; 3.02)	**0.18 (0.04; 0.32)**	5

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
100 vs. Lamivudine, 100						
Cindoruk, 2007[115] Peginterferon alfa-2a,2 6 + Lamivudine, 100 vs. Lamivudine, 100	9/9	Adjusted for treatment status odds ratio of sustained response : HBeAg seroconversion, HBV DNA disappearance and ALT normalization in HBeAg (+) patients. In HBeAg (-) patients: loss of HBV DNA, ALT normalization	Baseline ALT (IU/L)	**10.32 (9.71; 10.97)**		
Lau, 2005[56] Peginterferon alfa-2a,26 + Lamivudine, 100 vs. Lamivudine, 100	48/48	HBeAg seroconversion	Baseline ALT ≤2ULN	1.00 (0.54; 1.85)	0.00 (-0.04; 0.04)	3879
			Baseline ALT >2 to 5 ULN	1.51 (0.88; 2.58)	0.04 (-0.01; 0.09)	27
			Baseline ALT > 5ULN	1.93 (1.01; 3.69)	**0.04 (0.00; 0.09)**	22
Lau, 2005[56] Peginterferon alfa-2a,26 + Lamivudine,100 vs. peginterferon alfa-2a, 26	48/48	HBeAg seroconversion	Baseline ALT ≤2ULN	0.70 (0.40; 1.23)	-0.03 (-0.08; 0.02)	-34
			Baseline ALT >2 to 5 ULN	0.83 (0.53; 1.31)	-0.02 (-0.08; 0.03)	-45
			Baseline ALT > 5ULN	1.04 (0.61; 1.78)	0.00 (-0.04; 0.05)	271
Bonino, 2007[114] Peginterferon alfa-2a, 26 + placebo, vs. Lamivudine, 100	48/48	Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Baseline ALT>5ULN	1.44 (0.74; 2.82)	0.15 (-0.12; 0.41)	7
			Baseline ALT>2-5ULN	1.65 (0.96; 2.84)	0.14 (-0.01; 0.28)	7
			Baseline ALT<2ULN	1.49 (0.89; 2.52)	0.11 (-0.03; 0.24)	9
Lau, 2005[56] Peginterferon alfa-2a, 26 + placebo, vs. Lamivudine, 100	48/48	HBeAg Seroconversion	Baseline ALT ≤2ULN	1.43 (0.81; 2.50)	0.03 (-0.02; 0.08)	34
			Baseline ALT >2 to 5 ULN	1.81 (1.07; 3.04)	**0.06 (0.01; 0.11)**	17
			Baseline ALT > ULN	1.85 (0.96; 3.56)	**0.04 (0.00; 0.08)**	25
Zhao, 2007[81] Peginterferon alfa-2b, 11 vs. Interferon Alfa 2b, 1	24/24	Multivariate adjusted odds ratio of sustained combined response: HBeAg negative, HBV DNA <5 log10 copies/mL, and normal ALT level	Baseline ALT level >3.4 vs. <3.4 ULN	1.23 (0.51; 2.92)		
Chan, 2005[59] Peginterferon alfa-2b,14 + Lamivudine, 100 vs. Lamivudine, 100	60/52	Sustained virological response as HBeAg seroconversion and HBV DNA <500,000 copies/mL	Baseline ALT levels less than 5 times the upper limit of normal	2.08 (1.18; 3.67)	**0.26 (0.08; 0.44)**	4
		Adjusted for treatment allocation, HBV genotype and	Baseline ALT	1.00 (0.99; 1.00)		

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		log HBV DNA odds ratio of persistent HBeAg loss and had less than two occasions with HBV DNA <100,000 copies/mL at any time up to week 76 of post-treatment followup				
		Adjusted for treatment allocation, HBV DNA genotype, IL-1b-511 polymorphism, baseline log HBV DNA odds ratio of persistent HBeAg loss and had less than two occasions with HBV DNA <100 000 copies/mL	Baseline ALT	1.00 (0.99; 1.00)		
Flink, 2005[120] Peginterferon alfa-2b,14 + Lamivudine, 100 vs. peginterferon alfa-2b, 14	52/52	Adjusted relative risk of flares defined as an increase in serum ALT to at least three times the baseline level	Lower ALT at baseline	**1.40 (1.20; 1.60)**		
Janssen, 2005[78] Peginterferon alfa-2b,14 + Lamivudine, 100 vs. peginterferon alfa-2b, 14	52/52	Adjusted odds ratio of Sustained HBeAg loss	Higher baseline ALT	1.10 (1.00; 1.20)		
Baseline histological activity						
Jang, 2004[65] Interferon Alfa 2b, 2 + Lamivudine, 100 vs. Lamivudine, 100	176/174	Viral breakthrough as the reappearance of serum HBV-DNA by solution hybridization assay in at least 2 consecutive tests during lamivudine therapy following the disappearance of the serum HBV DNA	Histological activity	1.00 (1.00; 1.00)		
			Extent of fibrosis	1.00 (1.00; 1.00)		
Perrillo, 2002[104] Interferon Alfa 2b, 4 vs. Lamivudine, 100	24/24	HBeAg loss of detectable levels of HBeAg in serum irrespective of HBV-DNA status at baseline or week 56	Pretreatment HAI Score 5-9	1.43 (0.61; 3.36)	0.03 (-0.04; 0.10)	38
			Pretreatment HAI Score 0-4	2.65 (0.84; 8.38)	0.04 (-0.02; 0.09)	27
			Pretreatment HAI Score >10	0.49 (0.20; 1.17)	**-0.08 (-0.15; -0.01)**	-13

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Perrillo, 2002[104] Interferon Alfa 2b, 4 + Lamivudine, 100 vs. Interferon Alfa 2b, 4	24/24	HBeAg loss of detectable levels of HBeAg in serum irrespective of HBV-DNA status at baseline or week 56	Pretreatment HAI Score 5-9	0.92 (0.36; 2.39)	-0.01 (-0.09; 0.07)	-148
			Pretreatment HAI Score 0-4	0.88 (0.27; 2.91)	-0.01 (-0.07; 0.06)	-143
			Pretreatment HAI Score >10	1.61 (0.62; 4.21)	0.04 (-0.04; 0.13)	22
Barbaro, 2001[66] Interferon Alfa 2b, 4 + Lamivudine, 100 vs. Lamivudine, 100	24/52	Odds Ratio of sustained virologic response (sustained suppression of serum levels of HBeAg and HBV DNA) in those with a baseline inflammation score of 7 or more independent on gender and age	Baseline inflammation score	**2.91 (1.04; 8.22)**		
		Odds Ratio of sustained virologic response (sustained suppression of serum levels of HBeAg and HBV DNA) in those with a baseline fibrosis score of 2 or more independent on gender and age	baseline fibrosis score	2.58 (0.88; 7.60)		
Perrillo, 2002[104] Interferon Alfa 2b, 4 + Lamivudine, 100 vs. Lamivudine, 100	24/52	HBeAg loss of detectable levels of HBeAg in serum irrespective of HBV-DNA status at baseline or week 56	Pretreatment HAI Score 5-9	1.32 (0.67; 2.62)	0.02 (-0.03; 0.07)	50
			Pretreatment HAI Score 0-4	2.34 (0.89; 6.16)	0.03 (-0.01; 0.07)	34
			Pretreatment HAI Score >10	0.79 (0.47; 1.32)	-0.03 (-0.10; 0.03)	-32
Liaw, 2004[51] Lamivudine,100 vs. placebo	130/130	Overall disease progression by an increase of at least 2 points in the Child–Pugh score	Ishak fibrosis score = 6	0.37 (0.19; 0.71)	**-0.06 (-0.10; -0.02)**	-17
			Ishak fibrosis score = 5	0.60 (0.25; 1.43)	-0.02 (-0.05; 0.01)	-60
			Ishak fibrosis score <4	0.44 (0.17; 1.12)	-0.02 (-0.05; 0.01)	-43
			Baseline Child–Pugh score >7	0.55 (0.22; 1.42)	-0.02 (-0.05; 0.01)	-60
			Baseline Child–Pugh score = 6	0.37 (0.16; 0.86)	-0.04 (-0.07; 0.00)	-28
			Baseline Child–Pugh score = 5	0.44 (0.23; 0.84)	**-0.05 (-0.09; -0.01)**	-21
Lai, 1998[50] Lamivudine, 25 vs. Lamivudine, 100	48/48	Worsening of Knodell necroinflammatory score	Patients with moderate or severe hepatitis	2.52 (0.50; 12.76)	0.02 (-0.01; 0.06)	47
		Histological response -a reduction of 2 or more points in the Knodell necroinflammatory	Patients with moderate or severe hepatitis	0.94 (0.72; 1.23)	-0.03 (-0.14; 0.09)	-40

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		score (components 1 through 3) between baseline and week 52				
		Worsening of Knodell necroinflammatory score	Patients with mild hepatitis	0.88 (0.33; 2.37)	-0.01 (-0.06; 0.05)	-150
		Histological response -a reduction of 2 or more points in the Knodell necroinflammatory score (components 1 through 3) between baseline and week 52	Patients with mild hepatitis	0.65 (0.32; 1.34)	-0.04 (-0.11; 0.03)	-24
Cindoruk, 2007[115] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	9/9	Adjusted for treatment status odds ratio of sustained response: HBeAg seroconversion, HBV DNA disappearance and ALT normalization in HBeAg (+) patients. In HBeAg (-) patients: loss of HBV DNA, ALT normalization	Presence of steatosis	1.00 (1.00; 1.00)		
			Baseline Knodell HAI	**14.97 (2.43; 92.28)**		
Flink, 2005[120] Peginterferon alfa-2b, 14 + Lamivudine, 100 vs. peginterferon alfa-2b, 14	52/52	Adjusted relative risk of Flares defined as an increase in serum ALT to at least 3 times the baseline level	Preexisting cirrhosis, yes vs. no	2.00 (1.00; 4.00)		
Buster, 2007[124] Peginterferon alfa-2b, 14 + Lamivudine,100 vs. peginterferon alfa-2b, 14	52/52	Adjusted relative risk of HBeAg seroconversion and HBV DNA <10,000 copies/ml	Presence of advanced fibrosis- fibrosis score of 4-6 (HAI)	0.98 (0.17; 05.23)		
Baseline viral load						
Jang, 2004[65] Interferon Alfa 2b, 2 + Lamivudine, 100 vs. Lamivudine, 100	176/174	Viral breakthrough as the reappearance of serum HBV-DNA by solution hybridization assay in at least 2 consecutive tests during lamivudine therapy following the disappearance of the serum HBV DNA	Baseline HBV-DNA	1.00 (1.00; 1.00)		

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Barbaro, 2001[66] Interferon Alfa 2b, 4 + Lamivudine, 100 vs. Lamivudine, 100	24/52	Odds ratio of sustained virologic response (sustained suppression of serum levels of HBeAg and HBV DNA) in those with baseline viral load of 200 pg/ml or less independent on gender and age	Baseline HBV DNA	**7.23 (2.71; 19.57)**		
Wai, 2002[102] Interferon Alfa 2b, 4 + Prednisone, 15 vs. placebo for 6weeks + 2 weeks rest than Interferon Alfa 2b, 4	24/24	Adjusted for age, gender, baseline ALT ,HBV DNA, and histology, precore G1896A mutation, core promoter A1762T, G1764A, and treatment with Interferon with and without prednisone pretreatment odds ratios of antiviral response: as sustained clearance of serum HBV DNA	Low baseline HBV-DNA level	1.10 (1.03; 1.17)		
			Low baseline HBV-DNA in patients with elevated baseline ALT	1.10 (1.01; 1.21)		
Perrillo, 1990[96] Interferon Alfa 2b, 5 vs. Interferon Alfa 2b, 1	24/24	Loss of HBV DNA and HBeAg	Baseline HBV DNA 2-99pg/ml	1.67 (0.67; 4.16)	0.10 (-0.07; 0.27)	10
			Baseline HBV DNA 100-200 pg/ml	11.00 (0.63; 192.71)	**0.12 (0.01; 0.23)**	8
			Baseline HBV DNA >200 pg/ml	0.33 (0.01; 07.95)	-0.02 (-0.09; 0.04)	-41
Sarin, 2005[69] Interferon Alfa 2b, 5 + Lamivudine, 100 vs. Lamivudine, 100	52/52	HBV DNA loss and HBeAg seroconversion	Baseline HBV DNA >107 copies/mL	2.92 (0.63; 13.56)	0.10 (-0.03; 0.24)	10
	52/76			4.87 (1.14; 20.74)	**0.21 (0.05; 0.37)**	5
	52/52	HBeAg loss	Baseline HBV DNA >107 copies/mL	1.62 (0.66; 4.01)	0.10 (-0.08; 0.28)	10
	52/76			3.89 (1.20; 12.69)	**0.23 (0.06; 0.41)**	4
	52/52	HBeAg loss with anti-HBe appearance	Baseline HBV DNA >107 copies/mL	2.92 (0.63; 13.56)	0.10 (-0.03; 0.24)	10
	52/76			4.87 (1.14; 20.74)	**0.21 (0.05; 0.37)**	5
Perrillo, 1990[96] Interferon Alfa 2b, 5 + Prednisone,40 vs. Interferon Alfa 2b, 1	24/24	Loss of HBV DNA and HBeAg	Baseline HBV DNA 2-99 pg/ml	1.71 (0.70; 4.20)	0.10 (-0.06; 0.27)	10
			Baseline HBV DNA 100-200 pg/ml	8.40 (0.47; 151.34)	**0.09 (0.00; 0.18)**	11
			Baseline HBV DNA >200 pg/ml	0.93 (0.06; 14.42)	0.00 (-0.07; 0.06)	-601
Interferon Alfa 2b, 5 + Prednisone,40 vs. Interferon Alfa 2b, 5		Loss of HBV DNA and HBeAg	Baseline HBV DNA 2-99 pg/ml	1.03 (0.49; 2.16)	0.01 (-0.18; 0.19)	164
			Baseline HBV DNA 100-200 pg/ml	0.75 (0.21; 2.59)	-0.03 (-0.16; 0.10)	-32
			Baseline HBV DNA	2.80 (0.12; 66.85)	0.02 (-0.04; 0.08)	44

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
			>200 pg/ml			
Kim, 2006[54] Lamivudine,100 vs. placebo	80/80	Odds ratio of hepatic decompensation change in the Child-Turcotte-Pugh score of 2 or more points adjusted for treatments, ALT, HBV DNA, sex, YMDD variant, platelet, bilirubin, albumin	Baseline platelet count less vs. >65 000/µl	0.98 (0.97; 0.99)		
			Baseline HBV DNA	1.00 (1.00; 1.00)		
Liaw, 2004[51] Lamivudine,100 vs. Placebo	130/130	Overall disease progression	Baseline HBV DNA below the lower limit of quantitation	0.22 (0.07; 0.70)	-0.03 (-0.06; 0.00)	-31
			Baseline HBV DNA 0.7-10 meq/ml	0.77 (0.34; 1.74)	-0.01 (-0.04; 0.02)	-103
			Baseline HBV DNA >10-100 meq/ml	0.37 (0.13; 1.05)	-0.02 (-0.05; 0.00)	-43
			Baseline HBV DNA >100 meq/ml	0.41 (0.18; 0.94)	-0.03 (-0.07; 0.00)	-30
Bonino, 2007[114] Peginterferon alfa-2a, 26 vs. Lamivudine, 100	48/48	Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Baseline HBV DNA, per 1 log decrease	1.20 (1.00; 1.40)		
			Log10 HBV DNA (baseline)	1.06 (0.93; 1.21)		
			HBV DNA:1 log10 unit (copies/ml) decrease	1.28 (1.10; 1.40)		
Cindoruk, 2007[115] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	9/9	Adjusted for treatment status odds ratio of sustained response: HBeAg seroconversion, HBV DNA disappearance and ALT normalization in HBeAg (+) patients. In HBeAg (-) patients: loss of HBV DNA, ALT normalization	Baseline mean viral load (copy/mL)	1.05 (0.13; 8.14)		
Bonino, 2007[114] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	48/48	Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Baseline HBV DNA >8.42 log 10 copies/ml	1.37 (0.67; 2.80)	0.08 (-0.10; 0.26)	12
			Baseline HBV DNA >6.12-8.42 log 10 copies/ml	1.78 (1.11; 2.84)	**0.17 (0.04; 0.29)**	6
			Baseline HBV DNA <6.12 log 10 copies/ml	2.24 (1.31; 3.83)	**0.35 (0.13; 0.57)**	3

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lau, 2005[56] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	48/48	HBeAg Seroconversion	Baseline HBV DNA levels>10.26 (log copies/ml)	2.01 (0.82; 4.90)	0.03 (-0.01; 0.06)	39
			Baseline HBV DNA levels ≤9.07 (log copies/ml)	0.84 (0.47; 1.48)	-0.01 (-0.06; 0.03)	-69
			Baseline HBV DNA levels >9.07–10.26 (log copies/ml)	1.91 (1.16; 3.15)	**0.07 (0.02; 0.12)**	14
Lau, 2005[56] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. peginterferon alfa-2a, 26	48/48	HBeAg Seroconversion	Baseline HBV DNA levels>10.26 (log copies/ml)	1.27 (0.59; 2.75)	0.01 (-0.02; 0.05)	90
			Baseline HBV DNA levels ≤9.07 (log copies/ml)	0.54 (0.32; 0.91)	**-0.06 (-0.11; -0.01)**	-16
			Baseline HBV DNA levels >9.07–10.26 (log copies/ml)	1.03 (0.68; 1.54)	0.00 (-0.06; 0.06)	271
Bonino, 2007[114] Peginterferon alfa-2a, 26 + Placebo, vs. Lamivudine, 100	48/48	Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Baseline HBV DNA >8.42 log 10 copies/ml	1.80 (0.91; 3.57)	0.18 (-0.02; 0.37)	6
			Baseline HBV DNA >6.12-8.42 log 10 copies/ml	3.87 (2.55; 5.88)	**0.61 (0.46; 0.76)**	2
			Baseline HBV DNA <6.12 log 10 copies/ml	1.27 (0.71; 2.30)	0.08 (-0.11; 0.26)	13
Lau, 2005[56] Peginterferon alfa-2a, 26 + Placebo,. vs. Lamivudine, 100	48/48	HBeAg Seroconversion	Baseline HBV DNA levels >10.26 (log copies/ml)	1.58 (0.62; 4.01)	0.01 (-0.02; 0.04)	67
			Baseline HBV DNA levels ≤9.07 (log copies/ml)	1.55 (0.95; 2.51)	**0.05 (0.00; 0.10)**	21
			Baseline HBV DNA levels >9.07–10.26 (log copies/ml)	1.86 (1.13; 3.08)	**0.07 (0.01; 0.12)**	15
Zhao, 2007[81] Peginterferon alfa-2b,11 vs. Interferon Alfa 2b, 1	24/24	Multivariate adjusted odds ratio of sustained combined response: HBeAg negative, HBV DNA <5 log 10 copies/mL, and normal ALT level	Baseline HBV DNA >8.1 vs. < 8.1 log 10 copies/mL	0.53 (0.22; 1.28)		

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Chan, 2006[118] Peginterferon alfa-2b,14 + Lamivudine, 100 vs. Lamivudine, 100	60/52	Adjusted for treatment allocation, HBV genotype, baseline ALT odds ratio of persistent HBeAg loss	Log HBV DNA at baseline (copies/mL)	0.70 (0.38; 1.30)		
		Adjusted for treatment allocation, HBV DNA genotype, IL-1b-511 polymorphism, baseline ALT odds ratio of persistent HBeAg loss	Log HBV DNA at baseline (copies/mL)	0.65 (0.35; 1.20)		
Janssen, 2005[78] Peginterferon alfa-2b, 14 + Lamivudine,100 vs. Peginterferon alfa-2b, 14	52/52	Adjusted odds ratio of sustained HBeAg loss	Low baseline viral load	1.60 (1.30; 1.80)		
ALT normalization						
van Zonneveld, 2006[125] Peginterferon alfa-2b,14 +Lamivudine,100 vs. Peginterferon alfa-2b, 14	52/52	Improved inflammatory changes in the liver as decrease of at least 2 points for the necroinflammatory score (range 0-18)	No ALT normalization	0.61 (0.28; 1.36)	-0.04 (-0.10; 0.02)	-27
		Improved fibrosis scores as decrease of at least 1 point for the fibrosis score (range 0-6)	No ALT normalization	0.87 (0.30; 2.54)	-0.01 (-0.05; 0.04)	-176
Change in weight						
Bonino, 2007[114] Peginterferon alfa-2a, 26 vs. Lamivudine, 100	48/48	Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Weight (10 kg increase)	1.03 (0.81; 1.30)		
			Body weight: 10 kg increase	1.00 (1.00; 1.00)		
Duration of hepatitis						
Barbaro, 2001[66] Interferon Alfa 2b, 4 + Lamivudine, 100 vs. Lamivudine, 100	24/52	Odds Ratio of sustained virologic response (sustained suppression of serum levels of HBeAg and HBV DNA) in those with an estimated duration of disease of 10 years or less independent on gender and age	Duration of disease	2.55 (1.26; 5.19)		

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
HBeAg negative						
Chang, 2005[76] Entecavir, 0.10 vs. Lamivudine, 100	48/48	Undetectable HBV DNA level by bDNA assay and normal ALT level	HBeAg negative	10.11 (0.62; 164.68)	**0.35 (0.11; 0.60)**	3
Chang, 2005[76] Entecavir, 0.50 vs. Entecavir, 0.10	48/48	Undetectable HBV DNA level by bDNA assay and normal ALT level	HBeAg negative	1.13 (0.46; 2.77)	0.05 (-0.29; 0.38)	21
Chang, 2005[76] Entecavir,0.50 vs. Lamivudine,100	48/48	Undetectable HBV DNA level by bDNA assay and normal ALT level	HBeAg negative	11.38 (0.70; 184.38)	**0.40 (0.14; 0.66)**	2
Chang, 2005[76] Entecavir,1 vs. Entecavir, 0.10	48/48	Undetectable HBV DNA level by bDNA assay and normal ALT level	HBeAg negative	1.89 (0.90; 3.94)	0.31 (-0.02; 0.64)	3
Chang, 2005[76] Entecavir, 1 vs. Entecavir, 0.50	48/48	Undetectable HBV DNA level by bDNA assay and normal ALT level	HBeAg negative	1.67 (0.81; 3.41)	0.27 (-0.08; 0.61)	4
Chang, 2005[76] Entecavir, 1 vs. Lamivudine, 100	48/48	Undetectable HBV DNA level by bDNA assay and normal ALT level	HBeAg negative	18.38 (1.18; 285.96)	**0.67 (0.41; 0.92)**	1
Liaw, 2004[51] Lamivudine,100 vs. Placebo	130/130	Overall disease progression by the first occurrence of any of the following: an increase of at least 2 points in the Child–Pugh score	HBeAg negative	0.72 (0.36; 1.43)	-0.02 (-0.05; 0.02)	-59
Chan, 2005[117] Peginterferon alfa-2b, 14 + Lamivudine, 100 vs. Lamivudine, 100	60/52	Biochemical relapse as ALT elevation to >2 times upper limit of laboratory normal	Negative HBeAg at week 53	2.14 (0.96; 4.80)	**0.16 (0.00; 0.32)**	6
Lai, 2007[71] Telbivudine, 600 vs. Lamivudine, 100	52/52	ALT normalization	HBeAg-negative patients	0.94 (0.84; 1.04)	-0.05 (-0.13; 0.03)	-19
		Primary treatment failure - serum HBV DNA levels remained above 5 log10 copies per milliliter	HBeAg-negative patients	0.17 (0.02; 1.39)	-0.02 (-0.05; 0.00)	-45
		Reduction of at least two points in the Knodell necroinflammatory score, with no worsening in the Knodell fibrosis score	HBeAg-negative patients	1.01 (0.88; 1.15)	0.01 (-0.08; 0.09)	168

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Ishak fibrosis scores improved	HBeAg-negative patients	1.28 (1.07; 1.54)	**0.13 (0.04; 0.22)**	8
		Serum HBV DNA undetectable by PCR	HBeAg-negative patients	1.24 (1.12; 1.36)	**0.17 (0.10; 0.24)**	6
		Serum HBV DNA undetectable by PCR	HBeAg-negative patients	1.30 (1.15; 1.48)	**0.18 (0.10; 0.27)**	6
		HBV DNA <3 log10 copies/ml	HBeAg-negative patients	0.91 (0.49; 1.67)	-0.01 (-0.06; 0.04)	-122
		Reduction in serum HBV DNA levels to <5 log 10 copies per milliliter with HBeAg loss, or normalization of ALT	HBeAg-negative patients	0.97 (0.88; 1.08)	-0.02 (-0.10; 0.06)	-50
		HBV DNA <3-4 log10 copies/ml	HBeAg-negative patients	0.65 (0.35; 1.18)	-0.04 (-0.09; 0.01)	-25
		Viral breakthrough - at least two consecutive determinations of an increase in HBV DNA by at least 1 log 10 copy per milliliter from nadir	HBeAg-negative patients	0.18 (0.07; 0.46)	**-0.10 (-0.15; -0.05)**	-10
		Viral breakthrough - at least two consecutive determinations of an increase in HBV DNA by at least 1 log 10 copy per milliliter from nadir with treatment-emergent resistance mutations	HBeAg-negative patients	0.21 (0.08; 0.54)	**-0.08 (-0.13; -0.04)**	-12
		HBV DNA >4 log10copies/ml	HBeAg-negative patients	0.55 (0.27; 1.13)	-0.04 (-0.09; 0.01)	-25
HBeAg positive						
Chang, 2005[76] Entecavir, 0.10 vs. Lamivudine, 100	48/48	Undetectable HBV DNA level by bDNA assay, normal ALT level, and loss of HBeAg if HBeAg positive at baseline	HBeAg positive	0.21 (0.01; 4.26)	-0.06 (-0.16; 0.04)	-16
		HBeAg loss	HBeAg positive	0.15 (0.01; 2.83)	-0.09 (-0.21; 0.02)	-11
		HBeAg seroconversion	HBeAg positive	0.21 (0.01; 4.26)	-0.06 (-0.16; 0.04)	-16
Chang, 2005[76] Entecavir, 0.50 vs. Entecavir, 0.10	48/48	Undetectable HBV DNA level by bDNA assay, normal ALT level, and loss of HBeAg if HBeAg positive at baseline	HBeAg positive	6.58 (0.35; 122.21)	0.09 (-0.02; 0.21)	11
		HBeAg loss	HBeAg positive	6.58 (0.35; 122.21)	0.09 (-0.02; 0.21)	11
		HBeAg seroconversion	HBeAg positive	2.82 (0.12; 66.62)	0.03 (-0.05; 0.12)	32

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Entecavir,0.50 vs.Lamivudine,100		Undetectable HBV DNA level by bDNA assay, normal ALT level, and loss of HBeAg if HBeAg positive at baseline	HBeAg positive	1.50 (0.27; 8.38)	0.03 (-0.10; 0.16)	32
		HBeAg loss	HBeAg positive	1.00 (0.22; 4.59)	0.00 (-0.14; 0.14)	
		HBeAg seroconversion	HBeAg positive	0.50 (0.05; 5.24)	-0.03 (-0.13; 0.07)	-32
Chang, 2005[76] Entecavir, 1 vs. Entecavir, 0.10	48/48	Undetectable HBV DNA level by bDNA assay, normal ALT level, and loss of HBeAg if HBeAg positive at baseline	HBeAg positive	5.54 (0.28; 110.42)	0.07 (-0.04; 0.19)	13
		HBeAg loss	HBeAg positive	7.75 (0.42; 143.52)	0.11 (-0.02; 0.24)	9
		HBeAg seroconversion	HBeAg positive	3.32 (0.14; 78.25)	0.04 (-0.06; 0.13)	27
Chang, 2005[76] Entecavir, 1 vs. Entecavir, 0.50	48/48	Undetectable HBV DNA level by bDNA assay, normal ALT level, and loss of HBeAg if HBeAg positive at baseline	HBeAg positive	0.79 (0.14; 4.39)	-0.02 (-0.16; 0.12)	-51
		HBeAg loss	HBeAg positive	1.19 (0.26; 5.40)	0.02 (-0.14; 0.17)	58
		HBeAg seroconversion	HBeAg positive	1.19 (0.08; 18.06)	0.01 (-0.09; 0.10)	173
Chang, 2005[76] Entecavir, 1 vs. Lamivudine, 100	48/48	Undetectable HBV DNA level by bDNA assay, normal ALT level, and loss of HBeAg if HBeAg positive at baseline	HBeAg positive	1.19 (0.18; 7.86)	0.01 (-0.12; 0.14)	86
		HBeAg loss	HBeAg positive	1.19 (0.26; 5.40)	0.02 (-0.14; 0.17)	58
		HBeAg seroconversion	HBeAg positive	0.59 (0.06; 6.18)	-0.03 (-0.14; 0.08)	-39
Kim, 2006[54] Lamivudine, 100 vs. Placebo	80/80	Odds ratio of hepatic decompensation change in the Child-Turcotte-Pugh score of 2 or more points adjusted for treatments, ALT, HBV DNA, sex, YMDD variant, platelet, bilirubin, albumin	HBeAg positive status	1.00 (1.00; 1.00)		
Liaw, 2004[51] Lamivudine, 100 vs. Placebo	130/130	Overall disease progression	HBeAg positive	0.30 (0.16; 0.55)	**-0.08 (-0.13; -0.04)**	-12
Cindoruk, 2007[115] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	9/9	Adjusted for treatment status odds ratio of sustained response: HBeAg seroconversion, HBV DNA disappearance and ALT normalization in HBeAg (+)	Baseline HBeAg status	4.72 (2.66; 8.38)		

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		patients. In HBeAg (-) patients: loss of HBV DNA, ALT normalization				
Chan, 2005[117] Peginterferon alfa-2b, 14 + Lamivudine, 100 vs. Lamivudine, 100	60/52	Biochemical relapse as ALT elevation to >2 times upper limit of laboratory normal	Positive HBeAg at week 52	0.55 (0.35; 0.85)	**-0.28 (-0.47; -0.09)**	-4
Lai, 2007[71] Telbivudine, 600 vs. Lamivudine, 100	52/52	ALT normalization	HBeAg-positive patients	1.03 (0.96; 1.11)	0.02 (-0.03; 0.08)	43
		Primary treatment failure serum HBV DNA levels remained above 5 log10 copies per milliliter	HBeAg-positive patients	0.36 (0.22; 0.57)	**-0.09 (-0.12; -0.05)**	-12
		Reduction of at least two points in the Knodell necroinflammatory score, with no worsening in the Knodell fibrosis score	HBeAg-positive patients	1.15 (1.03; 1.27)	**0.08 (0.02; 0.15)**	12
		Ishak fibrosis scores improved	HBeAg-positive Patients	1.11 (1.01; 1.23)	**0.07 (0.01; 0.13)**	14
		HBV DNA level below 5 log10 copies per milliliter and HBeAg loss	HBeAg-positive patients	1.13 (0.90; 1.41)	0.03 (-0.03; 0.08)	35
		HBeAg loss	HBeAg-positive patients	1.10 (0.88; 1.39)	0.02 (-0.03; 0.08)	41
		HBeAg seroconversion	HBeAg-positive patients	1.04 (0.82; 1.33)	0.01 (-0.04; 0.06)	112
		Serum HBV DNA undetectable by PCR	HBeAg-positive patients	1.49 (1.30; 1.70)	**0.20 (0.13; 0.26)**	5
		Serum HBV DNA undetectable by PCR	HBeAg-positive patients	1.54 (1.27; 0.87)	**0.14 (0.08; 0.20)**	7
		HBV DNA <3 log10 copies/ml	HBeAg-positive patients	0.93 (0.67; 1.29)	-0.01 (-0.05; 0.03)	-107
		Reduction in serum HBV DNA levels to < 5 log10 copies per milliliter with loss of hepatitis B e antigen, or normalization of ALT	HBeAg-positive patients	1.13 (1.04; 1.22)	**0.08 (0.03; 0.14)**	12
		HBV DNA <3-4 log10 copies/ml	HBeAg-positive patients	1.05 (0.79; 1.39)	0.01 (-0.04; 0.06)	119
		Viral breakthrough - at least two consecutive determinations of an increase in HBV DNA by at least 1 log10 copy per milliliter from nadir	HBeAg-positive patients	0.38 (0.25; 0.59)	**-0.09 (-0.13; -0.06)**	-11

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		Viral breakthrough - at least two consecutive determinations of an increase in HBV DNA by at least 1 log10 copy per milliliter from nadir with treatment-emergent resistance mutations	HBeAg-positive patients	0.46 (0.28; 0.73)	**-0.06 (-0.09; -0.03)**	-17
		HBV DNA >4 log10copies/ml	HBeAg-positive patients	0.67 (0.54; 0.82)	**-0.12 (-0.18; -0.06)**	-8
Flink, 2005[120] Peginterferon alfa-2b, 14+Lamivudine,100 vs. Peginterferon alfa-2b, 14	52/52	Adjusted relative risk of HBeAg loss	Host induced flares followed by a decline of 1 log HBV DNA or more within the 4 months vs. no flares	2.40 (1.00; 5.80)		
Gender						
Jang, 2004[65] Interferon Alfa 2b, 2 + Lamivudine, 100 vs. Lamivudine, 100	176/174	Viral breakthrough as the reappearance of serum HBV-DNA by solution hybridization assay in at least two consecutive tests during lamivudine therapy following the disappearance of the serum HBV DNA	Sex	1.00 (1.00; 1.00)		
Kim, 2006[54] Lamivudine, 100 vs. Placebo	80/80	Odds ratio of hepatic decompensation change in the Child-Turcotte-Pugh score of 2 or more points adjusted for treatments, ALT, HBV DNA, sex, YMDD variant, platelet, bilirubin, albumin	Sex	1.00 (1.00; 1.00)		
Liaw, 2004[51] Lamivudine, 100 vs. Placebo	130/130	Overall disease progression	Male	0.53 (0.33; 0.84)	**-0.07 (-0.12; -0.01)**	-15
			Female	0.12 (0.03; 0.58)	**-0.03 (-0.06; -0.01)**	-31
Bonino, 2007[114] Peginterferon alfa-2a, 26 vs. Lamivudine, 100	48/48	Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Female	1.93 (1.1; 3.4)		
			Male	0.68 (0.34; 1.37)		
Bonino, 2007[114] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	48/48	Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Female	1.46 (0.74; 2.89)	0.15 (-0.10; 0.40)	7
			Male	1.65 (1.15; 2.39)	0.14 (0.04; 0.24)	7

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Bonino, 2007[114] Peginterferon alfa-2a, 26 + Placebo vs. Lamivudine, 100	48/48	Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Female	1.20 (0.57; 2.55)	0.06 (-0.20; 0.33)	15
			Male	1.61 (1.11; 2.33)	0.13 (0.03; 0.23)	8
Zhao, 2007[81] Peginterferon alfa-2b, 11 vs. Interferon Alfa 2b, 1	24/24	Multivariate adjusted odds ratio of sustained combined response: HBeAg negative, HBV DNA <5 log10 copies/mL, and normal ALT level	Female	0.59 (0.22;1.60)		
Genotype						
Wai, 2002[102] Interferon Alfa 2b, 4 + Prednisone, 15 vs. Placebo for 6 weeks + 2 weeks rest then Interferon Alfa 2b, 4	24/24	Adjusted for age, gender, baseline ALT, HBV DNA, and histology, precore G1896A mutation, core promoter A1762T, G1764A, and treatment with Interferon with and without prednisone pretreatment odds ratios of antiviral response: as sustained clearance of serum HBV DNA	HBV genotype B vs. C in patients with elevated baseline ALT	1.47 (1.18; 1.82)		
			HBV genotype B vs. C	1.28 (1.06; 1.42)		
Bonino, 2007[114] Peginterferon alfa-2a, 26 vs. Lamivudine, 100	48/48	Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Genotype C vs. D	3.30 (1.70; 6.50)		
			HBV genotype: A vs. D	0.97 0.30; 2.70)		
			HBV genotype C vs. D	2.90 (1.70; 5.00)		
			HBV genotype: A vs. C	0.33 (0.10; 0.90)		
			HBV genotype: A vs. B	0.42 (0.10; 1.20)		
			HBV genotype: B vs. D	2.31 (1.30; 4.20)		
			HBV genotype: B vs. C	0.79 (0.50; 1.30)		
			Genotype (C vs. D) 1 year of followup	5.46 (2.46; 12.10)		
			Genotype (B vs. D)	3.69 (1.54; 8.79)		
			Genotype (A vs. D)	2.58 (0.73; 9.20)		
Bonino, 2007[114] Peginterferon alfa-2a, 26+Lamivudine, 100 vs. Lamivudine, 100	48/48	Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Genotype B	0.57 (0.29; 1.11)	-0.17 (-0.35; 0.02)	-6
			Genotype D	3.33 (1.53; 7.27)	**0.26 (0.11; 0.41)**	4
			Genotype C	2.09 (1.29; 3.40)	**0.29 (0.12; 0.45)**	3
			Genotype A	1.60 (0.17; 14.63)	0.08 (-0.26; 0.41)	13
Lau, 2005[56] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	48/48	HBeAg Seroconversion	HBV genotype D	0.67 (0.11; 3.97)	0.00 (-0.02; 0.01)	-274
			HBV genotype C	1.49 (0.96; 2.31)	**0.05 (0.00; 0.11)**	19
			HBV genotype B	1.42 (0.78; 2.58)	0.03 (-0.02; 0.07)	38
			HBV genotype A	1.34 (0.30; 5.92)	0.00 (-0.02; 0.02)	268

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lau, 2005[56] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. peginterferon alfa-2a, 26	48/48	HBeAg Seroconversion	HBV genotype D	1.00 (0.14; 7.05)	0.00 (-0.01; 0.01)	
			HBV genotype C	0.86 (0.59; 1.25)	-0.03 (-0.09; 0.04)	-39
			HBV genotype B	1.04 (0.60; 1.80)	0.00 (-0.04; 0.05)	271
			HBV genotype A	0.33 (0.11; 1.02)	-0.03 (-0.06; 0.00)	-34
Bonino, 2007[114] Peginterferon alfa-2a, 26 + Placebo, vs. Lamivudine, 100	48/48	Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Genotype D	1.47 (0.59; 3.69)	0.05 (-0.07; 0.18)	19
			Genotype C	2.22 (1.36; 3.63)	**0.32 (0.15; 0.50)**	3
			Genotype B	1.14 (0.70; 1.85)	0.05 (-0.15; 0.26)	18
			Genotype A	2.18 (0.27; 17.32)	0.15 (-0.20; 0.50)	7
Lau, 2005[56] Peginterferon alfa-2a, 26 + Placebo vs. Lamivudine, 100	48/48	HBeAg Seroconversion	HBV genotype D	0.67 (0.11; 3.97)	0.00 (-0.02; 0.01)	-274
			HBV genotype C	1.73 (1.13; 2.65)	**0.08 (0.02; 0.14)**	13
			HBV genotype B	1.36 (0.74; 2.48)	0.02 (-0.02; 0.07)	45
			HBV genotype A	4.01 (1.15; 14.07)	**0.03 (0.01; 0.06)**	30
Zhao, 2007[81] Peginterferon alfa-2b, 11 vs. Interferon Alfa 2b, 1	24/24	Multivariate adjusted odds ratio of sustained combined response: HBeAg negative, HBV DNA <5 log10 copies/mL, and normal ALT level	Genotype C vs. B	0.19 (0.08; 0.46)		
Chan, 2006[118] Peginterferon alfa-2b, 14 +Lamivudine, 100 vs. Lamivudine, 100	60/52	Adjusted for treatment allocation, hepatitis B virus (HBV) genotype, baseline Alanine aminotransferase and log HBV DNA odds ratio of persistent HBeAg loss	interleukin (IL)-1b-511 baseline genotype T/T vs. C/C	4.10 (0.31; 55.90)		
			Interleukin (IL)-1b-511 baseline genotype C/T vs. C/C	10.37 (1.11; 96.96)		
			interleukin (IL)-1b-511 baseline genotype C/T and T/T vs. C/C	8.30 (0.93; 73.50)		
			interleukin (IL)-1b-31 baseline genotype C/T vs. T/T	7.90 00.85; 73.60)		
			interleukin (IL)-1b-31 baseline genotype C/T and C/C vs. T/T	7.97 (0.90; 70.95)		
			interleukin (IL)-1b-31 baseline genotype C/C vs. T/T	8.10 (0.73; 90.80)		
			IL-1 receptor antagonist genotype IL-1RN 1/2 vs. 1/1	0.82 (0.14; 5.10)		
			Haplotype -511/-31 of	0.53 (0.22; 1.30)		

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
			interleukin (IL)-1b C-T vs. T-C			
			Haplotype -511/-31 of interleukin (IL)-1b C-C vs. T-C	6.90 (0.49; 98.10)		
			Genotype HBV DNA C (vs. B)	2.10 (0.48; 8.60)		
			Genotype HBV DNA C (vs. B)	1.80 (0.44; 7.40)		
Janssen, 2005[78] Peginterferon alfa-2b, 14 + Lamivudine,100 vs. Peginterferon alfa-2b, 14	52/52	Adjusted odds ratio of sustained HBeAg loss	HBV genotype B vs. C	2.20 (0.70; 7.00)		
Buster, 2007[124] Peginterferon alfa-2b, 14 + Lamivudine, 100 vs. Peginterferon alfa-2b, 14	52/52	Adjusted relative risk of HBeAg seroconversion and HBV DNA <10,000 copies/ml.	HBV genotype and high baseline necroinflammatory score	1.31 (1.05; 1.65)		
Janssen, 2005[78] Peginterferon alfa-2b, 14 + Lamivudine, 100 vs. Peginterferon alfa-2b, 14	52/52	Adjusted odds ratio of Sustained HBeAg loss	HBV genotype A vs. D	2.40 (1.30; 4.60)		
			HBV genotype A vs. C	3.60 (1.40; 8.90)		
Buster, 2007[124] Peginterferon alfa-2b, 14 + Lamivudine, 100 vs. Peginterferon alfa-2b, 14	52/52	Adjusted relative risk of HBeAg seroconversion and HBV DNA <10,000 copies/ml	Genotype B vs. D	4.59 (1.14; 18.43)		
			Genotype B vs. C	12.13 (1.24; 118.30)		
			Genotype A vs. D	4.28 (1.39; 13.21)		
			Genotype A vs. C	11.30 (1.38; 92.57)		
Westland, 2003[126] Adefovir dipivoxil, 10 vs. Lamivudine, 100	48/0	Relative risk of viral response (reduction in HBV DNA) adjusted for baseline serum HBV DNA and ALT levels among different viral genotypes	Genotype			

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Mutation						
Barbaro, 2001[66] Interferon Alfa 2b, 4 + Lamivudine, 100 vs. Lamivudine, 100	24/52	Odds ratio of sustained virologic response (sustained suppression of serum levels of HBeAg and HBV DNA) in those with the absence of YMDD mutation independent on gender and age	No YMDD mutation	2.73 (1.09; 7.42)		
Kim, 2006[54] Lamivudine,100 vs. Placebo	80/80	Odds ratio of hepatic decompensation change in the Child-Turcotte-Pugh score of 2 or more points adjusted for treatments, ALT, HBV DNA, sex, YMDD variant, platelet, bilirubin, albumin	YMDD	1.00 (1.00; 1.00)		
Dienstag, 2003[107] Lamivudine, 100 vs. Lamivudine, 100	144/96	Worsened scores	YMDD for 1–2 years	1.50 (0.25; 8.85)	0.01 (-0.02; 0.04)	152
		Improved (decrease of 2 points) HAI necroinflammatory score	YMDD for 1–2 years	1.33 (0.30; 5.86)	0.01 (-0.03; 0.04)	152
		No change	YMDD for 1–2 years	0.60 (0.15; 2.47)	-0.01 (-0.05; 0.02)	-76
		Worsened scores	YMDD for >2 years	5.00 (0.59; 42.29)	**0.03 (0.00; 0.06)**	38
		Improved (decrease of 2 points) HAI necroinflammatory score	YMDD for >2 years	0.40 (0.13; 01.25)	-0.04 (-0.09; 0.01)	-25
		No change	YMDD for >2 years	1.18 (0.55; 2.55)	0.01 (-0.05; 0.07)	76
		Worsened scores	YMDD for <1 years	5.00 (0.24; 103.29)	0.01 (-0.01; 0.04)	76
		Improved (decrease of 2 points) HAI necroinflammatory score	YMDD for <1 years	0.17 (0.02; 1.37)	-0.03 (-0.07; 0.00)	-30
		No change	YMDD for <1 years	2.00 (0.51; 7.85)	0.02 (-0.02; 0.06)	51
Yuen, 2005[111] Lamivudine, 100 vs. Lamivudine, 100	48/48	Change in necroinflammation: Worsening	YMDD	1.09 (0.06; 19.21)	-0.05 (-0.23; 0.13)	-20
		Change in fibrosis: Worsening	YMDD	0.95 (0.14; 6.44)	-0.01 (-0.28; 0.27)	-140
		Change in necroinflammation: Improvement	YMDD	1.04 (0.53; 2.05)	0.02 (-0.37; 0.41)	47
		Change in fibrosis: Improvement	YMDD	2.54 (0.11; 57.25)	-0.02 (-0.19; 0.16)	-60
		Change in necroinflammation: No change	YMDD	1.07 (0.43; 2.66)	0.03 (-0.36; 0.42)	35
		Change in fibrosis: No change	YMDD	1.03 (0.74; 1.42)	0.02 (-0.25; 0.30)	42
Dienstag, 2003[107] Lamivudine, 100 vs. Lamivudine, 100	144/96	Worsened	No YMDD	7.00 (0.36; 134.37)	0.02 (-0.01; 0.05)	51
		Improved (decrease of 2 points)	No YMDD	0.18 (0.05; 0.59)	**-0.09 (-0.15; -0.04)**	-11

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
		HAI necroinflammatory score				
		No change	No YMDD	3.20 (1.20; 8.52)	**0.07 (0.02; 0.13)**	14
Lau, 2005[56] Peginterferon alfa-2a, 26+Lamivudine, 100 vs. Lamivudine, 100	48/48	HBeAg Seroconversion	Previous treatment: LAM	0.86 (0.29; 2.53)	0.00 (-0.03; 0.02)	-278
Treatment status						
Lau, 2005[56] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	48/48	HBeAg Seroconversion	Previous treatment: IFN	2.76 (0.89; 8.56)	**0.03 (0.00; 0.05)**	39
			No previous exposure to lamivudine	1.52 (1.08; 2.12)	**0.09 (0.02; 0.15)**	12
			No previous exposure to conventional interferon	1.32 (0.94; 1.84)	0.06 (-0.01; 0.12)	18
Lau, 2005[56] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. peginterferon alfa-2a, 26	48/48	HBeAg Seroconversion	Previous treatment: LAM	0.60 (0.22; 1.63)	-0.01 (-0.04; 0.01)	-68
			Previous treatment: IFN	0.85 (0.39; 1.86)	-0.01 (-0.04; 0.03)	-135
			No previous exposure to lamivudine	0.88 (0.67; 1.17)	-0.03 (-0.11; 0.04)	-30
			No previous exposure to conventional interferon	0.85 (0.64; 1.14)	-0.04 (-0.11; 0.03)	-25
Lau, 2005[56] Peginterferon alfa-2a,26 + Placebo vs. Lamivudine, 100	48/48	HBeAg Seroconversion	Previous treatment: LAM	1.43 (0.55; 3.71)	0.01 (-0.02; 0.04)	90
			Previous treatment: IFN	3.26 (1.08; 9.88)	**0.03 (0.00; 0.06)**	30
			No previous exposure to lamivudine	1.72 (1.24; 2.38)	**0.12 (0.05; 0.19)**	8
			No previous exposure to conventional interferon	1.55 (1.12; 2.14)	**0.10 (0.03; 0.17)**	10
Flink, 2006[121] Peginterferon alfa-2b, 14 + Lamivudine, 100 vs. Peginterferon alfa-2b, 14	52/52	ALT normalization	Previous treatment: LAM	1.36 (0.31; 5.97)	0.01 (-0.03; 0.04)	144
			Previous treatment: IFN and LAM	7.14 (0.37; 137.02)	0.02 (-0.01; 0.05)	51
			Previous treatment: IFN	1.27 (0.35; 4.66)	0.01 (-0.03; 0.04)	141
			Naive	0.94 (0.62; 1.41)	-0.02 (-0.11; 0.08)	-67
		HBeAg clearance	Previous treatment: LAM	0.25 (0.03; 2.25)	-0.02 (-0.05; 0.01)	-52
		HBV DNA <400 copies/mL	Previous treatment: LAM	3.06 (0.13; 74.50)	0.01 (-0.01; 0.02)	152
		HBeAg clearance	Previous treatment: IFN and LAM	1.02 (0.15; 7.15)	0.00 (-0.03; 0.03)	3926
		HBV DNA <400 copies/mL	Previous treatment: IFN and LAM		0.00 (-0.01; 0.01)	
		HBeAg clearance	Previous treatment: IFN	1.63 (0.55; 4.88)	0.02 (-0.02; 0.07)	49
		HBV DNA <400 copies/mL	Previous treatment: IFN	5.10 (0.25; 105.32)	0.01 (-0.01; 0.04)	76
		HBeAg clearance	Naive	0.94 (0.63; 1.40)	-0.01 (-0.11; 0.08)	-67
		HBV DNA <400 copies/mL	Naive	1.02 (0.42; 2.50)	0.00 (-0.05; 0.05)	873

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Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Janssen, 2005[78] Peginterferon alfa-2b, 14 + Lamivudine, 100 vs. peginterferon alfa-2b, 14	52/52	Adjusted odds ratio of sustained HBeAg loss	Absence of previous interferon therapy	**2.20 (1.10; 4.50)**		
Zhao, 2007[81] Peginterferon alfa-2b, 11 vs. Interferon Alfa 2b, 1	24/24	Multivariate adjusted odds ratio of sustained combined response: HBeAg negative, HBV DNA <5 log10 copies/mL, and normal ALT level	Pegylated IFN-a-2b vs. FN-a-2b	1.73 (0.72; 4.14)		
Bonino, 2007[114] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	48/48	Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	PEG-IFNa-2a+LAM vs. LAM	**2.16 (1.14; 4.10)**		
Bonino, 2007[114] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Interferon Alfa 2b, 26	48/48	Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	PEG-IFNa-2a+LAM vs. PEG-IFNa-2a	1.19 (0.80; 1.90)		
Bonino, 2007[114] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	48/48	Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	PEG-IFNa-2a+LAM vs. LAM	**2.19 (1.30; 3.60)**		
Bonino, 2007[114] Peginterferon alfa-2a,26 +Placebo,. vs. Lamivudine,100	48/48	Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	PEG-IFNa-2a vs. LAM	**1.84 (1.10; 3.00)**		
			PEG-IFNa-2a vs. LAM	**2.11 (1.11; 4.01)**		
Response to the treatment						
van Zonneveld, 2006[125] Peginterferon alfa-2b, 14 + Lamivudine, 100 vs. Peginterferon alfa-2b, 14	52/52	Improved fibrosis scores as decrease of at least 1 point for the fibrosis score (range 0-6)	ALT normalization	1.87 (0.71; 4.93)	0.03 (-0.02; 0.08)	30
		Improved inflammatory changes in the liver as decrease of at least 2 points for the necroinflammatory score (range 0-18)	ALT normalization	1.02 (0.53; 1.96)	0.00 (-0.07; 0.07)	491

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Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lau, 2005[56] Peginterferon alfa-2a, 26 + Placebo vs. Lamivudine, 100	48/48	HBeAg Seroconversion	Maximum ALT during treatment >10 ULN	6.69 (2.01; 22.26)	**0.06 (0.03; 0.10)**	16
			Maximum ALT during treatment >5-10 ULN	1.76 (0.97; 3.17)	**0.04 (0.00; 0.09)**	22
			Maximum ALT during treatment ≤5 ULN	1.19 (0.77; 1.83)	0.02 (-0.03; 0.08)	44
			Maximum ALT during treatment >5-10 ULN	0.96 (0.58; 1.59)	0.00 (-0.05; 0.05)	-271
			Maximum ALT during treatment ≤5 ULN	0.90 (0.59; 1.37)	-0.01 (-0.07; 0.04)	-68
			Maximum ALT during treatment >10 ULN	0.60 (0.30; 1.20)	-0.03 (-0.07; 0.01)	-34
Lau, 2005[56] Peginterferon alfa-2a, 26 + Lamivudine, 100 vs. Lamivudine, 100	48/48	HBeAg Seroconversion	Maximum ALT during treatment >10 ULN	4.01 (1.15; 14.07)	**0.03 (0.01; 0.06)**	30
			Maximum ALT during treatment >5-10 ULN	1.69 (0.93; 3.07)	**0.04 (0.00; 0.09)**	25
			Maximum ALT during treatment ≤5 ULN	1.06 (0.68; 1.66)	0.01 (-0.05; 0.06)	128
Gish, 2007[101] Entecavir, 0.50 vs. Lamivudine, 100	52/52	Normalization of ALT levels (<1 ULN)	Responders (HBV DNA level 0.7 MEq/mL and loss of HBeAg) in year 1	1.19 (0.92; 1.55)	0.11 (-0.05; 0.27)	9
	96/96	Normalization of ALT levels (<1 ULN)	Responders (HBV DNA 0.7 MEq/mL and loss of HBeAg) in year 2	0.90 (0.63; 1.29)	-0.07 (-0.31; 0.17)	-14
	52/52	HBeAg Seroconversion	Responders (HBV DNA level 0.7 MEq/mL and loss of HBeAg) in year 1	1.11 (0.89; 1.39)	0.07 (-0.08; 0.23)	14
	52/52	HBV DNA level 300 copies/mL by PCR	Responders (HBV DNA level 0.7 MEq/mL and loss of HBeAg) in year 1	1.18 (0.73; 1.90)	0.05 (-0.10; 0.21)	19
	96/96	HBeAg Seroconversion	Responders (HBV DNA 0.7 MEq/mL and loss of HBeAg) in year 2	0.95 (0.59; 1.53)	-0.02 (-0.28; 0.23)	-40
	96/96	HBV DNA level 300 copies/mL by PCR	Responders (HBV DNA 0.7 MEq/mL and loss of HBeAg) in year 2	1.12 (0.41; 3.05)	0.02 (-0.18; 0.23)	42
Bonino, 2007[114] Peginterferon alfa-2a, 26 vs. Lamivudine, 100	48/48	Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	End-of-treatment HBV DNA, per 1 log decrease	**2.90 (1.10; 7.70)**		

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Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Chan, 2005[117] Peginterferon alfa-2b, 14 + Lamivudine, 100 vs. Lamivudine, 100	60/52	Transient elevation of HBV DNA to 100,000 copies/mL	Sustained responders as sustained HBeAg loss and HBV DNA <100,000 copies/mL	0.50 (0.10; 2.61)	-0.04 (-0.13; 0.05)	-25
van Zonneveld, 2006[125] Peginterferon alfa-2b, 14 + Lamivudine, 100 vs. Peginterferon alfa-2b, 14	52/52	Improved inflammatory changes in the liver as decrease of at least 2 points for the necroinflammatory score (range 0-18)	No HBV DNA loss (PCR positive)	0.44 (0.23; 0.83)	**-0.10 (-0.18; -0.03)**	-10
		Improved fibrosis scores as decrease of at least 1 point for the fibrosis score (range 0-6)	No HBV DNA loss (PCR positive)	1.02 (0.46; 2.28)	0.00 (-0.06; 0.06)	714
		Improved inflammatory changes in the liver as decrease of at least 2 points for the necroin-flammatory score (range 0-18)	No HBe Ag loss	0.78 (0.39; 1.55)	-0.02 (-0.09; 0.04)	-41
		Improved fibrosis scores as decrease of at least 1 point for the fibrosis score (range 0-6)	No HBe Ag loss	1.87 (0.71; 4.93)	0.03 (-0.02; 0.08)	30
		Improved inflammatory changes in the liver as decrease of at least 2 points for the necroinflammatory score (range 0-18)	HBV DNA loss (PCR negative)	4.42 (1.28; 15.20)	**0.07 (0.02; 0.12)**	15
		Improved Fibrosis scores as decrease of at least 1 point for the fibrosis score (range 0-6)	HBV DNA loss (PCR negative)	3.06 (0.63; 14.92)	0.03 (-0.01; 0.06)	38
		Improved inflammatory changes in the liver as decrease of at least 2 points for the necroinflammatory score (range 0–18)	HBeAg loss	0.87 (0.42; 1.83)	-0.01 (-0.07; 0.05)	-88
		Improved fibrosis scores as decrease of at least 1 point for the fibrosis score (range 0-6)	HBeAg loss	0.87 (0.30; 2.54)	-0.01 (-0.05; 0.04)	-176

Appendix E. Table 9. Evidence tables of the effects of drug interventions on outcomes among patient subgroups (individual RCTs)

Author Treatments Daily Dose (MU for IFN and mg for RTI)	Length of Treatment in Active/Control Groups	Outcome	Definition of Predicting Variable	Relative Risk (95% CI)	Risk Difference (95% CI)	Number Needed to Treat
Lai, 2007[71] Telbivudine, 600 vs. Lamivudine, 100	52/52	Primary treatment failure - serum HBV DNA levels remained above 5 log 10 copies per milliliter	HBV DNA >4 log 10 copies/ml at week 24 in HBeAg-negative patients	0.60 (0.48; 0.77)	**-0.20 (-0.29; -0.11)**	-5
			HBV DNA >4 log 10 copies/ml at week 24 in HBeAg-positive patients	0.64 (0.46; 0.89)	**-0.06 (-0.11; -0.02)**	-16
			Undetectable HBV DNA at week 24 in HBeAg-negative patients	0.11 (0.01; 2.07)	-0.02 (-0.04; 0.00)	-56
			HBV DNA 3-4 log10 copies/ml at week 24 in HBeAg-negative patients	0.19 (0.12; 0.31)	**-0.31 (-0.38; -0.24)**	-3
			HBV DNA <3 log10 copies/ml at week 24 in HBeAg-negative patients	0.29 (0.16; 0.53)	**-0.14 (-0.20; -0.08)**	-7
			Undetectable HBV DNA at week 24 in HBeAg-positive patients	0.36 (0.13; 0.99)	-0.02 (-0.04; 0.00)	-52
			HBV DNA 3-4 log10 copies/ml at week 24 in HBeAg-positive patients	0.45 (0.31; 0.65)	**-0.10 (-0.14; -0.06)**	-10
			HBV DNA <3 log10 copies/ml at week 24 in HBeAg-positive patients	0.20 (0.10; 0.40)	**-0.08 (-0.11; -0.05)**	-13

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Baseline histology, outcomes at the end of the treatment						
Overall disease progression - an increase of at least 2 points in the Child–Pugh score (5 indicates good and 15 -poor liver function)	Lamivudine vs. placebo	130/0	1/651	Liaw, 2004[51]	**0.44 (0.23; 0.84)**	disease progression was lowered among patients with baseline Child–Pugh score=5
					0.37 (0.16; 0.86)	disease progression was lowered among patients with baseline Child–Pugh score=6
					0.37 (0.19; 0.71)	disease progression was lowered among patients with baseline Ishak fibrosis score=6
						Random differences among patients with baseline Child–Pugh score >7 and Ishak fibrosis score <4 or 5
Adjusted for treatment OR of HBeAg Loss	Lamivudine vs. placebo	52/0	1/602	Perrillo, 2002[104]	**1.17 (1.10; 1.24**)	HBeAg loss was higher per 1 unit increase in baseline HAI score
HBeAg loss irrespective of HBV-DNA status at baseline or week 56	Lamivudine vs. placebo	52/0	1/602	Perrillo, 2002[104]	1.45 (0.40; 5.29)	HBeAg loss did not differ after lamivudine vs. placebo among the patients with pretreatment HAI Score 0-4
					4.02 (1.23; 13.16)	HBeAg loss was higher among the patients with baseline HAI Score 5-9
					2.27 (1.28; 4.02)	HBeAg loss was higher among the patients with baseline HAI Score >10
Worsening of Knodell necroinflammatory score	Lamivudine vs. placebo	48/0	1/216	Lai, 1998[50]	**0.11 (0.03; 0.51)**	Worsening of Knodell necroinflammatory score after lamivudine vs. placebo was less frequent among patients with moderate or severe hepatitis
Histological response - reduction of 2 or more points in the Knodell necroinflammatory score between baseline and week 52	Lamivudine vs. placebo	48/0	1/216	Lai, 1998[50]	**2.30 (1.39; 3.81)**	Lamivudine improved histology compared to placebo among the patients with moderate or severe hepatitis
					2.17 (0.76; 6.21)	Lamivudine did not improve histology compared to placebo among the patients with mild hepatitis

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Baseline viral load, outcomes at the end of the treatment						
HBeAg loss, loss of detectable HBV DNA, and seroconversion to antiHBeAg	Interferon Alfa 2b+lamivudine vs. lamivudine	52/0	1/75	Sarin, 2005[69]	2.92 (0.63; 13.56)	Random differences among the patients with baseline HBV DNA >107 copies/mL
HBeAg loss					1.62 (0.66; 4.01)	Random differences among patients with baseline HBV DNA >107 copies/mL
HBeAg loss with antiHBeAg appearance					2.92 (0.63; 13.56)	Random differences among patients with baseline HBV DNA >107 copies/mL
HBeAg loss	Interferon Alfa 2b vs. no treatment	32/0	1/118	Janssen, 1999[83]	4.20 (0.95; 18.64)	Random differences among the patients with baseline HBV DNA <10pg/ml
					0.19 (0.01; 3.82)	Random differences among patients with baseline HBV DNA >10pg/ml
OR of hepatic decompensation: change in the Child-Turcotte-Pugh score of 2 or more points adjusted for treatments, ALT, HBV DNA, sex, YMDD variant, platelet, bilirubin, albumin	Lamivudine vs. no treatment	80/0	1/74	Kim, 2006[54]	Random association with baseline HBV DNA	
OR of flare - elevation of ALT activity to >10 times the ULN and to > twice the baseline value with detectable HBV DNA- adjusted for treatments, ALT, HBV DNA, sex,	Lamivudine vs. no treatment	80/0	1/74	Kim, 2006[54]	Random association with baseline HBV DNA	

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
YMDD variant, platelet, bilirubin, albumin						
Overall disease progression - an increase of at least 2 points in the Child–Pugh score	Lamivudine vs. placebo	130/0	1/651	Liaw, 2004[51]	**0.22 (0.07; 0.70)**	Disease progression was lower among the patients with baseline HBV DNA below the lower limit of quantitation
					0.77 (0.34; 1.74)	Disease progression was not lower among the patients with baseline HBV DNA 0.7–10 meq/ml
					0.37 (0.13; 1.05)	Disease progression was lower among the patients with baseline HBV DNA >10–100 meq/ml
					0.41 (0.18; 0.94)	Disease progression was lower among the patients with baseline HBV DNA >100 meq/ml
Adjusted for treatments odds ratio of HBeAg loss	Lamivudine vs. placebo	52/0	1/602	Perrillo, 2002[104]	0.99 (0.97; 1.00)	HBeAg loss was not associated with baseline HBV-DNA level (per 10-unit increase)
HBV DNA loss	Lamivudine vs. placebo	12/0	1/429	Yao, 1999[112]	**6.41 (3.92; 10.47)**	HBV DNA loss among patients with baseline HBV DNA >1.6pg/ml
Adjusted OR of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a vs. lamivudine	48/0	1/1036	Bonino, 2007[114]	**1.28 (1.10; 1.40)**	Sustained combined response was increased by 1 log 10 unit (copies/ml) decrease in baseline HBV DNA
Baseline HBeAg status, outcomes at the end of the treatment						
Overall disease progression - an increase of at least 2 points in the Child–Pugh score	Lamivudine vs. placebo	130/0	1/651	Liaw, 2004[51]	0.72 (0.36; 1.43)	lamivudine did not decrease compared to placebo disease progression among HBeAg- at baseline patients
					0.30 (0.16; 0.55)	lamivudine decreased compared to placebo disease progression among HBeAg+ at baseline patients
Undetectable HBV DNA level by bDNA assay and normal ALT level	Entecavir (dose)	48/0	1/182	Change, 2005[76]	No dose response association among patients with baseline HBeAg + or HBeAg - status	

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Undetectable HBV DNA level by bDNA assay and normal ALT level	Entecavir vs. lamivudine	48/0	1/182	Change, 2005[76]	**18.38 (1.18; 285.96)**	entecavir in dose 1 mg/day vs. lamivudine resulted in higher rates of undetectable HBV DNA level by bDNA assay and normal ALT level among the patients with HBeAg- baseline status
						Entecavir in doses 0.5 or 0.1mg/day did not result in significant differences compared to lamivudine
					1.19 (0.18; 7.86)	entecavir in dose 1, 0.5, or 0.1 mg/day vs. lamivudine did not result in higher rates of undetectable HBV DNA level by bDNA assay and normal ALT level among the patients with HBeAg+ baseline status
HBV DNA >4 log 10 copies/ml	Telbivudine vs. lamivudine	52/0	1/1367	Lai, 2007[71]	0.55 (0.27; 1.13)	No differences between telbivudine vs. lamivudine among patients with HBeAg- status at baseline
					0.67 (0.54; 0.82)	telbivudine vs. lamivudine reduced the rates of detectable HBV DNA among the patients with HBeAg+ baseline status
ALT normalization	Telbivudine vs. lamivudine	52/0	1/1367	Lai, 2007[71]	0.94 (0.84; 1.04)	No differences between telbivudine vs. lamivudine among patients with HBeAg- status at baseline
					1.03 (0.96; 1.11)	No differences between telbivudine vs. lamivudine among patients with HBeAg+ status at baseline
HBV DNA <3 log 10 copies/ml	Telbivudine vs. lamivudine	52/0	1/1367	Lai, 2007[71]	0.91 (0.49; 1.67)	No differences between telbivudine vs. lamivudine among patients with HBeAg- status at baseline
					0.93 (0.67; 1.29)	No differences between telbivudine vs. lamivudine among patients with HBeAg+ status at baseline
Ishak fibrosis scores improved	Telbivudine vs. lamivudine	52/0	1/1367	Lai, 2007[71]	**1.28 (1.07; 1.54)**	telbivudine vs. lamivudine improved fibrosis scores among patients with HBeAg - status at baseline
					1.11 (1.01; 1.23)	RR, telbivudine vs. lamivudine improved fibrosis scores among patients with HBeAg+ status at baseline

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Primary treatment failure -serum HBV DNA levels remained above 5 log 10 copies per milliliter	Telbivudine vs. lamivudine	52/0	1/1367	Lai, 2007[71]	0.17 (0.02; 1.39)	No differences between telbivudine vs. lamivudine among patients with HBeAg-status at baseline
					0.36 (0.22; 0.57)	telbivudine vs. lamivudine reduced the rates of treatment failure among patients with HBeAg + at baseline
Reduction of at least 2 points in the Knodell necroinflammatory score, with no worsening in the fibrosis score	Telbivudine vs. lamivudine	52/0	1/1367	Lai, 2007[71]	1.01 (0.88; 1.15)	no differences between telbivudine vs. lamivudine among patients with HBeAg-status at baseline
					1.15 (1.03; 1.27)	telbivudine vs. lamivudine improved necroinflammatory score, with no worsening in the Knodell fibrosis score among patients with HBeAg +status at baseline
Serum HBV DNA undetectable by PCR	Telbivudine vs. lamivudine	52/0	1/1367	Lai, 2007[71]	**1.24 (1.12; 1.36)**	telbivudine vs. lamivudine increased HBV DNA loss among patients with HBeAg -status at baseline
					1.49 (1.30; 1.70)	telbivudine vs. lamivudine increased HBV DNA loss among patients with HBeAg + status at baseline
Viral breakthrough - at least 2 consecutive determinations of an increase in HBV DNA by at least 1 log10 copy per milliliter from nadir	Telbivudine vs. lamivudine	52/0	1/1367	Lai, 2007[71]	**0.18 (0.07; 0.46)**	telbivudine vs. lamivudine reduced the rates of viral breakthrough among patients with HBeAg -status at baseline
					0.38 (0.25; 0.59)	telbivudine vs. lamivudine reduced the rates of viral breakthrough among patients with HBeAg + status at baseline
Viral breakthrough - at least 2 consecutive determinations of an increase in HBV DNA by at least 1 log10 copy per milliliter from nadir with treatment-emergent resistance mutations	Telbivudine vs. lamivudine	52/0	1/1367	Lai, 2007[71]	**0.21 (0.08; 0.54)**	telbivudine vs. lamivudine reduced the rates of viral breakthrough among patients with HBeAg -status at baseline
					0.46 (0.28; 0.73)	telbivudine vs. lamivudine reduced the rates of viral breakthrough among patients with HBeAg + status at baseline

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Genotype, outcomes at the end of the treatment						
Adjusted OR of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a vs. lamivudine	48/0	1/1036	Bonino, 2007[114]	0.42 (0.10; 1.20)	No differences in sustained response between genotype A vs. B
					0.33 (0.10; 0.90)	Patients with genotype A vs. C had lower adjusted rates of sustained response
					0.97 (0.30; 2.70)	No differences in sustained response between genotype A vs. D
					0.79 (0.50; 1.30)	No differences in sustained response between genotype B vs. C
					2.31 (1.30; 4.20)	Patients with genotype B vs. D had higher adjusted rates of sustained response
					2.90 (1.70; 5.00)	Patients with genotype C vs. D had higher adjusted rates of sustained response
YMDD mutation, outcomes at the end of the treatment						
OR of flare - elevation of ALT activity to >10 times the ULN and to > twice the baseline value with detectable HBV DNA-adjusted for treatments, ALT, HBV DNA, sex, YMDD variant, platelet, bilirubin, albumin	Lamivudine vs. no treatment	80/0	1/74	Kim, 2006[54]	Random association with YMDD mutation	
OR of hepatic decompensation change in the Child-Turcotte-Pugh score of 2 or more points adjusted for treatments, ALT, HBV DNA, sex,	Lamivudine vs. no treatment	80/0	1/74	Kim, 2006[54]	Random association with YMDD mutation	

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
YMDD variant, platelet, bilirubin, albumin						
Change in necroinflammation: worsening	Lamivudine vs. placebo	48/0	1/85	Yuen, 2005[111]	**0.15 (0.04; 0.54)**	Lamivudine vs. placebo reduced the rates of worsened histology among patients without YMDD mutation
					0.18 (0.01; 2.87)	Lamivudine vs. placebo did not reduce the rates of worsened histology among patients with YMDD mutation
Change in fibrosis: worsening	Lamivudine vs. placebo	48/0	1/85	Yuen, 2005[111]	0.90 (0.27; 2.98)	Lamivudine vs. placebo did not reduce the rates of worsened histology among patients without YMDD mutation
					0.86 (0.11; 6.92)	Lamivudine vs. placebo did not reduce the rates of worsened histology among patients with YMDD mutation
Change in necroinflammation: Improvement	Lamivudine vs. Placebo	48/0	1/85	Yuen, 2005[111]	**3.30 (1.15; 9.51)**	Lamivudine vs. placebo improved histology among patients without YMDD mutation
					3.43 (1.02; 11.57)	Lamivudine vs. placebo improved histology among patients with YMDD mutation
Change in fibrosis: Improvement	Lamivudine vs. placebo	48/0	1/85	Yuen, 2005[111]	0.30 (0.02; 4.56)	Lamivudine vs. placebo did not improve fibrosis scores among patients without YMDD mutation
					0.79 (0.04; 17.44)	Lamivudine vs. placebo did not improve fibrosis scores among patients with YMDD mutation
Baseline ALT, at followup off the treatment						
Active hepatitis	Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b	24/24	1/56	Zarski, 1994[91]	0.81 (0.22; 2.91)	random differences among patients with baseline ALT <3ULN
Cirrhosis	Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b	24/24	1/56	Zarski, 1994[91]	0.40 (0.04; 4.19)	random differences among patients with baseline ALT <3ULN
HBV DNA loss	Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b	24/24	1/115	Wai, 2002[102]	**1.22 (1.05; 1.42)**	HBV DNA loss was more frequent among patients with elevated baseline ALT
			1/56	Zarski, 1994[91]	2.42 (0.27; 21.86)	random differences among patients with baseline ALT <3ULN

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Loss of HBV DNA + HBeAg seroconversion	Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b	24/24	2/95	Zarski, 1994[91] Lok, 1992[93]	Random changes in both studies among elevated ALT	
Loss of HBV DNA and HBeAg	Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b	24/24	1/85	Perrillo, 1990[96]	Random changes in all groups with elevated ALT level	
Loss of HBV DNA, HBeAg, and HBsAg	Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b	24/24	1/39	Lok, 1992[93]	0.29 (0.01; 6.66)	random differences among patients with elevated baseline ALT
HBsAg loss	Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b	24/24	1/56	Zarski, 1994[91]	3.23 (0.38; 27.06)	random differences among patients with baseline ALT <3ULN
Loss of HBV DNA + HBeAg seroconversion	Interferon Alfa 2b+corticosteroid vs. no treatment	24/24	1/37	Lok, 1992[93]	2.29 (0.74; 7.10)	random differences among patients with elevated baseline ALT
Loss of HBV DNA, HBeAg, and HBsAg	Interferon Alfa 2b+corticosteroid vs. no treatment	24/24	1/37	Lok, 1992[93]	0 events in both treatment groups	
Loss of HBV DNA and HBeAg	Interferon Alfa 2b+corticosteroid vs. no treatment	24/24	1/43	Perrillo, 1990[96]	**7.82 (1.02; 59.88)**	Loss of HBV DNA and HBeAg was greater among patients with baseline ALT <100U/L with random differences among those with baseline ALT100-200 and >200U/L
HBeAg loss	Interferon Alfa 2b+lamivudine vs. interferon Alfa 2b	24/28	1/203	Perrillo, 2002[104]	Random differences among patients with baseline ALT <1ULN, 2-5ULN, and >5 ULN	
HBeAg seroconversion	Interferon Alfa 2b+lamivudine vs. interferon Alfa 2b	24/28	2/347	Schalm, 2000[67] Perrillo, 2002[104]	Random differences among patients with baseline ALT <1ULN, 2-5ULN, and >5 ULN	
Odds ratio of sustained virologic response (sustained suppression of serum levels of HBeAg and HBV DNA) in those with	Interferon Alfa 2b+lamivudine vs. lamivudine	24/48	1/150	Barbaro, 2001[66]	**3.12 (1.43; 6.82)**	Adjusted odds of virologic response were higher in patients with baseline ALT >150UL

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Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
baseline ALT levels of 150 or more independent of gender and age						
HBeAg loss	Interferon Alfa 2b+lamivudine vs. lamivudine	24/28	1/541	Perrillo, 2002[104]	Random differences among patients with baseline ALT <1ULN, 2-5ULN, and >5 ULN	
HBeAg seroconversion	Interferon Alfa 2b+lamivudine vs. lamivudine	24/28	2/698	Perrillo, 2002[104]	Random differences among patients with baseline ALT <1ULN, 2-5ULN, and >5 ULN	
				Schalm, 2000[67]		
HBeAg loss	Interferon Alfa 2b+lamivudine vs. placebo	24/28	1/331	Perrillo, 2002[104]	**2.90 (1.35; 6.27)**	HBeAg loss was higher among patients with ALT >2 but <5ULN with random differences among those with <1ULN or 1-2ULN
HBeAg seroconversion	Interferon Alfa 2b+lamivudine vs. placebo	24/28	1/331	Perrillo, 2002[104]	**2.70 (1.10; 6.58)**	HBeAg seroconversion was greater among patients with >2-<5 ULN
					3.27 (1.03; 10.39)	HBeAg seroconversion was greater among patients with ALT >5 ULN with random differences among those with baseline ALT<1ULN or 1-2ULN
HBeAg seroconversion	Interferon Alfa 2b+placebo vs. lamivudine	24/28	1/151	Schalm, 2000[67]	Random differences among patients with baseline ALT <2, 2-5, or >5ULN	
Partial antiviral response: sustained clearance of serum HBV DNA by direct spot hybridization (lower limit of detection of 10 pg/mL) and clearance of HBeAg but not HBsAg	Interferon Alfa 2b+placebo vs. no treatment	24/24	1/34	Lok, 1992[93]	1.48 (0.42; 5.24)	Random differences in patients with elevated ALT

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Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Complete antiviral response: sustained clearance of serum HBV DNA by direct spot hybridization (lower limit of detection of 10 pg/mL) and clearance of HBeAg and HBsAg		24/24	1/34	Lok, 1992[93]	2.68 (0.12; 61.58)	Random differences in patients with elevated ALT
HBeAg loss	Interferon Alfa 2b vs. lamivudine	24/28	1/474	Perrillo, 2002[104]	Random differences among patients with baseline ALT <1ULN, 2-5ULN, and >5 ULN	
HBeAg seroconversion	Interferon Alfa 2b vs. lamivudine	24/28	1/474	Perrillo, 2002[104]	Random differences among patients with baseline ALT <1ULN, 2-5ULN, and >5 ULN	
Loss of HBV DNA and HBeAg	Interferon Alfa 2b vs. no treatment	24/24	1/84	Perrillo, 1990[96]	Random differences among patients with baseline ALT <100, 100-200, and >200U/L	
HBeAg loss	Interferon Alfa 2b vs. .placebo	24/28	0/264	Perrillo, 2002[104]	Random differences among patients with baseline ALT <1ULN, 2-5ULN, and >5 ULN	
HBeAg seroconversion		24/28	0/264	Perrillo, 2002[104]	Random differences among patients with baseline ALT <1ULN, 2-5ULN, and >5 ULN	
Sustained combined response: ALT normalization and an HBV DNA level of <20 ,000 copies/ml	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/202	Bonino, 2007[114]	Random differences among patients with baseline ALT 2-5 and >5 ULN	

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Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Adjusted for treatment status odds ratio of sustained response: HBeAg seroconversion, HBV DNA loss and ALT normalization in HBeAg (+) patients. In HBeAg (-) patients: loss of HBV DNA+ALT normalization	peginterferon alfa-2a+lamivudine vs. lamivudine	9/24	1/140	Cindoruk, 2007[115]	**10.32 (9.71; 10.97)**	Sustained response was greater per increase in 1unit (U/L) in baseline ALT
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/542	Lau, 2005[56]	**1.93 (1.01; 3.69)**	Response was greater among patients with baseline ALT >5ULN, random differences among those with baseline ALT <2 or 2-5ULN
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a	48/24	1/542	Lau, 2005[56]	Random differences among patients with baseline ALT <2, 2-5, and >5 ULN	
Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/202	Bonino, 2007[114]	Random differences among patients with baseline ALT <2, 2-5, and >5 ULN	
HBeAg seroconversion	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/542	Lau, 2005[56]	**1.81 (1.07; 3.04)**	HBeAg seroconversion was greater in patients with baseline ALT >2 but <5ULN. Random differences among those with baseline ALT <2 or >5ULN
Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a vs. lamivudine	48/24	1/1036	Bonino, 2007[114]	Random association per 1 U/L increase in baseline ALT	

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Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Adjusted for treatment allocation, hepatitis B virus (HBV) genotype and log HBV DNA odds ratio of persistent HBeAg loss at any time up to week 76 of post-treatment followup	Peginterferon alfa-2b+lamivudine vs. lamivudine	60/24	1/100	Chan, 2006[118]	Random association per 1 U/L increase in baseline ALT	
Adjusted for treatment allocation, HBV DNA genotype, IL-1b-511 polymorphism, baseline log HBV DNA odds ratio of persistent HBeAg loss and at any time up to week 76 of post-treatment followup	Peginterferon alfa-2b+lamivudine vs. lamivudine	60/24	1/100	Chan, 2006[118]	Random association per 1 U/L increase in baseline ALT	
Adjusted odds ratio of sustained HBeAg loss	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/26	1/310	Janssen, 2005[78]	Random differences among patients with elevated vs. normal baseline ALT	
Multivariate adjusted odds ratio of sustained combined response: HBeAg negative, HBV DNA <5 log10 copies/mL, and normal ALT level	Peginterferon alfa-2b+vs. interferon Alfa 2b	24/24	1/230	Zhao, 2007[81]	1.23 (0.51; 2.92)	RR, random differences between patients with baseline ALT level >3.4 vs. <3.4 ULN

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Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Baseline histology at followup off the treatment						
HBeAg loss	Interferon Alfa 2b vs. placebo	24/28	1/264	Perrillo, 2002[104]	3.84 (0.88; 16.74)	Interferon Alfa 2b vs. placebo did not increase HBeAg loss among patients with pretreatment HAI score 0-4
					5.76 (1.48; 22.42)	Interferon Alfa 2b vs. placebo increased HBeAg loss among patients with pretreatment HAI score 5-9
					1.11 (0.41; 2.99)	Interferon Alfa 2b vs. placebo did not increase HBeAg loss among patients with pretreatment HAI score >10
HBeAg loss	Interferon Alfa 2b+lamivudine vs. placebo	24/28	1/331	Perrillo, 2002[104]	3.39 (0.89; 12.87)	Interferon Alfa 2b+lamivudine vs. placebo did not increase HBeAg loss in patients with pretreatment HAI Score 0-4
					5.32 (1.51; 18.72)	Interferon Alfa 2b+lamivudine vs. placebo increased HBeAg loss in patients with pretreatment HAI Score 5-9
					1.79 (0.89; 3.59)	Interferon Alfa 2b+lamivudine vs. placebo did not increase HBeAg loss in patients with pretreatment HAI Score >10
HBeAg loss	Interferon Alfa 2b vs. lamivudine	24/28	1/331	Perrillo, 2002[104]	2.65 (0.84; 8.38)	Interferon Alfa 2b vs. lamivudine did not increase HBeAg loss in patients with pretreatment HAI Score 0-4
					1.43 (0.61; 3.36)	Interferon Alfa 2b vs. lamivudine did not increase HBeAg loss in patients with pretreatment HAI Score 5-9
					0.49 (0.20; 1.17)	Interferon Alfa 2b vs. lamivudine did not increase HBeAg loss in patients with pretreatment HAI score >10
Odds ratio of sustained virologic response (sustained suppression of serum levels of HBeAg and HBV DNA) in those with	Interferon Alfa 2b+ lamivudine vs. lamivudine	24/48	1/151	Barbaro, 2001[66]	**2.91 (1.04; 8.22)**	The rate of sustained response after interferon Alfa 2b+ lamivudine vs. lamivudine was increased by an increase in baseline inflammation scores
					2.58 (0.88; 7.60)	The rate of sustained response after interferon Alfa 2b+ lamivudine vs. lamivudine was not increased by an

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
a baseline inflammation score of 7 or more independent on gender and age						increase in baseline fibrosis scores
HBeAg loss	Interferon Alfa 2b+ lamivudine vs. lamivudine	24/28	1/541	Perrillo, 2002[104]	2.34 (0.89; 6.16)	The rate of HBeAg loss after interferon Alfa 2b+ lamivudine vs. lamivudine was not different among patients with baseline HAI scores 0-4
					1.32 (0.67; 2.62)	The rate of HBeAg loss after interferon Alfa 2b+ lamivudine vs. lamivudine was not different among patients with baseline HAI scores 5-9
					0.79 (0.47; 1.32)	The rate of HBeAg loss after interferon Alfa 2b+ lamivudine vs. lamivudine was not different among patients with baseline HAI scores >10
HBeAg loss	Interferon Alfa 2b+lamivudine vs. interferon Alfa 2b	24/52	1/203	Perrillo, 2002[104]	0.88 (0.27; 2.91)	No differences between interferon Alfa 2b+lamivudine vs. interferon Alfa 2b among patients with baseline HAI scores 0-4
					0.92 (0.36; 2.39)	No differences between interferon Alfa 2b+lamivudine vs. interferon Alfa 2b among patients with baseline HAI scores 5-9
					1.61 (0.62; 4.21)	No differences between interferon Alfa 2b+lamivudine vs. interferon Alfa 2b among patients with baseline HAI scores >10
Adjusted for treatment status odds ratio of sustained response: HBeAg seroconversion, HBV DNA disappearance and ALT normalization in HBeAg (+)	Peginterferon alfa-2a+lamivudine vs. lamivudine	9/15	1/160	Cindoruk, 2007[115]	Presence of steatosis did not modify the effect of peginterferon alfa-2a + lamivudine vs. lamivudine on sustained response	
					14.97 (2.43; 92.28)	The adjusted rates of sustained response were increased per increase in baseline Knodell HAI

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
patients. In HBeAg (-) patients: loss of HBV DNA, ALT normalization						
Adjusted relative risk of flares defined as an increase in serum ALT to at least 3 times the baseline level	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/78	1/310	Flink, 2005[120]	2.00 (1.00; 4.00)	Preexisting cirrhosis increased adjusted relative risk of flares
Adjusted relative risk of HBeAg seroconversion and HBV DNA 10,000 copies/ml	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/78	1/310	Buster, 2007[124]	0.98 (0.17; 5.23)	Presence of advanced fibrosis- fibrosis score of 4–6 (HAI) did not change adjusted relative risk of HBV DAN loss and HBeAg seroconversion
Baseline viral load at followup off the treatment						
Negative HBV DNA with persistent HBeAg	Interferon Alfa 2b vs. no treatment	32/20-52w	1/118	Janssen, 1999[83]	1.87 (0.59; 5.87)	no association between baseline positive HBV DNA (per 1 unit increase) and the effects of interferon Alfa 2b vs. no treatment
Loss of HBV DNA and HBeAg	Interferon Alfa 2b vs. no treatment	24/24	1/169	Perrillo, 1990[96]	**5.24 (1.22; 22.50)**	interferon Alfa 2b, 5MU/day vs. no treatment increased rates of HBV DNA and HBeAg loss among patients with baseline HBV DNA 2-99pg/ml. Random differences after interferon 1MU/day.
					RR, random differences after interferon 1 or 5 MU/day among the patients with baseline HBV DNA 100-200 pg/ml or >200 pg/ml	
HBeAg loss	Interferon Alfa 2b vs. No treatment	32/20	1/118	Janssen, 1999[83]	**3.18 (1.25; 8.05)**	RR, Interferon Alfa 2b, 10 MU three times per week vs. no treatments increased rates of HBeAg loss among the patients with baseline HBV DNA <10pg/ml. Random differences among the patients with baseline HBV DNA >10pg/ml

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Loss of HBV DNA and HBeAg	Interferon Alfa 2b+corticosteroid vs. no treatment	24/24	1/169	Perrillo, 1990[96]	**5.38 (1.26; 22.84)**	interferon Alfa 2b+corticosteroid vs. no treatment increased rates of HBV and HBeAg loss among patients with baseline HBV DNA 2-99pg/ml
					8.80 (0.49; 158.66)	interferon Alfa 2b+corticosteroid vs. no treatment did not increase the rates of HBV DNA and HBeAg loss among patients with baseline HBV DNA 100-200 pg/ml
					0.98 (0.06; 15.13)	interferon Alfa 2b+corticosteroid vs. no treatment did not increase the rates of HBV DNA and HBeAg loss among patients with baseline HBV DNA >200 pg/ml
Loss of HBV DNA and HBeAg	Interferon Alfa 2b+Corticosteroid vs. Interferon Alfa 2b	24/24	1/169	Perrillo, 1990[96]	Random differences after interferon Alfa 2b+Corticosteroid vs. interferon Alfa 2b in patients with baseline HBV DNA 2-99pg/ml, 100-200 pg/ml, or >200 pg/ml	
HBeAg loss	Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b	24/24	1/183	Wai, 2002[102]	**1.10 (1.03; 1.17)**	Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b increased the rates of HBeAg loss in patients with low baseline HBV-DNA level
					1.10 (1.01; 1.21)	Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b increased the rates of HBeAg loss in patients with low baseline HBV-DNA and elevated baseline ALT
Odds ratio of sustained virologic response	Interferon Alfa 2b+lamivudine vs. lamivudine	24/48	1/151	Barbaro, 2001[66]	**7.23 (2.71; 19.57)**	Odds of sustained suppression of serum levels of HBeAg and HBV DNA was significant in those with baseline viral load of 200 pg/ml or less independent of gender and age
HBeAg loss	Interferon Alfa 2b+lamivudine vs. lamivudine	52/24	1/75	Sarin, 2005[69]	**3.89 (1.20; 12.69)**	Interferon Alfa 2b+lamivudine vs. lamivudine resulted in increase rates of HBeAg loss in patients with baseline HBV DNA >107 copies/mL

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
HBeAg loss, HBeAg seroconversion	Interferon Alfa 2b+lamivudine vs. lamivudine	52/24	1/75	Sarin, 2005[69]	**4.87 (1.14; 20.74)**	Interferon Alfa 2b+lamivudine vs. lamivudine resulted in increase rates of HBeAg seroconversion and HBV DNA loss in patients with baseline HBV DNA >107 copies/mL
Viral breakthrough as the reappearance of serum HBV-DNA by solution hybridization assay in at least 2 consecutive tests during lamivudine therapy following the disappearance of the serum HBV DNA	Interferon Alfa 2b+lamivudine vs. lamivudine	176/192	1/83	Jang, 2004[65]	Random association with baseline HBV DNA levels (1 unit increase)	
Adjusted for treatment status odds ratio of sustained response: HBeAg sero-conversion, HBV DNA disappearance and ALT normal-ization in HBeAg (+) patients. In HBeAg (-) patients: loss of HBV DNA, ALT normalization	Peginterferon alfa-2a+lamivudine vs. lamivudine	9/6	1/140	Cindoruk, 2007[115]	1.05 (0.13; 8.14)	Baseline mean viral load (copy/mL)was not associated with sustained response to the therapy
Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/76	Bonino, 2007[114]	**2.24 (1.31; 3.83)**	Peginterferon alfa-2a+lamivudine vs. lamivudine increased sustained response among patients with baseline HBV DNA <6.12 log10 copies/ml
					1.78 (1.11; 2.84)	Peginterferon alfa-2a+lamivudine vs. lamivudine increased sustained response among patients with baseline HBV DNA >6.12-8.42 log 10 copies/ml

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
					1.37 (0.67; 2.80)	Peginterferon alfa-2a+lamivudine vs. lamivudine did not increase sustained response among patients with baseline HBV DNA >8.42 log 10 copies/ml
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/543	Lau, 2005[56]	0.84 (0.47; 1.48)	Peginterferon alfa-2a+lamivudine vs. lamivudine did not increase HBeAg seroconversion among patients with baseline HBV DNA levels ≤9.07 (log copies/ml)
					1.91 (1.16; 3.15)	Peginterferon alfa-2a+lamivudine vs. lamivudine increased HBeAg seroconversion among patients baseline HBV DNA levels >9.07–10.26 (log copies/ml)
					2.01 (0.82; 4.90)	Peginterferon alfa-2a+lamivudine vs. lamivudine did not increase HBeAg seroconversion among patients with baseline HBV DNA levels >10.26 (log copies/ml)
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a	48/24	1/542	Lau, 2005[56]	0.54 (0.32; 0.91)	The rates of HBeAg seroconversion were lower after peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a among the patients with baseline HBV DNA levels ≤9.07 (log copies/ml)
					1.03 (0.68; 1.54)	Random differences among patients with baseline HBV DNA levels >9.07–10.26 (log copies/ml)
					1.27 (0.59; 2.75)	Random differences among patients with baseline HBV DNA levels>10.26 (log copies/ml)
Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/96	Bonino, 2007[114]	1.27 (0.71; 2.30)	Random differences among patients with baseline HBV DNA <6.12 log10 copies/ml
					3.87 (2.55; 5.88)	Peginterferon alfa-2a+ placebo vs. lamivudine increased the rates of sustained response among patients with baseline HBV DNA >6.12-8.42 log 10 copies/ml
					1.80 (0.91; 3.57)	Random differences among patients

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
						with baseline HBV DNA >8.42 log 10 copies/ml
HBeAg seroconversion	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/543	Lau, 2005[56]	1.55 (0.95; 2.51)	Random differences among patients with baseline HBV DNA levels ≤9.07 (log copies/ml)
					1.86 (1.13; 3.08)	Peginterferon alfa-2a+placebo vs. lamivudine increased rates of HBeAg seroconversion among patients with baseline HBV DNA levels >9.07–10.26 (log copies/ml)
					1.58 (0.62; 4.01)	Random differences among patients with baseline HBV DNA levels >10.26 (log copies/ml)
Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a vs. lamivudine	48/24	1/1036	Bonino, 2007[114]	1.06 (0.93; 1.21)	Baseline HBV DNA (Log10) was not associated with sustained response to therapy
Adjusted for treatment allocation, hepatitis B virus (HBV) genotype, baseline ALT odds ratio of persistent HBeAg loss at any time up to week 76 of post-treatment followup	Peginterferon alfa-2b+lamivudine vs. lamivudine	60/0	1/100	Chan, 2006[118]	0.70 (0.38; 1.30)	Baseline HBV DNA (log10) was not associated with sustained response to therapy
Adjusted for treatment allocation, HBV DNA genotype, IL-1b-511 polymorphism, baseline ALT odds ratio of persistent	Peginterferon alfa-2b+lamivudine vs. lamivudine	60/0	1/100	Chan, 2006[118]	0.65 (0.35; 1.20)	Baseline HBV DNA (log10) was not associated with sustained response to therapy

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
HBeAg loss and had less than 2 occasions with HBV DNA <100,000 copies/mL at any time up to week 76 of post-treatment						
Adjusted odds ratio of sustained HBeAg loss	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/0	1/307	Janssen, 2005[78]	**1.60 (1.30; 1.80)**	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b increased the rates of HBeAg loss among patients with low baseline viral load
Multivariate adjusted odds ratio of sustained combined response: HBeAg negative, HBV DNA <5 log10 copies/mL, and normal ALT level	Peginterferon alfa-2b vs. interferon Alfa 2b	24/0	1/230	Zhao, 2007[81]	0.53 (0.22; 1.28)	Random difference among patients with baseline HBV DNA >8.1 vs. <8.1 log 10 copies/mL
Genotype, the outcomes at followup off the treatment						
Adjusted for age, gender, baseline ALT ,HBV DNA, and histology, precore G1896A mutation, core promoter A1762T, G1764A, and treatment with interferon with and without prednisone pretreatment odds ratios of antiviral response: as sustained clearance of serum HBV DNA	Interferon Alfa 2b+corticosteroid vs. interferon Alfa 2b	24/0	1/115	Wai, 2002[102]	**1.28 (1.06; 1.42)**	Patients with HBV genotype B vs. C had better sustained response to the therapy
			1/68	Wai, 2002[102]	**1.47 (1.18; 1.82)**	Patients with HBV genotype B vs. C and elevated baseline ALT had better sustained response to the therapy

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/126	Bonino, 2007[114]	**2.09 (1.29; 3.40)**	Peginterferon alfa-2a+lamivudine vs. lamivudine increased the rates of sustained response among patients with genotype C
					3.33 (1.53; 7.27)	Peginterferon alfa-2a+lamivudine vs. lamivudine increased the rates of sustained response among patients with genotype D
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/543	Lau, 2005[56]	1.34 (0.30; 5.92)	Random difference among patients with HBV genotype A
					1.42 (0.78; 2.58)	Random difference among patients with HBV genotype B
					1.49 (0.96; 2.31)	Random difference among patients with HBV genotype C
					0.67 (0.11; 3.97)	Random difference among patients with HBV genotype D
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. peginterferon alfa-2a	48/24	1/542	Lau, 2005[56]	0.33 (0.11; 1.02)	Random difference among patients with HBV genotype A
					1.04 (0.60; 1.80)	Random difference among patients with HBV genotype B
					0.86 (0.59; 1.25)	Random difference among patients with HBV genotype C
					1.00 (0.14; 7.05)	Random difference among patients with HBV genotype D
Sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/19	Bonino, 2007[114]	2.18 (0.27; 17.32)	Random differences among patients with genotype A
					1.14 (0.70; 1.85)	Random differences among patients with genotype B
					2.22 (1.36; 3.63)	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of sustained response among patients with genotype C
					1.47 (0.59; 3.69)	Random differences among patients with genotype D
HBeAg seroconversion	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/543	Lau, 2005[56]	**4.01 (1.15; 14.07)**	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of HBeAg seroconversion among patients with HBV genotype A
					1.36 (0.74; 2.48)	Random differences among patients

Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
						with HBV genotype B
					1.73 (1.13; 2.65)	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of HBeAg seroconversion among patients with HBV genotype C
					0.67 (0.11; 3.97)	Random differences among patients with HBV genotype D
Adjusted odds ratios of sustained combined response: ALT normalization and an HBV DNA level of <20,000 copies/ml	Peginterferon alfa-2a vs. lamivudine	48/24	1/1036	Bonino, 2007[114]	2.58 (0.73; 9.20)	Random difference between genotypes (A vs. D)
					3.69 (1.54; 8.79)	Rates of sustained response were higher among patients with genotype B vs. D
					5.46 (2.46; 12.10)	Rates of sustained response were higher among patients with genotype C vs. D
Adjusted for treatment allocation, hepatitis B virus (HBV) genotype, baseline alanine aminotransferase and log HBV DNA odds ratio of persistent HBeAg loss at any time up to week 76 of post-treatment	Peginterferon alfa-2b+lamivudine vs. lamivudine	60/24	1/100	Chan, 2006[118]	**10.37 (1.11; 96.96)**	Rates of response were higher among patients with interleukin (IL)-1b-511 baseline genotype C/T vs. C/C
					Random differences in patients with genotype C vs. B	
					Random differences in patients with Haplotype -511/-31 of interleukin (IL)-1b C-T vs. T-C	
					Random differences in patients with interleukin (IL)-1b-511 baseline genotype T/T vs. C/C	
					Random differences in patients with interleukin (IL)-1b-31 baseline genotype C/T vs. T/T or C/C vs. T/T	
					Random differences in patients with IL-1 receptor antagonist genotype IL-1RN 1/2 vs. 1/1	
					Random differences in patients with interleukin (IL)-1b-511 baseline genotype C/T and T/T vs. C/C	
					Random differences in patients with interleukin (IL)-1b-31 baseline genotype C/T and C/C vs. T/T	
Adjusted relative risk of HBeAg seroconversion and HBV DNA 10,000 copies/ml.	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/26	1/307	Buster, 2007[124]	**11.30 (1.38; 92.57)**	adjusted rates of sustained response were higher among patients with genotype A vs. C
					4.28 (1.39; 13.21)	Adjusted rates of sustained response were higher among patients with genotype A vs. D
					12.13 (1.24; 118.30)	Adjusted rates of sustained response were higher among patients with

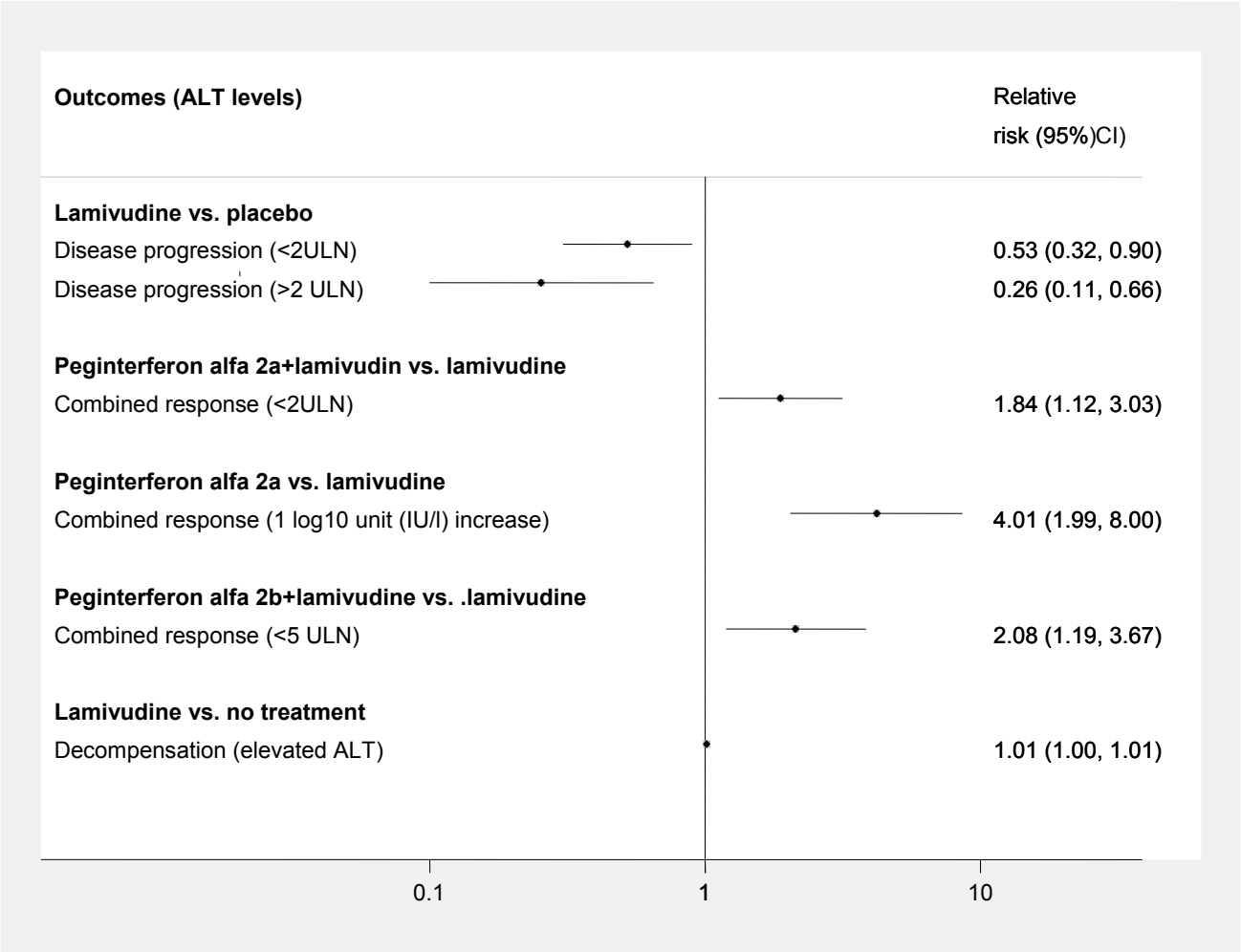
Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
						genotype B vs. C
					4.59 (1.14; 18.43)	Adjusted rates of sustained response were higher among patients with genotype B vs. D
Adjusted odds ratio of sustained HBeAg loss	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/26	1/307	Janssen, 2005[78]	**2.40 (1.30; 4.60)**	Adjusted rates of sustained response were higher among patients with HBV genotype A vs. D
					3.60 (1.40; 8.90)	Adjusted rates of sustained response were higher among patients with HBV genotype A vs. C
					2.20 (0.70; 7.00)	Random difference among patients with HBV genotype B vs. C
Multivariate adjusted odds ratio of sustained combined response: HBeAg negative, HBV DNA <5 log 10 copies/mL, and normal ALT level	Peginterferon alfa-2b vs. interferon Alfa 2b	24/24	0/250	Zhao, 2007[81]	**0.19 (0.08; 0.46)**	RR, genotype C vs. B
Previous treatment, outcomes at followup off the treatment						
HBeAg seroconversion	Peginterferon alfa-2a+lamivudine vs. lamivudine	48/24	1/543	Lau, 2005[56]	**1.52 (1.08; 2.12)**	Rates of HBeAg seroconversion were higher among patients with no previous exposure to lamivudine
					Random differences among those with previous LAM or Interferon therapy	
HBeAg seroconversion	Peginterferon alfa-2a + lamivu-dine vs. peginterferon alfa-2a	48/24	1/542	Lau, 2005[56]	Random differences among all patients with and without previous treatment	
HBeAg seroconversion	Peginterferon alfa-2a+placebo vs. lamivudine	48/24	1/543	Lau, 2005[56]	**1.58 (1.11; 2.23)**	peginterferon alfa-2a+placebo vs. lamivudine increased the rates of HBeAg seroconversion among patients with no previous anti-HBV therapy
					1.43 (0.55; 3.71)	Random differences among patients with previous treatment: LAM
					1.72 (1.24; 2.38)	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of HBeAg seroconversion among patients with no previous exposure to lamivudine

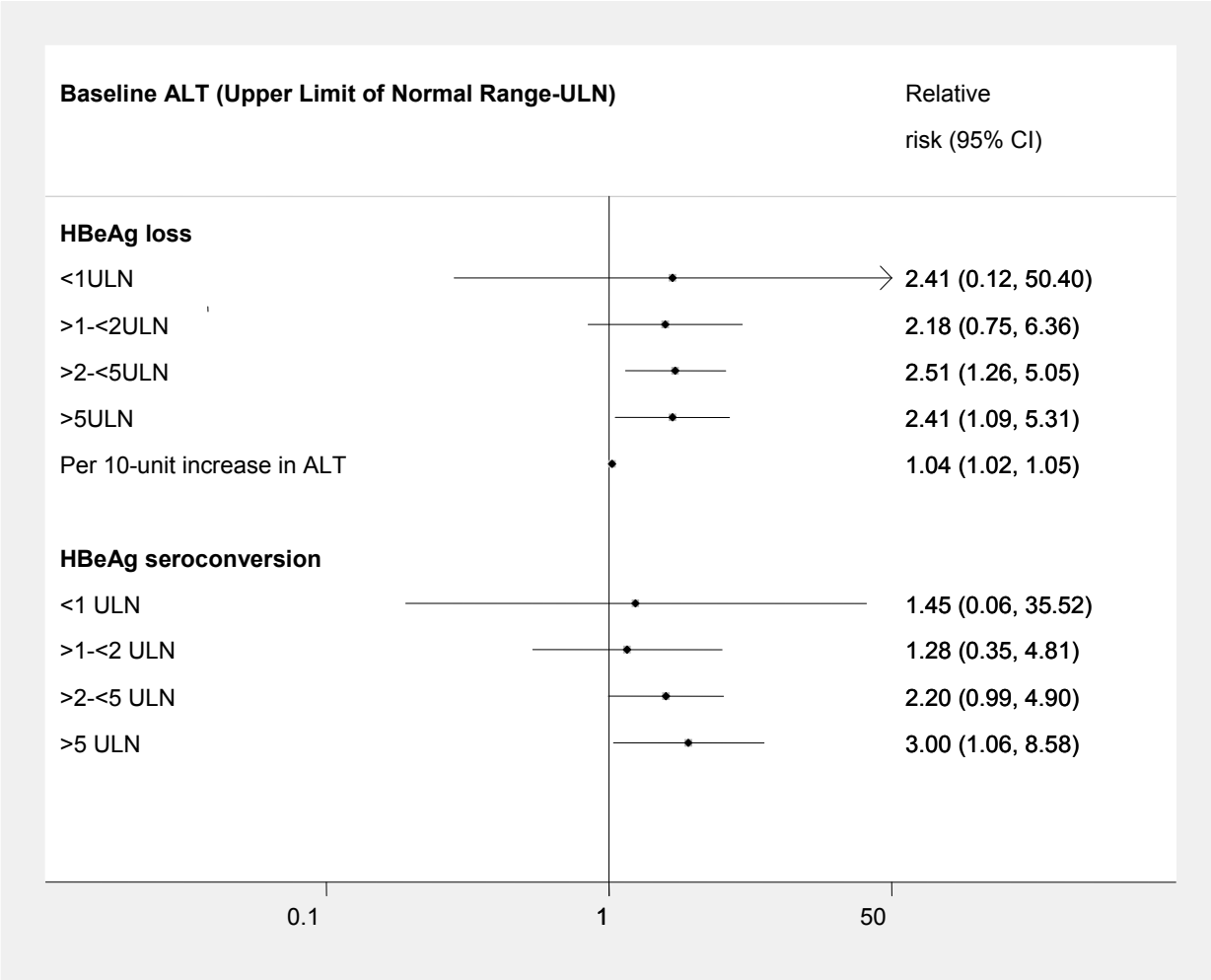
Appendix E. Table 10. Summary tables of the effects of therapies for CHB in patient subpopulations by baseline status of chronic hepatitis B

Outcome	Comparison	Weeks of Treatments/ Followup off the Treatment	N Studies/ Enrolled	Author	Relative Risk or Odds ratios (95% CI)	Comments
					3.26 (1.08; 9.88)	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of HBeAg seroconversion among patients with previous treatment: IFN
					1.55 (1.12; 2.14)	Peginterferon alfa-2a+placebo vs. lamivudine increased the rates of HBeAg seroconversion among patients with no previous exposure to conventional interferon
HBeAg loss	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b	52/26	2/307	Janssen, 2005[78]	**2.20 (1.10; 4.50)**	Peginterferon alfa-2b+lamivudine vs. peginterferon alfa-2b increased the rates of HBeAg loss among patients without previous interferon therapy
				Flink, 2006[121]	0.94 (0.63; 1.40)	Random differences among naïve to any treatments patients
			1/307	Flink, 2006[121]	Random differences among patients with previous IFN, LAM, and combined therapy	
HBV DNA loss, normalization of ALT					Random differences among patients naïve to any antiviral treatment	

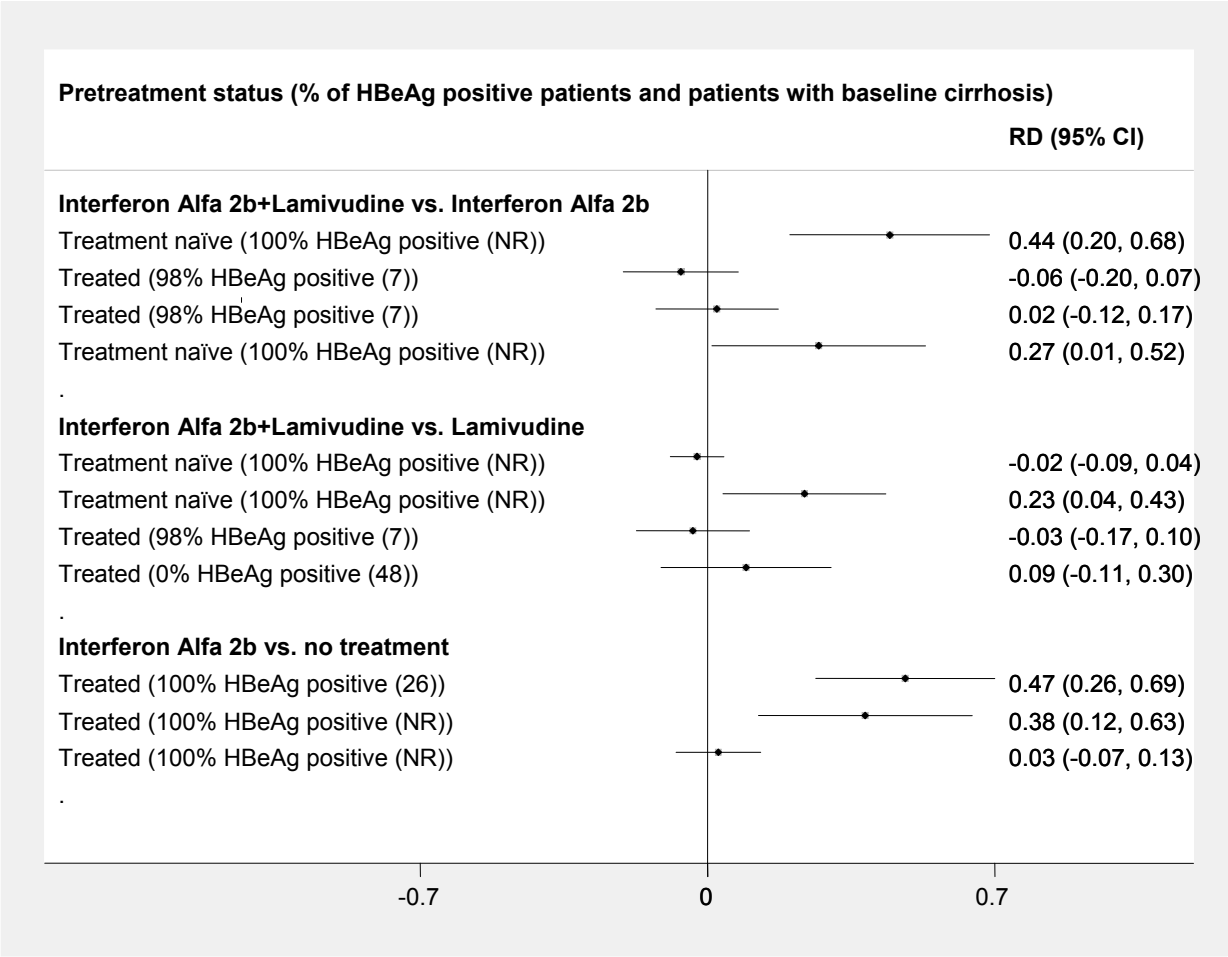
Appendix E. Figure 20. Combined outcomes at the end of the treatments by baseline ALT levels (individual RCTs[51,54,59,114]



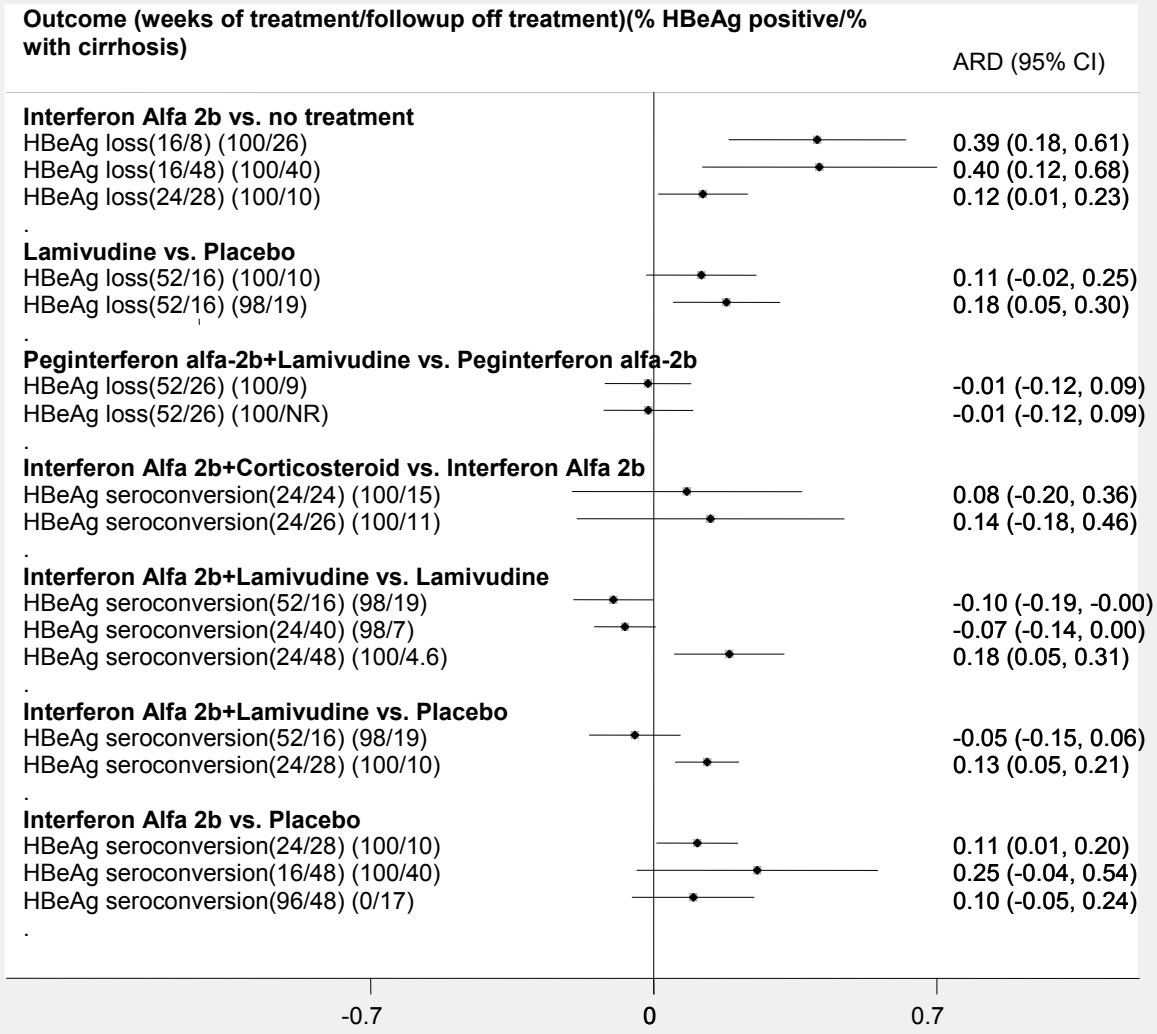
Appendix E. Figure 21. The effects of lamivudine, 100mg/day compared to placebo at the end of the treatment depending on baseline ALT level (4 lamivudine-controlled Phase III trials)[104]



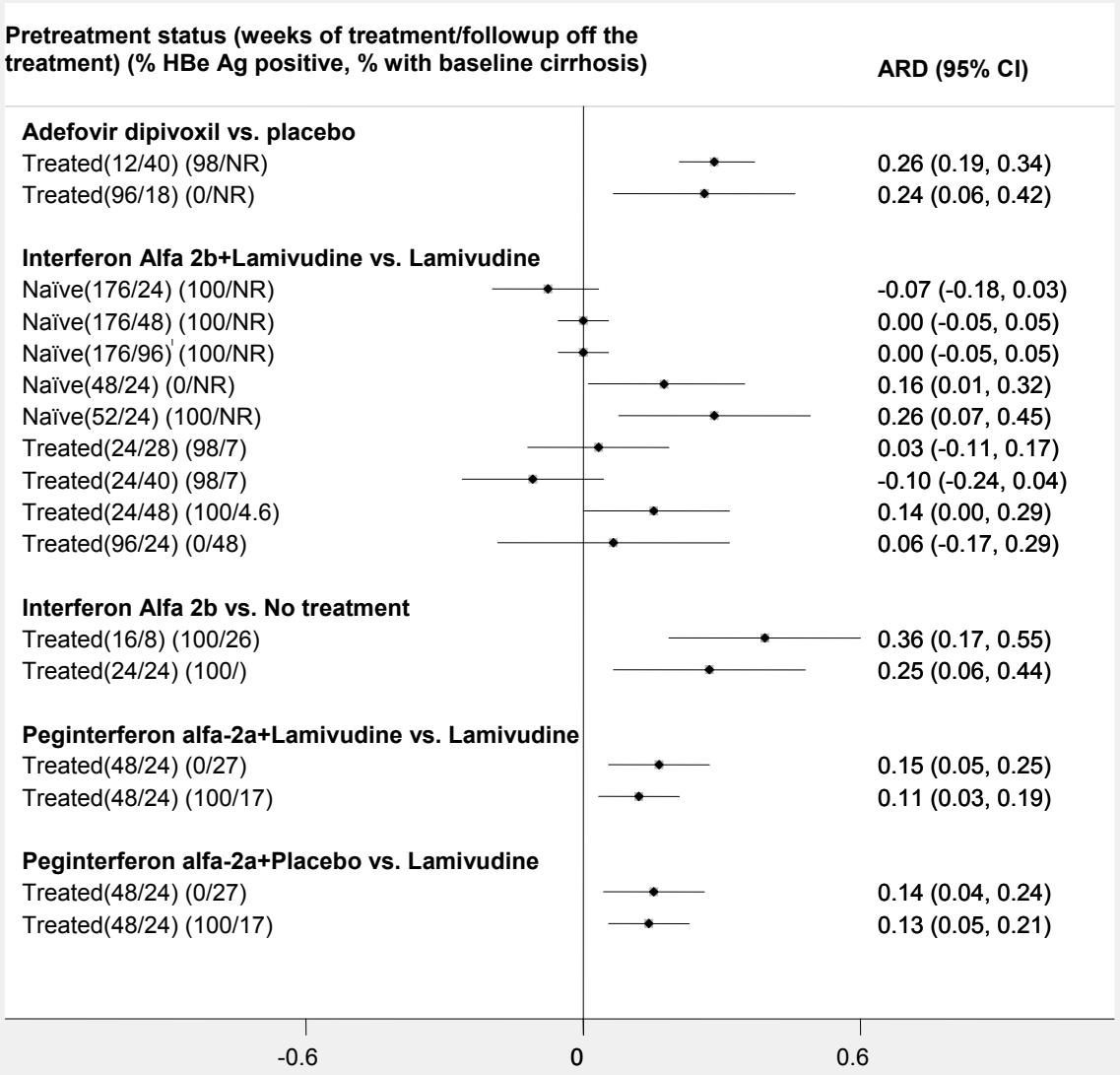
Appendix E. Figure 22. HBV DNA loss at followup off the drug therapies for chronic hepatitis B by patient pretreatment status, baseline HBeAg positivity, and the proportion of the patients with baseline cirrhosis, the results from individual studies[63,65,67,69,79,86,94,96]



Appendix E. Figure 23. HBeAg loss and seroconversion at followup off drug therapies for chronic hepatitis B by patient pretreatment status, baseline HBeAg positivity, and the proportion of the patients with baseline cirrhosis, results from individual studies[47,48,66,67,78,84,86,89,92,95,104,122]



Appendix E. Figure 24. ALT normalization at followup off drug therapies for chronic hepatitis B by patient pretreatment status, baseline HBeAg positivity, and the proportion of the patients with baseline cirrhosis, results from individual studies[40,56,57,62,63,65-67,69,86,96,98]



Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
HBeAg-negative patients				
Entecavir [74]	1	End	Flare	1.00 (0.98;1.02)
	1	End	Death	1.00 (0.98;1.02)
	1	End	Relapse	1.99 (1.96;2.03)
	1	End	Resistance	17.99 (17.30;18.71)
	1	End	Improved histology	64.07 (60.41;67.95)
	1	End	Normalization ALT	78.26 (75.25;81.39)
	1	End	HBV DNA loss	90.02 (86.56;93.62)
	1	Followup off treatment	Flare	7.03 (6.89;7.17)
	1		Any adverse event	75.94 (73.03;78.98)
	1		Serious adverse event	5.99 (5.87;6.11)
	1		Discontinuation due to adverse event	2.00 (1.98;2.02)
	1		ALT >2× baseline and >5× ULN	4.69 (0.88;25.05)
Adefovir dipivoxil [41,97,98]				
	1	End	Death	0.63 (0.26;1.56)
	1	End	Failure	3.47 (2.61;4.61)
	2	End	HBsAg seroconversion	1.36 (0.76;2.45)
	3	End	HBV DNA loss	62.84 (57.20;69.03)
	1	End	HCC	2.00 (0.51;7.82)
	3	End	Improved histology	36.43 (24.62;53.90)
	3	End	Mutation	3.93 (1.59;9.71)
	3	End	Normalization ALT	65.83 (62.72;69.09)
	2	End	Resistance	7.33 (4.02;13.37)
	1	End	HBsAg loss	1.41 (0.12;16.85)
	1	Followup off treatment	HBV DNA loss	66.02 (61.60;70.76)
	1	Followup off treatment	Improved histology	70.81 (65.47;76.59)
	1	Followup off treatment	Mutation	4.48 (3.96;5.08)
	1	Followup off treatment	Normalization ALT	54.06 (50.44;57.93)
	1		Any adverse events	70.31 (59.85;82.59)
	3		Headache	14.94 (11.10;20.12)
	3		Abdominal pain	15.38 (11.44;20.68)
	3		Asthenia	10.09 (7.32;13.91)
	2		Flu-like syndrome	11.10 (8.64;14.25)
	3		Back pain	7.25 (5.65;9.29)
	3		Pain	8.65 (6.72;11.13)
	2		Accidental injury	5.53 (4.01;7.62)
	1		Diarrhea	4.41 (2.56;7.61)
	3		Dyspepsia	4.66 (3.20;6.78)
	3		Pharyngitis	19.20 (15.82;23.31)
	2		Increased cough	4.81 (3.49;6.62)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	2		Bronchitis	4.20 (2.48;7.09)
	1		Increased ALT	2.44 (1.89;3.14)
	1		Arthralgia	4.41 (2.56;7.61)
	1		Increased creatinine PK	1.68 (1.06;2.66)
	1		Hematuria	1.64 (1.24;2.17)
	1		Kidney calculus	1.18 (0.85;1.63)
	1		Kidney pain	1.86 (0.96;3.62)
	1		Infection	2.52 (0.07;93.79)
	1		Cough increased	8.12 (4.47;14.77)
	2		Rhinitis	2.71 (0.32;22.88)
	1		At least one adverse event	75.94 (70.22;82.14)
	1		Serious adverse event	3.00 (2.89;3.12)
	1		Insomnia	5.00 (4.81;5.20)
Interferon alfa-2b [84,88]	2	End	Combined	34.78 (27.52;43.95)
	1	End	HBsAg loss	2.39 (2.25;2.53)
	1	End	Flare	18.92 (16.17;22.13)
	1	End	Improved histology	33.12 (27.76;39.50)
	1	End	Resistance	8.32 (0.72;96.40)
	2	Followup off treatment	Combined	26.96 (17.71;41.05)
	2	Followup off treatment	Relapse	12.60 (7.95;19.97)
	1	Followup off treatment	HBsAg loss	9.97 (8.87;11.22)
	1	Followup off treatment	HBsAg seroconversion	9.97 (8.87;11.22)
	1		Discontinuation due to adverse effects	24.05 (20.16;28.69)
	1		Persistent headache	5.00 (4.63;5.41)
	1		Persistent Myalgia	14.01 (12.22;16.07)
	1		Moderate depression	5.00 (4.63;5.41)
Interferon alfa-2b+Lamivudine [60,62-64]	2	End	HBV DNA loss	96.03 (92.45;99.76)*
	3	End	Relapse	6.87 (2.84;16.61)
	2	End	Normalization ALT	68.05 (51.22;90.40)
	2	End	Flare	5.10 (1.92;13.57)
	3	End	Mutation	2.19 (1.65;2.91)
	1	End	HBsAg loss	1.25 (1.20;1.30)
	2	End	Combined	64.87 (42.58;98.85)
	1	Followup off treatment	HBV DNA loss	20.91 (17.87;24.45)
	2	Followup off treatment	Normalization ALT	36.48 (17.50;76.08)
	2	Followup off treatment	HBsAg loss	1.27 (0.49;3.32)
	1	Followup off treatment	Combined	18.92 (16.17;22.13)
	1		Serious adverse events including pyrexia, fatigue, myalgia and headache	9.03 (8.51;9.57)
	2		Discontinuation due to adverse events	12.88 (11.02;15.07)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Thrombocytopenia	27.94 (24.36;32.05)
	1		Dose reduction due to adverse effects	9.97 (9.04;11.00)
Lamivudine [46,49,57,60,62-64,74,114]	5	End	Normalization ALT	68.33 (63.19;73.89)
	4	End	Combined	36.27 (4.21;312.53)
	4	End	HBV DNA loss	53.96 (31.34;92.89)
	4	End	Relapse	15.07 (9.59;23.68)
	3	End	Flare	4.93 (2.76;8.79)
	3	End	Mutation	14.75 (5.08;42.82)
	1	End	HBsAg loss	1.25 (1.20;1.30)
	2	End	Improved histology	18.48 (5.04;67.72)
	2	End	Resistance	20.84 (15.69;27.70)
	1	End	Death	0.16 (0.16;0.16)
	1	End	Failure	1.41 (0.72;2.78)
	4	Followup off treatment	Combined	14.61 (9.07;23.55)
	1	Followup off treatment	Failure	5.99 (3.08;11.65)
	1	Followup off treatment	Flare	9.03 (8.68;9.39)
	2	Followup off treatment	HBV DNA loss	10.83 (9.09;12.91)
	1	Followup off treatment	Improved histology	24.52 (15.31;39.25)
	1	Followup off treatment	Normalization ALT	38.23 (28.66;50.99)
	3	Followup off treatment	HBsAg loss	0.99 (0.54;1.81)
	1		>1 Reported adverse event	48.00 (47.95;48.05) †
	1		>1 Reported serious AE	3.00 (2.99;3.01) †
	1		Abdominal discomfort	8.50 (5.56;11.44) †
	1		Alopecia	1.00 (0.99;1.01) †
	1		ALT >2× baseline	12.00 (11.23;12.82)
	1		Any adverse event	79.00 (78.96;79.04) †
	1		Arthralgia	3.00 (2.99;3.01) †
	1		At least 1 adverse event	50.00 (44.12;55.88) †
	1		Back pain	3.00 (2.99;3.01) †
	2		Cough	4.25 (2.93;5.57) †
	1		Death	0.28 (0.28;0.28) †
	1		Decreased appetite	3.00 (2.99;3.01) †
	2		Diarrhea	4.00 (3.14;4.86) †
	1		Discontinuation due to adverse effects	1.92 (1.87;1.97) †
	1		Discontinuation for safety reasons	0.28 (0.27;0.28) †
	1		Dizziness	4.00 (3.97;4.03) †
	1		Dose modification	0.28 (0.27;0.28) †
	1		Dose modification due to adverse event	0.28 (0.27;0.28) †
	1		Dose modification due to Laboratory abnormality	0.28 (0.27;0.28) †

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Dose modification due to Alanine aminotransferase elevation	0.28 (0.27;0.28) †
	1		Dose modification due to Neutropenia	0.28 (0.27;0.28) †
	1		Dose modification due to thrombocytopenia	0.28 (0.27;0.28) †
	1		Dose reduction	1.25 (1.22;1.28) †
	1		Dyspepsia	9.00 (8.94;9.06) †
	1		Dyspeptic symptoms	4.00 (2.04;5.96) †
	1		Fatigue	18.00 (17.96;18.04) †
	1		Gastrointestinal infection	5.00 (4.97;5.04) †
	3		Headache	11.60 (8.38;14.82) †
	1		Insomnia	3.00 (2.99;3.01) †
	1		Irritability	2.00 (1.99;2.01) †
	1		Malaise and fatigue	15.50 (10.60;20.40) †
	1		Musculoskeletal pain	3.00 (2.97;3.03) †
	1		Myalgia	6.00 (5.98;6.02) †
	1		Nausea	5.00 (4.98;5.02) †
	1		Nausea and vomiting	8.00 (7.95;8.05) †
	1		Pruritus	2.00 (1.99;2.01) †
	1		Pyrexia	4.00 (3.98;4.02) †
	1		Rigors	0.28 (0.28;0.28) †
	1		Sore throat	4.00 (3.98;4.02) †
	2		Thrombocytopenia	8.00 (7.95;8.05) †
	1		Tonsillitis	7.00 (6.58;7.45)
	1		Upper abdominal pain	8.00 (7.97;8.03) †
	1		Upper respiratory tract infection	4.00 (3.98;4.02) †
	1		URTI symptoms	33.00 (32.90;33.10) †
	1		Viral respiratory infection	6.00 (4.04;7.96) †
	1		Increased ALP	10.00 (9.94;10.06) †
	1		Increased ALT	12.00 (11.93;12.07) †
	1		Increased amylase	3.00 (2.97;3.03) †
	1		Increased bilirubin	1.00 (0.98;1.02) †
	1		Increased CPK	3.00 (2.97;3.03) †
	1		Low neutrophil count	0.56 (0.55;0.58) †
	1		Serious adverse event	8.00 (7.97;8.03) †
	1		Serious adverse events including pyrexia, fatigue, myalgia and headache	0.51 (0.50;0.52) †
	1		Right upper quadrant discomfort	17.00 (16.92;17.08) †
	1		Prolonged PT level	1.00 (0.98;1.02) †
	1		Temperature regulation disturbance	8.00 (7.93;8.07) †

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Vertigo	2.50 (1.52;3.48) †
Peginterferon alfa-2a [57,114]	1	End	Combined	30.23 (22.53;40.56)
	1	End	Normalization ALT	36.97 (34.18;39.98)
	2	Followup off treatment	Combined	21.03 (12.94;34.18)
	1	Followup off treatment	Normalization ALT	57.97 (53.60;62.70)
	1	Followup off treatment	Improved histology	29.07 (10.61;79.62)
	1	End	Failure	7.35 (4.92;10.99)
	1	End	≥1 Reported adverse event	86.00 (85.95;86.05)
	1	End	≥1 Reported serious adverse event	5.00 (4.97;5.03)
	1	End	Alopecia	13.00 (12.95;13.05)
	1	End	Arthralgia	15.00 (14.95;15.05)
	1	End	Back pain	2.00 (1.98;2.02)
	1	End	Cough	6.00 (5.97;6.03)
	1	End	Death	1.00 (0.99;1.01)
	1	End	Decreased appetite	17.00 (16.95;17.05)
	1	End	Diarrhea	11.00 (10.95;11.05)
	1	End	Discontinuation for other reasons	1.00 (0.99;1.01)
	1	End	Discontinuation for safety reasons	7.00 (6.96;7.04)
	1	End	Dizziness	8.00 (7.96;8.04)
	1	End	Dose modification	46.00 (45.93;46.07)
	1	End	Dose modification due to adverse event	7.00 (6.96;7.04)
	1	End	Dose modification due to Alanine aminotransferase elevation	8.00 (7.96;8.04)
	1	End	Dose modification due to Laboratory abnormality	36.00 (35.93;36.07)
	1	End	Dose modification due to Neutropenia	17.00 (16.95;17.05)
	1	End	Dose modification due to thrombocytopenia	19.00 (18.94;19.06)
	1	End	Fatigue	41.00 (40.93;41.07)
	1	End	Headache	23.00 (22.94;23.06)
	1	End	Injection-site reaction	6.00 (5.97;6.03)
	1	End	Insomnia	8.00 (7.96;8.04)
	1	End	Irritability	7.00 (6.96;7.04)
	1	End	Myalgia	26.00 (25.94;26.06)
	1	End	Nausea	8.00 (7.96;8.04)
	1	End	Pruritus	5.00 (4.97;5.03)
	1	End	Pyrexia	58.00 (57.93;58.07)
	1	End	Rigors	6.00 (5.97;6.03)
	1	End	Sore throat	6.00 (5.97;6.03)
	1	End	Upper abdominal pain	5.00 (4.97;5.03)
	1	End	Upper respiratory tract infection	5.00 (4.97;5.03)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
Peginterferon alfa-2a+Lamivudine [57]	1	End	Normalization ALT	47.94 (44.33;51.85)
	1	End	Combined	46.53 (43.87;49.34)
	1	Followup off treatment	Normalization ALT	59.15 (54.69;63.97)
	1	Followup off treatment	Combined	24.65 (10.51;57.81)
	1	Followup off treatment	Improved histology	23.88 (8.88;64.17)
	1	Followup off treatment	Failure	10.18 (6.36;16.29)
	1	End	Death	0.28 (0.27;0.28)
	1	End	Discontinuation for other reasons	2.00 (1.98;2.02)
	1	End	Upper respiratory tract infection	2.00 (1.98;2.02)
	1	End	Dose modification due to Alanine aminotransferase elevation	3.00 (2.98;3.02)
	1	End	Sore throat	3.00 (2.98;3.02)
	1	End	Rigors	3.00 (2.98;3.02)
	1	End	Cough	3.00 (2.98;3.02)
	1	End	Discontinuation for safety reasons	4.00 (3.97;4.03)
	1	End	Irritability	4.00 (3.97;4.03)
	1	End	Diarrhea	6.00 (5.97;6.03)
	1	End	Pruritus	6.00 (5.97;6.03)
	1	End	Back pain	6.00 (5.97;6.03)
	1	End	≥1 Reported serious adverse event	7.00 (6.96;7.04)
	1	End	Dizziness	7.00 (6.96;7.04)
	1	End	Nausea	7.00 (6.96;7.04)
	1	End	Upper abdominal pain	7.00 (6.96;7.04)
	1	End	Insomnia	8.00 (7.96;8.04)
	1	End	Alopecia	11.00 (10.95;11.05)
	1	End	Dose modification due to thrombocytopenia	12.00 (11.95;12.05)
	1	End	Injection-site reaction	12.00 (11.95;12.05)
	1	End	Dose modification due to adverse event	13.00 (12.95;13.05)
	1	End	Decreased appetite	14.00 (13.95;14.05)
	1	End	Arthralgia	15.00 (14.95;15.05)
	1	End	Headache	19.00 (18.94;19.06)
	1	End	Dose modification due to Neutropenia	24.00 (23.94;24.06)
	1	End	Myalgia	27.00 (26.94;27.06)
	1	End	Dose modification due to Laboratory abnormality	35.00 (34.93;35.07)
	1	End	Fatigue	41.00 (40.93;41.07)
	1	End	Dose modification	48.00 (47.93;48.07)
	1	End	Pyrexia	54.00 (53.93;54.07)
	1	End	≥1 Reported adverse event	86.00 (85.95;86.05)
	1	End	Normalization of Alanine	16.00 (15.95;16.05)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
			aminotransferase and HBV DNA <400 copies/ml	
	1	End	Normalization of Alanine aminotransferase and HBV DNA <20,000 copies/ml	38.00 (37.93;38.07)
	1	End	Normalization of Alanine aminotransferase and HBV DNA <400 copies/ml	45.00 (44.93;45.07)
	1	End	Normalization of Alanine aminotransferase and HBV DNA <20,000 copies/ml	48.00 (47.93;48.07)
Placebo or no treatment [46,49,84,88,98,99]	3	All	Improved histology	10.40 (3.35;32.34)
	4	All	HBV DNA loss	5.06 (2.04;12.55)
	3	All	Normalization ALT	31.70 (28.73;34.99)
	2	All	Mutation	1.98 (0.92;4.25)
	2	All	HBsAg seroconversion	1.55 (1.08;2.21)
	4	All	Combined	6.41 (3.52;11.65)
	3	All	HBsAg loss	1.86 (1.17;2.98)
	2	All	Relapse	8.91 (7.19;11.06)
	1	All	HCC	2.39 (2.25;2.53)
	1	All	Flare	70.81 (59.36;84.47)
	4	All	Resistance	16.40 (5.10;52.75)
	2	All	Failure	12.32 (3.11;48.81)
HBeAg-positive patients				
Adefovir dipivoxil [40,42,44,99,100]	4	End	HBV DNA loss	24.83 (15.74;39.18)
	4	End	Normalization ALT	59.46 (52.08;67.89)
	2	End	Flare	2.72 (0.96;7.71)
	4	End	HBeAg loss	16.53 (12.33;22.16)
	4	End	HBeAg seroconversion	12.35 (10.03;15.20)
	2	End	Relapse	8.97 (5.76;13.98)
	1	End	HBsAg loss	2.64 (2.49;2.80)
	1	End	Improved histology	51.72 (45.88;58.30)
	2	End	Resistance	21.64 (16.35;28.64)
	1	End	Failure	10.07 (8.85;11.47)
	1	End	Mutation	27.94 (26.86;29.06)
	1	Followup off treatment	Normalization ALT	38.86 (36.64;41.22)
	1		Insomnia	20.91 (18.71;23.36)
	1		Discontinuation	7.50 (6.97;8.07)
	1		Discontinuation due to adverse effects	1.00 (0.99;1.01)
	1		Dose reduced due to an adverse event or	8.49 (3.83;18.83)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
			abnormal laboratory result	
	2		Fatigue	3.31 (2.12;5.15)
	1		Flu-like syndrome	16.95 (15.83;18.14)
	1		Hematuria10–100 RBCs	13.65 (10.84;17.19)
	2		Pharyngitis	30.21 (25.01;36.48)
	1		Proteinuria mg/dL100–1000	8.80 (5.82;13.29)
	1		Rash	20.91 (18.71;23.36)
	1		Sinusitis	15.96 (14.28;17.83)
	1		Any adverse event	95.00 (94.94;95.06) †
	2		Asthenia	29.84 (26.48;33.62)
	1		Fever	15.96 (14.28;17.83)
	3		Headache	17.27 (12.27;24.29)
	1		Hematuria>100 RBCs	8.46 (5.72;12.50)
	2		Nasopharyngitis	5.75 (4.98;6.63)
	1		Reactivation of hepatitis	1.00 (0.99;1.01)
	1		Serum Glucose Grade 3 abnormalities	11.02 (10.00;12.15)
	1		Total adverse effect	63.75 (59.53;68.28)
	2		Upper respiratory tract infection	9.71 (8.67;10.88)
	1		Incidence of elevation of serum ALT to >5 times the ULN	28.19 (20.26;39.23)
	1		Increases from baseline of 0.5 mg per deciliter (44 µmol per liter) or greater in the serum creatinine level	8.00 (7.70;8.32)
	1		Hypophosphatemia mg/dL (<1.0)	1.00 (0.99;1.01)
	1		Hypophosphatemia mg/dL (1.0–1.5)	1.73 (0.93;3.23)
	1		Bacterial infection	2.64 (2.53;2.75)
	1		ALT Grade 4 >10 times the ULN)	2.64 (2.53;2.75)
	1		Grade 4 (>10 times the ULN)	2.64 (2.53;2.75)
	1		Amylase Grade 3 (>2–5 times the ULN)	2.64 (2.53;2.75)
	1		Grade4 (□5 times the ULN)	2.64 (2.53;2.75)
	1		Grade4 (>30 mg/dL; <500 mg/dL)	2.63 (2.57;2.70)
	1		Grade4 (4+)	2.64 (2.53;2.75)
	1		Cough	3.79 (2.02;7.12)
	2		Dizziness	4.73 (2.29;9.80)
	1		Malaise	2.12 (1.30;3.45)
	1		Epigastric discomfort	1.49 (1.13;1.97)
	1		Gastritis	1.10 (1.08;1.12)
	1		Myalgia	2.12 (1.30;3.45)
	1		Hordeolum	1.10 (1.08;1.12)
	3		Abdominal pain	7.08 (3.35;14.95)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Hepatic steatosis	1.47 (1.09;1.97)
	1		Toothache	1.47 (1.09;1.97)
	1		Allergic rhinitis	2.33 (1.30;4.18)
	1		Creatinine mg/dL (1.5–2.0)	2.51 (1.11;5.68)
	1		Glycosuria (+1)	1.41 (0.96;2.09)
	1		Glycosuria (+2)	1.41 (0.96;2.09)
	1		Glycosuria (+3)	1.00 (0.99;1.01)
	1		Discontinuation due to adverse events	2.45 (1.94;3.09)
	3		Diarrhea	7.24 (3.97;13.22)
	3		Nausea	7.22 (4.15;12.57)
	1		Pharyngolaryngeal pain	3.74 (2.04;6.87)
	1		Mouth ulceration	3.16 (1.93;5.17)
	1		Anorexia	6.33 (4.08;9.81)
	1		Hypophosphatemia mg/dL (2.0–2.2)	5.55 (4.16;7.40)
	2		Arthralgia	6.00 (4.69;7.67)
	1		Gastroenteritis	5.00 (4.67;5.36)
	1		Infection	5.00 (4.67;5.36)
	1		Rhinitis	5.00 (4.67;5.36)
	1		AST Grade3 (>5–10 times the ULN)	5.00 (4.67;5.36)
	1		Upper abdominal pain	7.42 (4.80;11.46)
	3		Back pain	7.96 (6.78;9.36)
	2		Increased cough	8.97 (6.78;11.87)
	1		Influenza	7.97 (6.91;9.18)
	2		Pain	9.86 (8.50;11.44)
	1		Flatulence	8.94 (7.89;10.12)
	1		Severe (grade 3 or 4) clinical adverse events	9.49 (8.97;10.04)
	1		Dyspepsia	9.97 (8.91;11.17)
	1		Urine Glucose Grade3	11.02 (10.00;12.15)
	1		Hematuria>100 RBCs	12.37 (11.84;12.91)
	1		Proteinuria mg/dL(<100)	17.55 (13.60;22.64)
	1		ALT Grade 3 (>5–10 times the ULN)	36.97 (32.18;42.46)
Adefovir dipivoxil + Lamivudine [43]	1	End	HBV DNA loss	35.16 (30.61;40.39)
	1	End	HBeAg loss	15.03 (13.64;16.56)
	1	End	HBeAg seroconversion	5.00 (4.73;5.29)
	1	End	Normalization ALT	49.90 (43.44;57.32)
	1	End	HBsAg loss	5.00 (4.73;5.29)
	1		Any adverse event	90.02 (82.84;97.82)
	1		Asthenia	49.90 (43.44;57.32)
	1		Headache	29.96 (26.45;33.95)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Pharyngitis	5.00 (4.73;5.29)
	1		Abdominal pain	29.96 (26.45;33.95)
	1		Back pain	15.03 (13.64;16.56)
	1		Nausea	20.09 (17.98;22.44)
	1		Pain	20.09 (17.98;22.44)
	1		Infection	15.03 (13.64;16.56)
	1		ALT Grade 3 (>5–10 times ULN)	2.51 (2.41;2.62)
	1		Insomnia	2.51 (2.41;2.62)
	1		Rash	2.51 (2.41;2.62)
	1		Fever	2.51 (2.41;2.62)
	1		Increased cough	2.51 (2.41;2.62)
	1		Gastroenteritis	2.51 (2.41;2.62)
	1		Grade4 (>10 times the ULN)	2.51 (2.41;2.62)
	1		Grade4 (□5 times the ULN)	2.51 (2.41;2.62)
	1		Grade4 (>30 mg/dL; <500 mg/dL)	2.51 (2.41;2.62)
	1		Grade4 (4+)	2.51 (2.41;2.62)
	1		Sinusitis	5.00 (4.73;5.29)
	1		Arthralgia	5.00 (4.73;5.29)
	1		ALT Grade 4 >10 times ULN	5.00 (4.73;5.29)
	1		Serum glucose Grade3 abnormalities	5.00 (4.63;5.41)
	1		Urine Glucose Grade3	5.00 (4.73;5.29)
	1		Diarrhea	9.97 (9.18;10.84)
	1		Rhinitis	9.97 (9.18;10.84)
	1		Amylase Grade3 (>2–5 ULN)	9.97 (9.18;10.84)
	1		Bacterial infection	15.03 (13.64;16.56)
Entecavir[73,75,101]	1	End	Improved histology	43.51 (31.63;59.85)
	2	End	Resistance	19.76 (7.85;49.71)
	3	End	Failure	5.42 (1.89;15.52)
	3	End	Combined	42.68 (26.13;69.70)
	3	End	Normalization ALT	73.28 (62.93;85.34)
	2	End	HBeAg loss	14.81 (6.83;32.11)
	3	End	HBeAg seroconversion	16.98 (8.79;32.81)
	3	End	Flare	2.08 (1.02;4.27)
	3	End	Death	1.00 (0.98;1.02)
	2	End	HBV DNA loss	73.20 (65.17;82.23)
	2	End	HBsAg loss	3.74 (1.09;12.87)
	1	End	HBsAg seroconversion	1.99 (1.96;2.03)
	1	End	Relapse	4.02 (3.94;4.09)
	1	End	Decompensation	0.14 (0.14;0.15)
	2	Followup off treatment	Combined	9.84 (4.06;23.85)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1	Followup off treatment	Flare	1.00 (0.98;1.02)
	1	Followup off treatment	Death	1.00 (0.98;1.02)
	1	Followup off treatment	HBV DNA loss	7.03 (6.89;7.17)
	1	Followup off treatment	Relapse	1.99 (1.96;2.03)
	1	Followup off treatment	Decompensation	0.14 (0.14;0.15)
	2	All	Any adverse event	85.36 (82.63;88.19)
	2	All	Serious adverse events	6.84 (3.97;11.80)
	1	All	Discontinuations because of adverse events	1.00 (0.98;1.02)
	1	All	Discontinuation due to adverse effects	0.14 (0.14;0.15)
	1	All	ALT >2× baseline and >5× ULN	1.00 (0.99;1.01)
	1	All	ALT > 2× reference value and >5× ULN	10.00 (9.97;10.03)
	1	All	Any adverse effect	77.20 (77.17;77.23)*
Interferon Alfa-2b [82,83,85-87,89,90,94,96,104,105]	3	End	Normalization ALT	46.38 (27.43;78.42)
	5	End	HBV DNA loss	46.97 (34.69;63.61)
	4	End	HBeAg loss	50.78 (33.81;76.25)
	3	End	HBeAg seroconversion	40.09 (20.44;78.63)
	2	End	HBsAg loss	6.14 (3.47;10.88)
	1	End	Combined	24.99 (17.81;35.07)
	1	End	Resistance	7.03 (6.50;7.60)
	1	End	Improved histology	25.03 (20.57;30.45)
	2	End	Death	6.83 (3.05;15.27)
	1	End	Flare	5.99 (5.43;6.61)
	6	Followup off treatment	Normalization ALT	36.49 (26.10;51.03)
	11	Followup off treatment	HBV DNA loss	26.97 (18.34;39.67)
	10	Followup off treatment	HBeAg loss	42.96 (32.25;57.23)
	5	Followup off treatment	HBeAg seroconversion	31.86 (19.64;51.66)
	8	Followup off treatment	HBsAg loss	7.41 (4.20;13.07)
	8	Followup off treatment	Combined	13.49 (8.41;21.64)
	3	Followup off treatment	Resistance	7.64 (4.46;13.08)
	3	Followup off treatment	Relapse	2.24 (1.72;2.91)
	2	Followup off treatment	Death	4.16 (2.27;7.62)
	2	Followup off treatment	HBsAg seroconversion	6.32 (0.66;60.79)
	2	Followup off treatment	Improved histology	26.91 (15.24;47.50)
	1	Followup off treatment	Cirrhosis	8.92 (2.86;27.81)
	1	Followup off treatment	Failure	25.03 (22.69;27.61)
	1	Followup off treatment	Mutation	0.73 (0.71;0.74)
	1		Abdominal discomfort and pain	33.00 (32.89;33.11)
	1		Adverse effects	75.00 (74.92;75.08)
	1		Anorexia	47.00 (46.89;47.11)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Arthralgia	33.00 (32.89;33.11)
	1		Arthralgia	8.00 (7.90;8.10)
	1		Collapse after dizziness	2.00 (1.97;2.03)
	1		Depression	4.00 (3.93;4.07)
	1		Diarrhea	23.00 (22.90;23.10)
	1		Discontinuation due to depression	3.00 (2.94;3.06)
	1		Dizziness	27.00 (26.90;27.10)
	1		Dose reduction due to depression, fatigue, hair loss, and headache	11.00 (10.92;11.08)
	1		Fatigue	48.00 (47.82;48.18)
	1		Fever/chills	61.00 (60.89;61.11)
	1		Hair loss and alopecia	30.00 (29.90;30.10)
	1		Headache	67.00 (66.89;67.11)
	1		Infections	8.00 (7.90;8.10)
	1		Jaundice	4.00 (3.93;4.07)
	1		Malaise and fatigue	100.00 (100.00;100.00)
	1		Marrow suppression	8.00 (7.90;8.10)
	1		mouth dryness	19.00 (18.83;19.17)
	1		Muscle pain	57.00 (56.89;57.11)
	1		Nausea	12.00 (11.88;12.12)
	1		Nausea and vomiting	49.00 (48.89;49.11)
	1		Discontinuation due to drug-related adverse effects	3.00 (2.97;3.03)
	1		Discontinuation due to psychosis	3.00 (2.94;3.06)
	1		Reduction in dose because of severe side effects	8.00 (7.90;8.10)
	1		Viral respiratory infections	53.00 (52.89;53.11)
	5		Discontinuation due to adverse effects	2.91 (1.41;5.99)
	1		Discontinuation due to neuropsychiatric disorder	3.63 (1.93;6.80)
	2		Reduction in dose due to adverse effects	20.70 (18.64;22.98)*
Interferon Alfa-2b + Corticosteroid[90-96,103]	2	End	Combined	39.50 (33.32;46.83)
	1	End	Death	2.77 (2.56;3.00)
	3	End	HBsAg loss	9.22 (6.42;13.24)
	2	End	HBV DNA loss	37.38 (23.78;58.77)
	1	End	Resistance	47.85 (42.56;53.80)*
	2	End	HBeAg loss	42.02 (19.39;91.04)
	2	Followup off treatment	Combined	7.03 (2.37;20.89)
	1	Followup off treatment	Death	5.00 (4.45;5.63)
	2	Followup off treatment	Relapse	3.33 (2.11;5.26)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	3	Followup off treatment	HBsAg loss	17.25 (5.51;54.07)
	6	Followup off treatment	HBV DNA loss	24.44 (16.31;36.63)
	2	Followup off treatment	Resistance	18.36 (9.25;36.45)
	1	Followup off treatment	Cirrhosis	9.97 (9.04;11.00)
	3	Followup off treatment	Normalization ALT	35.77 (20.48;62.47)
	3	Followup off treatment	HBeAg loss	45.64 (33.35;62.46)
	2	Followup off treatment	HBeAg seroconversion	51.10 (44.58;58.58)
	1		Reduction in dose because of severe side effects	8.00 (7.90;8.10)
	1		Leucopenia	20.00 (19.79;20.21)
	1		Discontinuation due to adverse effects	2.94 (2.87;3.01)
	1		Reduction in dose due to adverse effects	12.00 (11.86;12.14)
Interferon Alfa-2b + Lamivudine [47,65-69,79,80,104]	3	End	Mutation	3.30 (1.55;7.06)
	1	End	HBsAg loss	5.99 (5.75;6.24)
	4	End	HBeAg seroconversion	31.30 (13.42;73.00)
	3	End	Failure	13.17 (8.74;19.85)
	4	End	HBeAg loss	38.85 (21.64;69.72)
	4	End	Normalization ALT	44.07 (22.58;86.02)
	6	End	HBV DNA loss	59.03 (41.91;83.15)
	5	End	Improved histology	36.77 (31.13;43.43)
	1	End	Flare	1.52 (1.46;1.58)
	1	End	Relapse	4.02 (3.86;4.18)
	2	End	Combined	55.02 (31.63;95.72)
	1	End	Resistance	57.02 (50.92;63.85)
	1	Followup off treatment	Mutation	0.66 (0.66;0.67)
	2	Followup off treatment	HBsAg loss	2.54 (0.52;12.36)
	6	Followup off treatment	HBeAg seroconversion	35.15 (20.28;60.93)
	2	Followup off treatment	Failure	21.96 (19.92;24.22)
	5	Followup off treatment	HBeAg loss	39.96 (29.41;54.30)
	6	Followup off treatment	Normalization ALT	61.61 (50.09;75.77)
	7	Followup off treatment	HBV DNA loss	49.14 (28.67;84.21)
	1	Followup off treatment	Improved histology	27.94 (26.07;29.94)
	1	Followup off treatment	Flare	5.00 (4.72;5.31)
	2	Followup off treatment	Relapse	6.68 (3.57;12.50)
	2	Followup off treatment	Combined	32.39 (27.06;38.76)
	1		ALT> 2 than at baseline	1.26 (0.81;1.96)
	4		Discontinuation due AE	4.77 (3.34;6.81)
	1		Arthralgia	11.94 (11.30;12.62)
	1		Dizziness	11.94 (11.30;12.62)
	1		Abnormal enzymes	12.94 (12.24;13.67)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Abdominal discomfort	14.01 (13.26;14.81)
	1		Abnormal ALT/AST	15.96 (15.10;16.87)
	1		Pain	15.96 (15.10;16.87)
	1		Musculoskeletal pain	15.96 (15.10;16.87)
	4		Diarrhea	14.08 (7.59;26.10)
	1		Decreased WBCs	25.03 (23.35;26.82)
	1		Rheumatism	25.03 (23.35;26.82)
	2		Depression	11.35 (1.52;84.71)
	1		Feeding problems	29.96 (27.57;32.56)
	2		Viral respiratory in	38.48 (34.75;42.60)
	1		Anorexia	38.86 (36.26;41.65)
	1		Hair loss and alopecia	38.86 (36.26;41.65)
	1		Nausea and vomiting	42.95 (39.52;46.67)
	2		Muscle pain	46.53 (43.87;49.34)
	1		Nausea/vomiting	59.15 (54.43;64.27)
	1		Fever/chills	60.95 (56.87;65.32)
	4		Headache	44.65 (43.37;45.97)
	1		Malaise and fatigue	87.36 (82.65;92.34)
	1		Malaise/fatigue	94.63 (90.78;98.65)
	2		Fever	94.63 (90.78;98.65)
	3		Albumin: 2.0–2.4 g/d	3.00 (2.89;3.12)
	2		Influenza-like symptoms	64.18 (58.99;69.82)
Interferon Alfa-2b + Placebo [67,93]	1	End	HBeAg loss	83.10 (76.83;89.87)
	1	End	HBV DNA loss	83.10 (76.83;89.87)
	1	End	Normalization ALT	83.93 (77.60;90.78)
	1	End	HBeAg seroconversion	92.76 (87.46;98.38)
	1	Followup off treatment	Mutation	0.73 (0.71;0.74)
	1	Followup off treatment	Failure	25.03 (22.69;27.61)
	1	Followup off treatment	Improved histology	35.87 (31.89;40.35)
	1	Followup off treatment	HBeAg loss	75.19 (65.55;86.25)
	1	Followup off treatment	HBV DNA loss	75.19 (66.85;84.57)
	1	Followup off treatment	Normalization ALT	75.94 (68.86;83.76)
	1	Followup off treatment	HBeAg seroconversion	92.76 (88.98;96.70)
	1	Followup off treatment	Combined	8.67 (2.95;25.46)
	1		Discontinuation due to adverse effects	0.71 (0.70;0.73)
	1		Hepatitis flares (ALT levels >500 IU/l and >2' baseline)	9.00 (8.93;9.07)
	1		Hepatitis flares (ALT levels >500 IU/l and >2' baseline)	11.00 (10.93;11.07)
	1		Diarrhea	23.00 (22.90;23.10)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Dizziness	27.00 (26.90;27.10)
	1		Hair loss and alopecia	30.00 (29.90;30.10)
	1		Abdominal discomfort and pain	33.00 (32.89;33.11)
	1		Arthralgia	33.00 (32.89;33.11)
	1		Anorexia	47.00 (46.89;47.11)
	1		Nausea and vomiting	49.00 (48.89;49.11)
	1		Viral respiratory infections	53.00 (52.89;53.11)
	1		Muscle pain	57.00 (56.89;57.11)
	1		Fever/chills	61.00 (60.89;61.11)
	1		Headache	67.00 (66.89;67.11)
	1		Malaise and fatigue	100.00 (100.00;100.00)
Lamivudine[43,47,48,50,53,55,72,104,107-112]	12	End	HBeAg loss	19.08 (11.82;30.78)
	15	End	HBeAg seroconversion	15.42 (9.99;23.80)
	11	End	Improved histology	30.76 (22.17;42.67)
	11	End	Failure	10.04 (7.65;13.18)
	17	End	HBV DNA loss	43.86 (32.37;59.44)
	15	End	Normalization ALT	38.41 (25.65;57.51)
	4	End	Resistance	38.06 (27.41;52.85)
	4	End	HBsAg loss	1.99 (1.29;3.07)
	5	End	Flare	7.74 (5.84;10.27)
	3	End	Death	1.00 (0.99;1.01)
	8	End	Combined	27.95 (19.58;39.89)
	5	End	Relapse	12.62 (5.93;26.86)
	1	End	Decompensation	0.14 (0.14;0.14)
	1	End	HBsAg seroconversion	5.00 (4.81;5.20)
	6	End	Mutation	13.45 (6.59;27.45)
	7	Followup off treatment	HBeAg loss	32.22 (26.08;39.81)
	7	Followup off treatment	HBeAg seroconversion	24.49 (14.88;40.31)
	2	Followup off treatment	Improved histology	34.12 (32.73;35.57)
	2	Followup off treatment	Failure	11.94 (11.04;12.92)
	5	Followup off treatment	HBV DNA loss	9.30 (4.83;17.91)
	5	Followup off treatment	Normalization ALT	39.26 (23.18;66.48)
	3	Followup off treatment	HBsAg loss	1.56 (0.80;3.05)
	3	Followup off treatment	Flare	4.82 (1.96;11.90)
	3	Followup off treatment	Death	1.00 (0.99;1.01)
	6	Followup off treatment	Combined	9.89 (4.83;20.26)
	4	Followup off treatment	Relapse	14.06 (4.72;41.86)
	2	Followup off treatment	Decompensation	2.00 (1.15;3.48)
	1	Followup off treatment	Mutation	23.00 (21.51;24.59)
	3		>1 Reported adverse	47.41 (31.02;72.47)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		>1 Reported serious AE	1.99 (1.97;2.02)
	4		Abdominal discomfort	8.02 (4.81;13.38)
	1		Abdominal discomfort or pain	15.26 (12.66;18.39)
	1		Abdominal distention	8.00 (7.82;8.20)
	1		Abdominal pain	26.05 (23.00;29.51)
	1		Abnormal ALT/AST	17.99 (17.26;18.76)
	1		Abnormal enzymes (amylase/CPK)	15.96 (15.31;16.64)
	2		Abnormal liver function tests	7.04 (4.30;11.53)
	1		Acne and folliculitis	3.66 (2.79;4.81)
	1		Albumin: 2.0–2.4 g/d	3.00 (2.89;3.12)
	1		Allergic rashes	1.99 (1.92;2.07)
	2		Alopecia	2.51 (1.98;3.19)
	1		ALT > 2× reference value and >5× ULN	5.00 (4.91;5.10)
	1		ALT >2× baseline and >5× ULN	16.95 (16.29;17.62)
	1		ALT »2 times above base-line levels	26.05 (24.09;28.17)
	2		ALT> 2 than at baseline and >500U/l	3.02 (1.57;5.80)
	1		ALT »3 times above base-line levels	15.17 (6.66;34.54)
	1		ALT Grade 3 (>5–10 times the ULN)	2.64 (2.53;2.75)
	1		ALT Grade 4 >10 times the ULN)	15.96 (14.28;17.83)
	1		Amylase >2X upper limit of normal	3.66 (2.79;4.81)
	1		Amylase Grade3 (>2–5 times the ULN)	15.96 (14.28;17.83)
	1		Amylase: value 3.1-10 times the baseline value and >10 times the baseline value	1.00 (0.98;1.02)
	1		Anorexia	5.00 (4.87;5.14)
	1		Any adverse effect	66.11 (41.30;105.81)
	3		Any adverse event	36.11 (24.98;52.19)
	4		Arthralgia	5.74 (4.53;7.27)
	1		AST Grade3 (>5–10 times the ULN)	5.00 (4.67;5.36)
	1		Asthenia	32.14 (27.98;36.91)
	1		At least one adverse event	5.00 (4.93;5.07)
	1		At least one adverse effect	68.03 (61.68;75.04)
	2		Back pain	4.77 (3.18;7.15)
	1		Bacterial infection	2.64 (2.53;2.75)
	1		Chest symptoms	2.45 (1.94;3.09)
	2		Constipation	3.83 (2.91;5.05)
	5		Cough	14.63 (10.43;20.53)
	1		CPK >5X upper limit	4.74 (3.21;7.01)
	1		Creatine kinase: value 7-9.9 times the baseline value and at least 10 times the baseline value	7.03 (6.63;7.45)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Decreased appetite	1.99 (1.97;2.02)
	1		Decreased neutrophil count	1.00 (0.98;1.02)
	1		Decreased phosphate level	1.99 (1.92;2.07)
	1		Decreased WBCs	1.00 (0.99;1.01)
	4		Depression	4.02 (2.47;6.53)
	12		Diarrhea	9.44 (7.31;12.18)
	7		Discontinuation due to adverse effect	3.76 (2.61;5.43)
	8		Dizziness	5.16 (4.55;5.87)
	3		Dyspepsia	6.26 (4.98;7.86)
	1		Ear, nose, and throat infection	21.33 (19.20;23.69)
	1		Dose modification due to adverse effects	0.18 (0.18;0.19)
	1		Dose modification due to Laboratory abnormality: Alanine aminotransferase elevation, Neutropenia, and thrombocytopenia	0.18 (0.18;0.19)
	1		Eczema	3.66 (2.79;4.81)
	1		events of the hepatobiliary tract and pancreas	4.60 (2.00;10.57)
	4		Fatigue	9.03 (6.36;12.82)
	1		Feeding problems	1.99 (1.97;2.02)
	4		Fever	5.89 (5.16;6.71)
	1		Fever/chills	7.03 (6.74;7.33)
	1		Gastroenteritis	15.96 (14.28;17.83)
	1		Gastrointestinal events	9.58 (7.78;11.81)
	1		Grade III abnormality in ALT	14.14 (7.12;28.07)
	1		Grade III or IV laboratory abnormalities in Alanine aminotransferase	9.97 (9.41;10.58)
	1		Grade III or IV laboratory abnormalities in Albumin	0.70 (0.69;0.72)
	1		Grade III or IV laboratory abnormalities in Amylase	0.70 (0.69;0.72)
	1		Grade III or IV laboratory abnormalities in Creatine kinase	9.00 (8.94;9.06)
	1		Grade III or IV laboratory abnormalities in Lipase	9.00 (8.94;9.06)
	1		Grade III or IV laboratory abnormalities in Platelets	0.70 (0.69;0.72)
	1		Grade IV abnormality in ALT	1.46 (0.35;6.03)
	1		Grade4 (>10 times the ULN)	11.02 (10.00;12.15)
	1		Grade4 (>30 mg/dL; <500 mg/dL)	2.64 (2.53;2.75)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Grade4 (4+)	2.64 (2.53;2.75)
	1		Grade4 (>5 times the ULN)	2.64 (2.53;2.75)
	1		Hair loss	1.99 (1.97;2.02)
	1		Hair loss and alopecia	9.97 (9.57;10.40)
	1		Hair loss or alopecia	1.99 (1.97;2.02)
	13		Headache	11.93 (9.48;15.01)
	1		Hypoglycemia	3.65 (3.06;4.36)
	1		Increased alkaline phosphatase level	2.00 (1.96;2.04)
	1		Increased ALT level	24.00 (23.89;24.11)
	1		Increased cough	15.96 (14.28;17.83)
	2		Increased Creatine phosphokinase level	4.16 (2.49;6.94)
	1		Infection	5.00 (4.67;5.36)
	1		Influenza	20.91 (19.33;22.61)
	3		Influenza-like symptoms	17.27 (14.63;20.40)
	2		Insomnia	6.46 (5.30;7.87)
	1		Leucopenia	5.00 (4.98;5.02)
	1		Lipase: value 2.6 to five times ULNand >5 times the upper limit of normal	3.00 (2.96;3.04)
	1		Liver symptoms	5.00 (4.98;5.02)
	1		Local erythematous reaction	1.00 (0.97;1.03)
	1		Malaise	14.00 (13.91;14.09)
	3		Malaise and fatigue	17.98 (14.62;22.12)
	4		Malaise or fatigue	18.47 (12.74;26.78)
	6		Muscle pain	4.79 (2.87;8.00)
	3		Musculoskeletal pain	4.77 (2.43;9.36)
	2		Nasal signs and symptoms	8.93 (7.83;10.18)
	1		Nasopharyngitis	5.00 (4.76;5.25)
	3		Nausea	3.96 (3.07;5.12)
	4		Nausea and vomiting	8.13 (6.08;10.86)
	5		Nausea or vomiting	8.77 (5.52;13.94)
	1		Neurological events	6.94 (6.04;7.98)
	2		Pain	4.49 (2.69;7.51)
	1		Paresthesias	3.00 (2.89;3.12)
	1		Pharyngitis	32.14 (27.98;36.91)
	1		Pharyngolaryngeal pain	15.96 (14.76;17.26)
	1		Pigmentary skin disorders	3.66 (2.79;4.81)
	1		Platelets: value of 20 000–49 000/mm3 and less than 20 000/mm3	3.00 (2.96;3.04)
	1		Pruritis	5.00 (4.91;5.10)
	1		Pyrexia	4.02 (3.96;4.07)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	4		Rash	7.45 (6.16;9.01)
	1		Reduced appetite	1.00 (0.98;1.02)
	1		Respiratory infection	35.16 (33.81;36.57)
	1		Rheumatism	5.00 (4.87;5.14)
	1		Rhinitis	26.05 (23.00;29.51)
	1		Severe Myalgia	1.19 (1.14;1.23)
	1		Serum glucose Grade3 (30–39 mg/dL; 251–500 mg/dL)	15.96 (14.28;17.83)
	1		Sinusitis	26.05 (23.00;29.51)
	2		Skin rash	4.84 (3.37;6.97)
	1		Sleep disorder	7.03 (6.63;7.45)
	1		Sleep disturbance	5.00 (4.91;5.10)
	1		Sore throat	7.03 (6.84;7.23)
	1		Temperature regulation disturbance	8.94 (8.11;9.84)
	1		Throat and tonsil discomfort/pain	22.53 (21.82;23.27)
	1		Throat discomfort or pain	14.37 (12.76;16.18)
	2		Upper abdominal pain	5.63 (4.89;6.49)
	1		Upper respiratory tract infection	6.53 (4.72;9.03)
	1		Upper respiratory tract symptoms	38.00 (37.87;38.13)
	1		Upper respiratory viral infection	5.00 (4.98;5.02)
	1		Urine Glucose Grade3 (3+)	21.00 (20.83;21.17)
	1		Vertigo	3.66 (2.79;4.81)
	1		Viral respiratory infection	27.70 (25.30;30.32)
	1		Viral respiratory infections (multiple)	9.48 (3.53;25.46)
	1		Vomiting or diarrhea	6.00 (5.94;6.06)
	1		Weight loss (>10%)	2.00 (1.96;2.04)
	1		Withdrawal due to side effects	1.35 (1.32;1.39)
Peginterferon alfa-2a [56,116]	1	End	HBeAg loss	29.96 (28.74;31.24)
	1	End	HBeAg seroconversion	27.11 (26.01;28.26)
	1	End	Normalization ALT	38.86 (37.28;40.51)
	1	End	Combined	9.97 (9.70;10.26)
	1	End	HBV DNA loss	25.03 (24.01;26.09)
	1	End	Flare	5.00 (4.93;5.07)
	1	End	Mutation	0.18 (0.18;0.19)
	2	Follow	HBeAg loss	33.60 (31.77;35.53)
	2	Follow	HBeAg seroconversion	31.98 (29.91;34.20)
	2	Follow	Normalization ALT	37.26 (34.12;40.70)
	2	Follow	Combined	23.88 (21.65;26.34)
	1	Follow	HBV DNA loss	14.01 (13.63;14.41)
	1	Follow	Improved histology	38.09 (36.54;39.71)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1	Follow	Death	0.18 (0.18;0.19)
	1		Discontinuation due to AE	3.00 (2.96;3.05)
	1		>1 Reported serious AE	4.02 (3.96;4.07)
	2		Cough	8.04 (6.56;9.84)
	1		Dyspepsia	5.00 (4.93;5.07)
	1		Depression	5.00 (4.93;5.07)
	1		Sore throat	5.99 (5.91;6.07)
	1		Gingival bleeding	5.99 (5.91;6.07)
	1		Dose modification due to adverse effects	7.03 (6.84;7.23)
			Dose modification due to laboratory abnormality: alanine aminotransferase elevation, neutropenia, and thrombocytopenia	36.97 (35.46;38.54)
	2		Insomnia	12.39 (9.30;16.52)
	1		Rigors	7.03 (6.84;7.23)
	1		Upper abdominal pain	7.03 (6.84;7.23)
	1		Upper respiratory tract infection	13.35 (9.25;19.26)
	1		Anorexia	13.96 (9.68;20.11)
	2		Diarrhea	12.15 (9.75;15.15)
	2		Dizziness	14.19 (11.26;17.89)
	2		Nausea	12.45 (10.30;15.05)
	1		Injection-site reaction	9.03 (8.78;9.28)
	1		Arthralgia	9.03 (8.78;9.28)
	1		Rash	9.97 (9.70;10.26)
	1		Pruritus	9.97 (9.70;10.26)
	1		Decreased appetite	15.03 (14.62;15.45)
	2		Alopecia	26.31 (21.71;31.89)
	2		Fatigue	28.96 (24.23;34.61)
	2		Myalgia	35.59 (30.05;42.15)
	2		Headache	38.55 (32.46;45.78)
	2		Pyrexia	56.61 (50.87;63.00)
	1		>1 reported AE	89.12 (86.69;91.63)
Peginterferon alfa-2a+Lamivudine [56]	1	End	HBeAg seroconversion	24.05 (23.07;25.07)
	1	End	HBeAg loss	27.11 (26.01;28.26)
	1	End	HBV DNA loss	68.72 (65.92;71.64)
	1	End	Normalization ALT	46.06 (44.19;48.02)
	1	End	Combined	15.03 (14.62;15.45)
	1	End	Flare	5.99 (5.91;6.07)
	1	End	Mutation	3.00 (2.96;3.05)
	1	Follow	Death	1.00 (0.99;1.01)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1	Follow	HBV DNA loss	14.01 (13.63;14.41)
	1	Follow	Combined	20.91 (20.33;21.49)
	1	Follow	HBeAg seroconversion	27.11 (26.01;28.26)
	1	Follow	HBeAg loss	27.94 (26.80;29.12)
	1	Follow	Normalization ALT	38.86 (37.28;40.51)
	1	Follow	Improved histology	40.85 (39.19;42.59)
	1		≥1 Reported adverse event	89.00 (88.96;89.04)
	1		≥1 Reported serious adverse event	6.00 (5.97;6.03)
	1		Alopecia	29.00 (28.95;29.05)
	1		Arthralgia	9.00 (8.97;9.03)
	1		Cough	7.00 (6.97;7.03)
	1		Decreased appetite	13.00 (12.96;13.04)
	1		Depression	6.00 (5.97;6.03)
	1		Diarrhea	10.00 (9.96;10.04)
	1		Discontinuation due to adverse effects	4.00 (3.98;4.02)
	1		Dizziness	12.00 (11.96;12.04)
	1		Dose modification due to adverse effects	8.00 (7.97;8.03)
	1		Dose modification due to Laboratory abnormality: Alanine aminotransferase elevation, Neutropenia, and thrombocytopenia	38.00 (37.94;38.06)
	1		Dyspepsia	2.00 (1.98;2.02)
	1		Fatigue	37.00 (36.94;37.06)
	1		Gingival bleeding	6.00 (5.97;6.03)
	1		Headache	30.00 (29.95;30.05)
	1		Injection-site reaction	6.00 (5.97;6.03)
	1		Insomnia	8.00 (7.97;8.03)
	1		Myalgia	28.00 (27.95;28.05)
	1		Nausea	10.00 (9.96;10.04)
	1		Pruritus	10.00 (9.96;10.04)
	1		Pyrexia	55.00 (54.94;55.06)
	1		Rash	8.00 (7.97;8.03)
	1		Rigors	10.00 (9.96;10.04)
	1		Sore throat	8.00 (7.97;8.03)
	1		Upper abdominal pain	5.00 (4.97;5.03)
	1		Upper respiratory tract infection	6.00 (5.97;6.03)
Peginterferon alfa-2b [81]	1	End	Mutation	0.32 (0.31;0.33)
	1	End	HBeAg seroconversion	8.71 (1.91;39.80)
	1	End	Failure	7.50 (2.20;25.53)
	1	End	HBsAg loss	5.00 (4.81;5.20)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1	End	Improved histology	20.09 (18.94;21.30)
	1	End	Resistance	14.51 (13.55;15.54)
	1	End	Flare	24.05 (22.67;25.50)
	1	End	HBeAg loss	26.05 (24.56;27.63)
	1	End	Normalization ALT	29.96 (27.71;32.41)
	1	Follow	HBsAg seroconversion	0.44 (0.43;0.45)
	2	Follow	HBeAg seroconversion	14.01 (4.38;44.82)
	2	Follow	HBsAg loss	6.49 (5.55;7.59)
	1	Follow	Improved histology	8.00 (7.70;8.32)
	1	Follow	Combined	16.95 (15.98;17.97)
	2	Follow	HBeAg loss	30.27 (23.96;38.24)
	2	Follow	Normalization ALT	30.88 (25.38;37.56)
	1		Abdominal pain	17.00 (16.94;17.06)
	1		Adverse effects	75.00 (74.92;75.08)
	1		Alopecia	17.00 (16.94;17.06)
	1		Anorexia	14.00 (13.95;14.05)
	1		Arthralgia	14.00 (13.95;14.05)
	1		Depression	19.00 (18.94;19.06)
	1		Diarrhea	10.00 (9.95;10.05)
	1		Discontinuation due to drug-related adverse effects	0.43 (0.42;0.45)
	1		Fatigue	38.00 (37.92;38.08)
	1		Flu-like syndrome	54.00 (53.92;54.08)
	1		Headache	35.00 (34.93;35.07)
	1		Insomnia	7.00 (6.96;7.04)
	1		Local reaction	23.00 (22.93;23.07)
	1		Loss of >10% bodyweight	18.00 (17.94;18.06)
	1		Myalgia	26.00 (25.93;26.07)
	1		Nausea	16.00 (15.94;16.06)
	1		Neutropenia (<1·5*109/L)	19.00 (18.94;19.06)
	1		Pruritus	9.00 (8.96;9.04)
	1		Reduction in dose of Interferon due to adverse events	21.00 (20.94;21.06)
	1		Thrombocytopenia (<75*109/L)	11.00 (10.95;11.05)
Peginterferon alfa-2b + Lamivudine [59,78,117,122]	1	End	Combined	59.74 (52.08;68.53)
	2	End	HBeAg loss	47.53 (30.58;73.87)
	2	End	Failure	12.20 (4.04;36.80)
	2	End	Flare	19.97 (16.41;24.29)
	2	End	HBeAg seroconversion	18.52 (5.02;68.37)
	1	End	HBV DNA loss	9.97 (9.22;10.79)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	2	End	Improved histology	8.00 (3.40;18.87)
	2	End	Mutation	13.45 (6.14;29.45)
	2	End	Normalization ALT	62.18 (58.83;65.72)
	1	End	Relapse	15.47 (6.53;36.64)
	1	End	Resistance	11.81 (8.47;16.49)
	1	End	HBsAg loss	5.99 (5.76;6.23)
	1	Follow	Combined	23.72 (22.26;25.27)
	1	Follow	Death	1.99 (1.92;2.07)
	1	Follow	Decompensation	1.08 (1.06;1.09)
	2	Follow	HBeAg loss	32.46 (30.71;34.31)
	1	Follow	Flare	14.01 (12.71;15.46)
	2	Follow	HBeAg seroconversion	10.67 (10.35;11.00)
	1	Follow	HBV DNA loss	1.16 (1.14;1.18)
	1	Follow	Improved histology	11.02 (10.39;11.69)
	1	Follow	Normalization ALT	29.96 (27.71;32.41)
	1	Follow	Relapse	1.19 (1.17;1.21)
	2	Follow	HBsAg loss	6.49 (6.31;6.67)
	2		Alopecia	33.19 (16.23;67.87)
	2		Arthralgia	17.60 (9.59;32.31)
	2		Headache	39.63 (37.03;42.43)
	1		Abdominal discomfort	44.00 (43.87;44.13)
	1		Abdominal pain	16.00 (15.94;16.06)
	1		Allergic rashes	18.00 (17.90;18.10)
	1		Anorexia	14.00 (13.95;14.05)
	1		Decreased neutrophil count	2.00 (1.96;2.04)
	1		Decreased phosphate level	4.00 (3.95;4.05)
	1		Depression	18.00 (17.94;18.06)
	1		Diarrhea	9.00 (8.96;9.04)
	1		Dizziness	16.00 (15.90;16.10)
	1		Fatigue	36.00 (35.92;36.08)
	1		Fever	72.00 (71.88;72.12)
	1		Flu-like syndrome	63.00 (62.92;63.08)
	1		Increased alkaline phosphatase level	1.00 (0.97;1.03)
	1		Increased ALT level	16.00 (15.90;16.10)
	1		Increased Creatine kinase level	1.00 (0.97;1.03)
	1		Insomnia	13.00 (12.95;13.05)
	1		Local erythematous reaction	24.00 (23.89;24.11)
	1		Local reaction	25.00 (24.93;25.07)
	1		Loss of >10% bodyweight	16.00 (15.94;16.06)
	1		Malaise	44.00 (43.87;44.13)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Myalgia	26.00 (25.88;26.12)
	1		Myalgia	28.00 (27.93;28.07)
	1		Nausea	9.00 (8.96;9.04)
	1		Neutropenia (<1·5*109/L)	22.00 (21.93;22.07)
	1		Pruritus	12.00 (11.95;12.05)
	1		Reduced appetite	24.00 (23.89;24.11)
	1		Reduction in dose of Interferon due to adverse events	24.00 (23.93;24.07)
	1		Thrombocytopenia (<75*109/L)	9.00 (8.96;9.04)
	1		Upper respiratory tract symptoms	74.00 (73.88;74.12)
	1		Vomiting or diarrhea	14.00 (13.91;14.09)
	1		Weight loss (>10%)	14.00 (13.91;14.09)
Telbivudine[44,72]	2	End	Normalization ALT	82.35 (77.60;87.38)
	2	End	Combined	49.71 (30.50;81.01)
	2	End	HBeAg loss	27.44 (19.93;37.79)
	2	End	HBeAg seroconversion	25.95 (19.72;34.14)
	2	End	HBV DNA loss	55.26 (46.49;65.67)
	2	End	Relapse	5.00 (4.80;5.22)
	2	End	Resistance	1.99 (1.94;2.05)
	1		Abdominal pain	4.02 (3.85;4.19)
	1		Allergic rhinitis	1.12 (1.10;1.13)
	1		Arthralgia	4.02 (3.85;4.19)
	1		At least one adverse event	70.42 (66.40;74.68)
	2		Back pain	4.74 (3.28;6.87)
	2		Cough	5.24 (3.63;7.56)
	1		Depression	2.48 (2.16;2.84)
	2		Diarrhea	7.36 (5.82;9.30)
	2		Dizziness	3.37 (2.61;4.36)
	1		Dyspepsia	3.26 (2.54;4.18)
	1		Epigastric discomfort	4.02 (3.85;4.19)
	2		Fatigue	8.10 (6.03;10.90)
	1		Gastritis	7.03 (6.65;7.43)
	2		Headache	8.92 (6.77;11.75)
	1		Hepatic steatosis	4.02 (3.85;4.19)
	1		Hordeolum	4.02 (3.85;4.19)
	1		Increased Creatine phosphokinase level	5.00 (4.87;5.14)
	2		Influenza	17.16 (14.26;20.64)
	1		Malaise	7.03 (6.65;7.43)
	1		Mouth ulceration	1.12 (1.10;1.13)
	1		Myalgia	1.99 (1.94;2.05)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	2		Nasopharyngitis	4.23 (3.16;5.67)
	2		Nausea	5.10 (4.57;5.68)
	2		Pharyngolaryngeal pain	5.79 (3.88;8.64)
	1		Toothache	4.02 (3.85;4.19)
	1		Total adverse effect	75.94 (69.89;82.53)
	2		Upper abdominal pain	7.00 (5.95;8.24)
	2		Upper respiratory tract infection	6.70 (4.06;11.04)
Telbivudine + Lamivudine [72]	1		Back pain	10.00 (9.88;10.12)
	1		Depression	5.00 (4.91;5.09)
	1		Diarrhea	5.00 (4.91;5.09)
	1		Increased Creatine phosphokinase level	5.00 (4.91;5.09)
	1		Upper respiratory tract infection	10.00 (9.88;10.12)
	1	End	Normalization ALT	78.08 (74.29;82.07)
	1	End	Combined	35.49 (18.71;67.30)
	1	End	HBeAg loss	16.95 (15.59;18.42)
	1	End	HBeAg seroconversion	15.03 (14.02;16.11)
	1	End	HBV DNA loss	48.91 (44.39;53.89)
	1	End	Relapse	11.94 (11.14;12.80)
	1		At least one adverse	70.51 (65.96;75.37)
	1		Cough	7.05 (3.59;13.87)
	1		Dizziness	7.05 (3.59;13.87)
	1		Dyspepsia	2.45 (2.33;2.57)
	1		Fatigue	7.05 (3.59;13.87)
	1		Headache	13.71 (7.32;25.66)
	1		Influenza	23.76 (15.14;37.30)
	1		Nasopharyngitis	7.05 (3.59;13.87)
	1		Nausea	4.88 (1.20;19.80)
	1		Pharyngolaryngeal pain	5.98 (0.99;36.31)
	1		Upper abdominal pain	4.88 (1.20;19.80)
Placebo or no treatment [40,42,47,48,50,53,83,86,87,93,94,96,99,100,103,104,108,110,112; 89,105]	11		HBV DNA loss	7.18 (4.44;11.61)
	7		HBsAg loss	1.73 (1.46;2.06)
	2		Mutation	2.26 (1.50;3.39)
	2		Flare	12.85 (6.00;27.49)
	4		Failure	17.60 (11.63;26.64)
	8		HBeAg loss	10.15 (8.61;11.97)
	8		HBeAg seroconversion	7.33 (6.36;8.44)
	4		Relapse	3.32 (1.53;7.17)
	9		Normalization ALT	12.32 (9.05;16.78)
	6		Improved histology	23.18 (18.44;29.12)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	3		Resistance	32.44 (11.19;94.07)
	7		Combined	4.82 (3.24;7.16)
	2		Death	7.91 (4.73;13.21)
	1		HBsAg seroconversion	5.00 (4.63;5.41)
	1		Cirrhosis	9.97 (8.87;11.22)
	1		Flatulence	5.99 (5.83;6.16)
	6		Headache	17.23 (10.96;27.08)
	1		Respiratory infection	29.08 (27.13;31.17)
	1		Abdominal distention	6.22 (3.08;12.59)
	1		Abnormal ALT/AST	15.96 (14.89;17.10)
	1		ALT> 2 than at baseline	5.31 (3.87;7.29)
	1		Anorexia	5.00 (4.87;5.14)
	1		Back pain	7.03 (6.84;7.23)
	1		Chest symptoms	7.03 (6.74;7.33)
	3		Cough	11.45 (6.74;19.44)
	1		Creatinine mg/dL (>2.0–3.0)	0.30 (0.29;0.31)
	2		Depression	3.32 (2.29;4.82)
	6		Diarrhea	7.11 (3.58;14.09)
	4		Dizziness	7.00 (5.33;9.20)
	1		Ear, nose, and throat	29.58 (27.49;31.82)
	2		Fever	1.64 (0.92;2.94)
	1		Hair loss	5.00 (4.87;5.14)
	2		Leucopenia	4.45 (3.59;5.52)
	2		Malaise and fatigue	22.00 (18.42;26.28)
	2		Muscle pain	8.64 (7.94;9.41)
	2		Musculoskeletal pain	4.16 (3.31;5.23)
	2		Nasal signs and symptoms	6.21 (5.17;7.47)
	2		Nausea and vomiting	2.88 (1.66;5.00)
	1		Nausea/vomiting	20.09 (18.74;21.53)
	2		Pain	9.54 (6.75;13.47)
	2		Rash	5.67 (2.88;11.14)
	1		Rheumatism	4.02 (3.85;4.19)
	1		Throat discomfort	8.00 (7.68;8.34)
	1		Viral respiratory infection	0.90 (0.88;0.91)
	1		>1 treatment-related event	12.00 (11.94;12.06)
	1		»1 adverse event	76.71 (71.57;82.21)
	1		Abdominal discomfort	20.31 (17.65;23.37)
	1		Abdominal pain and discomfort	4.00 (3.96;4.04)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Abnormal enzymes (amylase/CPK)	7.03 (6.74;7.33)
	1		Abnormal liver-function	8.00 (7.68;8.34)
	1		ALT »2 times above base-line levels and bilirubin »2 times above baseline levels	0.84 (0.59;1.19)
	1		Collapse after dizziness	0.00 (0.85;0.90)
	1		Constipation	4.00 (3.96;4.04)
	1		Creatinine mg/dL (>3.0–6.0)	0.30 (0.29;0.31)
	1		Creatinine mg/dL (>6.0)-	0.30 (0.29;0.31)
	1		Creatinine mg/dL (1.5–2.0)	0.30 (0.29;0.31)
	1		Decreased WBCs	0.90 (0.88;0.91)
	1		Developing of IFN neutralizing antibodies	0.00 (1.74;1.83)
	1		Discontinuation due to adverse events	1.00 (0.99;1.01)
	1		Discontinuation due to depression	0.00 (1.74;1.83)
	3		Discontinuation due to adverse effects	1.65 (0.83;3.29)
	1		Discontinuation due to psychosis	0.00 (1.74;1.83)
	1		Dose reduced due to an adverse event or abnormal laboratory result	1.00 (0.99;1.01)
	1		Dose reduction due to depression, fatigue, hair loss, and headache	0.00 (0.85;0.90)
	3		Fatigue	4.61 (2.91;7.30)
	1		Feeding problems	4.02 (3.85;4.19)
	1		Gastrointestinal events	6.00 (5.96;6.04)
	1		Glycosuria(+1)	3.00 (2.97;3.03)
	1		Glycosuria(+2)	2.00 (1.98;2.02)
	1		Glycosuria(+3)	3.00 (2.97;3.03)
	1		Glycosuria(+4)	0.30 (0.29;0.31)
	1		Grade III or IV laboratory abnormalities in Alanine aminotransferase	13.00 (12.92;13.08)
	1		Grade III or IV laboratory abnormalities in Albumin	3.00 (2.96;3.04)
	1		Grade III or IV laboratory abnormalities in Amylase	1.00 (0.98;1.02)
	1		Grade III or IV laboratory abnormalities in Creatine kinase	4.00 (3.96;4.04)
	1		Grade III or IV laboratory abnormalities in Lipase	7.00 (6.94;7.06)
	1		Grade III or IV laboratory abnormalities in Platelets	3.00 (2.96;3.04)
	1		Grade IV abnormality in ALT	0.84 (0.59;1.19)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Hair loss/alopecia	4.02 (3.85;4.19)
	1		Hematuria Obstructive or Rx required	0.00 (0.29;0.31)
	1		Hematuria<10 RBCs	7.00 (6.96;7.04)
	1		Hematuria>100 RBCs	13.00 (12.95;13.05)
	1		Hematuria10–100 RBCs	10.00 (9.96;10.04)
	1		Hypophosphatemia mg/dL (<1.0)	0.30 (0.29;0.31)
	1		Hypophosphatemia mg/dL (1.0–1.5)	0.30 (0.29;0.31)
	1		Hypophosphatemia mg/dL (1.5–<2.0)	1.00 (0.99;1.01)
	1		Hypophosphatemia mg/dL (2.0–2.2)	1.00 (0.99;1.01)
	1		Incidence of elevation of serum ALT to >5 times the ULN	55.15 (52.17;58.29)
	1		Infections	0.00 (2.22;2.33)
	1		Jaundice	0.00 (2.22;2.33)
	1		Liver symptoms	4.00 (3.96;4.04)
	1		Malaise/fatigue	32.14 (29.57;34.92)
	1		Marrow suppression	0.00 (2.22;2.33)
	1		Muscular or skeletal pain	4.00 (3.96;4.04)
	1		Nasopharyngitis	1.99 (1.97;2.02)
	2		Nausea	7.64 (2.33;25.09)
	1		Paresthesias	7.00 (6.94;7.06)
	1		Proteinuria mg/dL(Nephrotic syndrome)	0.00 (0.29;0.31)
	1		Proteinuria mg/dL(<100)	10.00 (9.96;10.04)
	1		Proteinuria mg/dL(>1000)	0.30 (0.29;0.31)
	1		Proteinuria mg/dL100–1000)	7.00 (6.96;7.04)
	1		Pruritis	4.00 (3.96;4.04)
	1		Sleep disorder	4.00 (3.96;4.04)
	1		Sleep disturbance	4.00 (3.96;4.04)
	1		Temperature regulation disturbance	6.92 (5.88;8.16)
	1		Throat and tonsil disorder	16.95 (15.83;18.14)
	1		Upper respiratory tract infection	8.00 (7.79;8.23)
	1		Upper respiratory viral infection	4.00 (3.96;4.04)
	1		Viral respiratory infection	27.52 (18.01;42.07)
HBeAg-positive patients				
Adefovir dipivoxil [40,42,44,99,100]	4	End	HBV DNA loss	24.83 (15.74;39.18)
	4	End	Normalization ALT	59.46 (52.08;67.89)
	2	End	Flare	2.72 (0.96;7.71)
	4	End	HBeAg loss	16.53 (12.33;22.16)
	4	End	HBeAg seroconversion	12.35 (10.03;15.20)
	2	End	Relapse	8.97 (5.76;13.98)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1	End	HBsAg loss	2.64 (2.49;2.80)
	1	End	Improved histology	51.72 (45.88;58.30)
	2	End	Resistance	21.64 (16.35;28.64)
	1	End	Failure	10.07 (8.85;11.47)
	1	End	Mutation	27.94 (26.86;29.06)
	1	Followup off treatment	Normalization ALT	38.86 (36.64;41.22)
	1		Insomnia	20.91 (18.71;23.36)
	1		Discontinuation	7.50 (6.97;8.07)
	1		Discontinuation due to adverse effects	1.00 (0.99;1.01)
	1		Dose reduced due to an adverse event/ abnormal lab result	8.49 (3.83;18.83)
	2		Fatigue	3.31 (2.12;5.15)
	1		Flu-like syndrome	16.95 (15.83;18.14)
	1		Hematuria10–100 RBCs	13.65 (10.84;17.19)
	2		Pharyngitis	30.21 (25.01;36.48)
	1		Proteinuria mg/dL100–1000	8.80 (5.82;13.29)
	1		Rash	20.91 (18.71;23.36)
	1		Sinusitis	15.96 (14.28;17.83)
	1		Any adverse event	95.00 (94.94;95.06)
	2		Asthenia	29.84 (26.48;33.62)
	1		Fever	15.96 (14.28;17.83)
	3		Headache	17.27 (12.27;24.29)
	1		Hematuria>100 RBCs	8.46 (5.72;12.50)
	2		Nasopharyngitis	5.75 (4.98;6.63)
	1		Reactivation of hepatitis	1.00 (0.99;1.01)
	1		Serum Glucose Grade 3 abnormalities	11.02 (10.00;12.15)
	1		Total adverse effect	63.75 (59.53;68.28)
	2		Upper respiratory tract infection	9.71 (8.67;10.88)
	1		Incidence of elevation of serum ALT to >5 times the ULN	28.19 (20.26;39.23)
	1		Increases from baseline of 0.5 mg per deciliter (44 µmol per liter) or greater in the serum creatinine level	8.00 (7.70;8.32)
	1		Hypophosphatemia mg/dL (<1.0)	1.00 (0.99;1.01)
	1		Hypophosphatemia mg/dL (1.0–1.5)	1.73 (0.93;3.23)
	1		Bacterial infection	2.64 (2.53;2.75)
	1		ALT Grade 4 >10 times the ULN)	2.64 (2.53;2.75)
	1		Grade 4 (>10 times the ULN)	2.64 (2.53;2.75)
	1		Amylase Grade3 (>2–5 times the ULN)	2.64 (2.53;2.75)
	1		Grade4 (□5 times the ULN)	2.64 (2.53;2.75)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Grade4 (>30 mg/dL; <500 mg/dL)	2.63 (2.57;2.70)
	1		Grade4 (4+)	2.64 (2.53;2.75)
	1		Cough	3.79 (2.02;7.12)
	2		Dizziness	4.73 (2.29;9.80)
	1		Malaise	2.12 (1.30;3.45)
	1		Epigastric discomfort	1.49 (1.13;1.97)
	1		Gastritis	1.10 (1.08;1.12)
	1		Myalgia	2.12 (1.30;3.45)
	1		Hordeolum	1.10 (1.08;1.12)
	3		Abdominal pain	7.08 (3.35;14.95)
	1		Hepatic steatosis	1.47 (1.09;1.97)
	1		Toothache	1.47 (1.09;1.97)
	1		Allergic rhinitis	2.33 (1.30;4.18)
	1		Creatinine mg/dL (1.5–2.0)	2.51 (1.11;5.68)
	1		Glycosuria (+1)	1.41 (0.96;2.09)
	1		Glycosuria (+2)	1.41 (0.96;2.09)
	1		Glycosuria (+3)	1.00 (0.99;1.01)
	1		Discontinuation due to adverse events	2.45 (1.94;3.09)
	3		Diarrhea	7.24 (3.97;13.22)
	3		Nausea	7.22 (4.15;12.57)
	1		Pharyngolaryngeal pain	3.74 (2.04;6.87)
	1		Mouth ulceration	3.16 (1.93;5.17)
	1		Anorexia	6.33 (4.08;9.81)
	1		Hypophosphatemia mg/dL (2.0–2.2)	5.55 (4.16;7.40)
	2		Arthralgia	6.00 (4.69;7.67)
	1		Gastroenteritis	5.00 (4.67;5.36)
	1		Infection	5.00 (4.67;5.36)
	1		Rhinitis	5.00 (4.67;5.36)
	1		AST Grade3 (>5–10 times the ULN)	5.00 (4.67;5.36)
	1		Upper abdominal pain	7.42 (4.80;11.46)
	3		Back pain	7.96 (6.78;9.36)
	2		Increased cough	8.97 (6.78;11.87)
	1		Influenza	7.97 (6.91;9.18)
	2		Pain	9.86 (8.50;11.44)
	1		Flatulence	8.94 (7.89;10.12)
	1		Severe (grade 3 or 4) clinical adverse events	9.49 (8.97;10.04)
	1		Dyspepsia	9.97 (8.91;11.17)
	1		Urine Glucose Grade3	11.02 (10.00;12.15)
	1		Hematuria>100 RBCs	12.37 (11.84;12.91)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Proteinuria mg/dL(<100)	17.55 (13.60;22.64)
	1		ALT Grade 3 (>5–10 times the ULN)	36.97 (32.18;42.46)
Adefovir dipivoxil + Lamivudine [43]	1	End	HBV DNA loss	35.16 (30.61;40.39)
	1	End	HBeAg loss	15.03 (13.64;16.56)
	1	End	HBeAg seroconversion	5.00 (4.73;5.29)
	1	End	Normalization ALT	49.90 (43.44;57.32)
	1	End	HBsAg loss	5.00 (4.73;5.29)
	1		Any adverse event	90.02 (82.84;97.82)
	1		Asthenia	49.90 (43.44;57.32)
	1		Headache	29.96 (26.45;33.95)
	1		Pharyngitis	5.00 (4.73;5.29)
	1		Abdominal pain	29.96 (26.45;33.95)
	1		Back pain	15.03 (13.64;16.56)
	1		Nausea	20.09 (17.98;22.44)
	1		Pain	20.09 (17.98;22.44)
	1		Infection	15.03 (13.64;16.56)
	1		ALT Grade 3 (>5–10 times ULN)	2.51 (2.41;2.62)
	1		Insomnia	2.51 (2.41;2.62)
	1		Rash	2.51 (2.41;2.62)
	1		Fever	2.51 (2.41;2.62)
	1		Increased cough	2.51 (2.41;2.62)
	1		Gastroenteritis	2.51 (2.41;2.62)
	1		Grade4 (>10 times the ULN)	2.51 (2.41;2.62)
	1		Grade4 (□5 times the ULN)	2.51 (2.41;2.62)
	1		Grade4 (>30 mg/dL; <500 mg/dL)	2.51 (2.41;2.62)
	1		Grade4 (4+)	2.51 (2.41;2.62)
	1		Sinusitis	5.00 (4.73;5.29)
	1		Arthralgia	5.00 (4.73;5.29)
	1		ALT Grade 4 >10 times ULN	5.00 (4.73;5.29)
	1		Serum glucose Grade3 abnormalities	5.00 (4.63;5.41)
	1		Urine Glucose Grade3	5.00 (4.73;5.29)
	1		Diarrhea	9.97 (9.18;10.84)
	1		Rhinitis	9.97 (9.18;10.84)
	1		Amylase Grade3 (>2–5 ULN)	9.97 (9.18;10.84)
	1		Bacterial infection	15.03 (13.64;16.56)
Entecavir [73,75,101]	1	End	Improved histology	43.51 (31.63;59.85)
	2	End	Resistance	19.76 (7.85;49.71)
	3	End	Failure	5.42 (1.89;15.52)
	3	End	Combined	42.68 (26.13;69.70)
	3	End	Normalization ALT	73.28 (62.93;85.34)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	2	End	HBeAg loss	14.81 (6.83;32.11)
	3	End	HBeAg seroconversion	16.98 (8.79;32.81)
	3	End	Flare	2.08 (1.02;4.27)
	3	End	Death	1.00 (0.98;1.02)
	2	End	HBV DNA loss	73.20 (65.17;82.23)
	2	End	HBsAg loss	3.74 (1.09;12.87)
	1	End	HBsAg seroconversion	1.99 (1.96;2.03)
	1	End	Relapse	4.02 (3.94;4.09)
	1	End	Decompensation	0.14 (0.14;0.15)
	2	Followup off treatment	Combined	9.84 (4.06;23.85)
	1	Followup off treatment	Flare	1.00 (0.98;1.02)
	1	Followup off treatment	Death	1.00 (0.98;1.02)
	1	Followup off treatment	HBV DNA loss	7.03 (6.89;7.17)
	1	Followup off treatment	Relapse	1.99 (1.96;2.03)
	1	Followup off treatment	Decompensation	0.14 (0.14;0.15)
	2	All	Any adverse event	85.36 (82.63;88.19)
	2	All	Serious adverse events	6.84 (3.97;11.80)
	1	All	Discontinuations because of adverse events	1.00 (0.98;1.02)
	1	All	Discontinuation due to adverse effects	0.14 (0.14;0.15)
	1	All	ALT >2× baseline and >5× ULN	1.00 (0.99;1.01)
	1	All	ALT > 2× reference value and >5× ULN	10.00 (9.97;10.03)
	1	All	Any adverse effect	77.20 (77.17;77.23)*†
Interferon Alfa-2b [82,83,85-87,89,90,94,96,104,105]	3	End	Normalization ALT	46.38 (27.43;78.42)
	5	End	HBV DNA loss	46.97 (34.69;63.61)
	4	End	HBeAg loss	50.78 (33.81;76.25)
	3	End	HBeAg seroconversion	40.09 (20.44;78.63)
	2	End	HBsAg loss	6.14 (3.47;10.88)
	1	End	Combined	24.99 (17.81;35.07)
	1	End	Resistance	7.03 (6.50;7.60)
	1	End	Improved histology	25.03 (20.57;30.45)
	2	End	Death	6.83 (3.05;15.27)
	1	End	Flare	5.99 (5.43;6.61)
	6	Followup off treatment	Normalization ALT	36.49 (26.10;51.03)
	11	Followup off treatment	HBV DNA loss	26.97 (18.34;39.67)
	10	Followup off treatment	HBeAg loss	42.96 (32.25;57.23)
	5	Followup off treatment	HBeAg seroconversion	31.86 (19.64;51.66)
	8	Followup off treatment	HBsAg loss	7.41 (4.20;13.07)
	8	Followup off treatment	Combined	13.49 (8.41;21.64)
	3	Followup off treatment	Resistance	7.64 (4.46;13.08)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	3	Followup off treatment	Relapse	2.24 (1.72;2.91)
	2	Followup off treatment	Death	4.16 (2.27;7.62)
	2	Followup off treatment	HBsAg seroconversion	6.32 (0.66;60.79)
	2	Followup off treatment	Improved histology	26.91 (15.24;47.50)
	1	Followup off treatment	Cirrhosis	8.92 (2.86;27.81)
	1	Followup off treatment	Failure	25.03 (22.69;27.61)
	1	Followup off treatment	Mutation	0.73 (0.71;0.74)
	1		Abdominal discomfort and pain	33.00 (32.89;33.11)
	1		Adverse effects	75.00 (74.92;75.08)
	1		Anorexia	47.00 (46.89;47.11)
	1		Arthralgia	33.00 (32.89;33.11)
	1		Arthralgia	8.00 (7.90;8.10)
	1		Collapse after dizziness	2.00 (1.97;2.03)
	1		Depression	4.00 (3.93;4.07)
	1		Diarrhea	23.00 (22.90;23.10)
	1		Discontinuation due to depression	3.00 (2.94;3.06)
	1		Dizziness	27.00 (26.90;27.10)
	1		Dose reduction due to depression, fatigue, hair loss, headache	11.00 (10.92;11.08)
	1		Fatigue	48.00 (47.82;48.18)
	1		Fever/chills	61.00 (60.89;61.11)
	1		Hair loss and alopecia	30.00 (29.90;30.10)
	1		Headache	67.00 (66.89;67.11)
	1		Infections	8.00 (7.90;8.10)
	1		Jaundice	4.00 (3.93;4.07)
	1		Malaise and fatigue	100.00 (100.00;100.00)
	1		Marrow suppression	8.00 (7.90;8.10)
	1		mouth dryness	19.00 (18.83;19.17)
	1		Muscle pain	57.00 (56.89;57.11)
	1		Nausea	12.00 (11.88;12.12)
	1		Nausea and vomiting	49.00 (48.89;49.11)
	1		Discontinuation due to drug-related adverse effects	3.00 (2.97;3.03)
	1		Discontinuation due to psychosis	3.00 (2.94;3.06)
	1		Reduction in dose because of severe side effects	8.00 (7.90;8.10)
	1		Viral respiratory infections	53.00 (52.89;53.11)
	5		Discontinuation due to adverse effects	2.91 (1.41;5.99)
	1		Discontinuation due to neuropsychiatric disorder	3.63 (1.93;6.80)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	2		Reduction in dose due to adverse effects	20.70 (18.64;22.98)
Interferon Alfa-2b + Corticosteroid [90] {Perez, 1990 #562,91-94,96,103	2	End	Combined	39.50 (33.32;46.83)
	1	End	Death	2.77 (2.56;3.00)
	3	End	HBsAg loss	9.22 (6.42;13.24)
	2	End	HBV DNA loss	37.38 (23.78;58.77)
	1	End	Resistance	47.85 (42.56;53.80)
	2	End	HBeAg loss	42.02 (19.39;91.04)
	2	Followup off treatment	Combined	7.03 (2.37;20.89)
	1	Followup off treatment	Death	5.00 (4.45;5.63)
	2	Followup off treatment	Relapse	3.33 (2.11;5.26)
	3	Followup off treatment	HBsAg loss	17.25 (5.51;54.07)
	6	Followup off treatment	HBV DNA loss	24.44 (16.31;36.63)
	2	Followup off treatment	Resistance	18.36 (9.25;36.45)
	1	Followup off treatment	Cirrhosis	9.97 (9.04;11.00)
	3	Followup off treatment	Normalization ALT	35.77 (20.48;62.47)
	3	Followup off treatment	HBeAg loss	45.64 (33.35;62.46)
	2	Followup off treatment	HBeAg seroconversion	51.10 (44.58;58.58)
	1		Reduction in dose because of severe side effects	8.00 (7.90;8.10)
	1		Leucopenia	20.00 (19.79;20.21)
	1		Discontinuation due to adverse effects	2.94 (2.87;3.01)
	1		Reduction in dose due to adverse effects	12.00 (11.86;12.14)
Interferon Alfa-2b + Lamivudine [47,65-69,79,80,104]	3	End	Mutation	3.30 (1.55;7.06)
	1	End	HBsAg loss	5.99 (5.75;6.24)
	4	End	HBeAg seroconversion	31.30 (13.42;73.00)
	3	End	Failure	13.17 (8.74;19.85)
	4	End	HBeAg loss	38.85 (21.64;69.72)
	4	End	Normalization ALT	44.07 (22.58;86.02)
	6	End	HBV DNA loss	59.03 (41.91;83.15)
	5	End	Improved histology	36.77 (31.13;43.43)
	1	End	Flare	1.52 (1.46;1.58)
	1	End	Relapse	4.02 (3.86;4.18)
	2	End	Combined	55.02 (31.63;95.72)
	1	End	Resistance	57.02 (50.92;63.85)
	1	Followup off treatment	Mutation	0.66 (0.66;0.67)
	2	Followup off treatment	HBsAg loss	2.54 (0.52;12.36)
	6	Followup off treatment	HBeAg seroconversion	35.15 (20.28;60.93)
	2	Followup off treatment	Failure	21.96 (19.92;24.22)
	5	Followup off treatment	HBeAg loss	39.96 (29.41;54.30)
	6	Followup off treatment	Normalization ALT	61.61 (50.09;75.77)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	7	Followup off treatment	HBV DNA loss	49.14 (28.67;84.21)
	1	Followup off treatment	Improved histology	27.94 (26.07;29.94)
	1	Followup off treatment	Flare	5.00 (4.72;5.31)
	2	Followup off treatment	Relapse	6.68 (3.57;12.50)
	2	Followup off treatment	Combined	32.39 (27.06;38.76)
	1		ALT> 2 than at baseline	1.26 (0.81;1.96)
	4		Discontinuation due AE	4.77 (3.34;6.81)
	1		Arthralgia	11.94 (11.30;12.62)
	1		Dizziness	11.94 (11.30;12.62)
	1		Abnormal enzymes	12.94 (12.24;13.67)
	1		Abdominal discomfort	14.01 (13.26;14.81)
	1		Abnormal ALT/AST	15.96 (15.10;16.87)
	1		Pain	15.96 (15.10;16.87)
	1		Musculoskeletal pain	15.96 (15.10;16.87)
	4		Diarrhea	14.08 (7.59;26.10)
	1		Decreased WBCs	25.03 (23.35;26.82)
	1		Rheumatism	25.03 (23.35;26.82)
	2		Depression	11.35 (1.52;84.71)
	1		Feeding problems	29.96 (27.57;32.56)
	2		Viral respiratory in	38.48 (34.75;42.60)
	1		Anorexia	38.86 (36.26;41.65)
	1		Hair loss and alopecia	38.86 (36.26;41.65)
	1		Nausea and vomiting	42.95 (39.52;46.67)
	2		Muscle pain	46.53 (43.87;49.34)
	1		Nausea/vomiting	59.15 (54.43;64.27)
	1		Fever/chills	60.95 (56.87;65.32)
	4		Headache	44.65 (43.37;45.97)
	1		Malaise and fatigue	87.36 (82.65;92.34)
	1		Malaise/fatigue	94.63 (90.78;98.65)
	2		Fever	94.63 (90.78;98.65)
	3		Albumin: 2.0–2.4 g/d	3.00 (2.89;3.12)
	2		Influenza-like symptoms	64.18 (58.99;69.82)
Interferon Alfa-2b + Placebo [67,93]	1	End	HBeAg loss	83.10 (76.83;89.87)
	1	End	HBV DNA loss	83.10 (76.83;89.87)
	1	End	Normalization ALT	83.93 (77.60;90.78)
	1	End	HBeAg seroconversion	92.76 (87.46;98.38)
	1	Followup off treatment	Mutation	0.73 (0.71;0.74)
	1	Followup off treatment	Failure	25.03 (22.69;27.61)
	1	Followup off treatment	Improved histology	35.87 (31.89;40.35)
	1	Followup off treatment	HBeAg loss	75.19 (65.55;86.25)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1	Followup off treatment	HBV DNA loss	75.19 (66.85;84.57)
	1	Followup off treatment	Normalization ALT	75.94 (68.86;83.76)
	1	Followup off treatment	HBeAg seroconversion	92.76 (88.98;96.70)
	1	Followup off treatment	Combined	8.67 (2.95;25.46)
	1		Discontinuation due to adverse effects	0.71 (0.70;0.73)
	1		Hepatitis flares (ALT levels >500 IU/l and >2' baseline)	9.00 (8.93;9.07)
	1		Hepatitis flares (ALT levels >500 IU/l and >2' baseline)	11.00 (10.93;11.07)
	1		Diarrhea	23.00 (22.90;23.10)
	1		Dizziness	27.00 (26.90;27.10)
	1		Hair loss and alopecia	30.00 (29.90;30.10)
	1		Abdominal discomfort and pain	33.00 (32.89;33.11)
	1		Arthralgia	33.00 (32.89;33.11)
	1		Anorexia	47.00 (46.89;47.11)
	1		Nausea and vomiting	49.00 (48.89;49.11)
	1		Viral respiratory infections	53.00 (52.89;53.11)
	1		Muscle pain	57.00 (56.89;57.11)
	1		Fever/chills	61.00 (60.89;61.11)
	1		Headache	67.00 (66.89;67.11)
	1		Malaise and fatigue	100.00 (100.00;100.00)
Lamivudine[43,47,48,50,53,55,72,104,107-112]	12	End	HBeAg loss	19.08 (11.82;30.78)
	15	End	HBeAg seroconversion	15.42 (9.99;23.80)
	11	End	Improved histology	30.76 (22.17;42.67)
	11	End	Failure	10.04 (7.65;13.18)
	17	End	HBV DNA loss	43.86 (32.37;59.44)
	15	End	Normalization ALT	38.41 (25.65;57.51)
	4	End	Resistance	38.06 (27.41;52.85)
	4	End	HBsAg loss	1.99 (1.29;3.07)
	5	End	Flare	7.74 (5.84;10.27)
	3	End	Death	1.00 (0.99;1.01)
	8	End	Combined	27.95 (19.58;39.89)
	5	End	Relapse	12.62 (5.93;26.86)
	1	End	Decompensation	0.14 (0.14;0.14)
	1	End	HBsAg seroconversion	5.00 (4.81;5.20)
	6	End	Mutation	13.45 (6.59;27.45)
	7	Followup off treatment	HBeAg loss	32.22 (26.08;39.81)
	7	Followup off treatment	HBeAg seroconversion	24.49 (14.88;40.31)
	2	Followup off treatment	Improved histology	34.12 (32.73;35.57)
	2	Followup off treatment	Failure	11.94 (11.04;12.92)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	5	Followup off treatment	HBV DNA loss	9.30 (4.83;17.91)
	5	Followup off treatment	Normalization ALT	39.26 (23.18;66.48)
	3	Followup off treatment	HBsAg loss	1.56 (0.80;3.05)
	3	Followup off treatment	Flare	4.82 (1.96;11.90)
	3	Followup off treatment	Death	1.00 (0.99;1.01)
	6	Followup off treatment	Combined	9.89 (4.83;20.26)
	4	Followup off treatment	Relapse	14.06 (4.72;41.86)
	2	Followup off treatment	Decompensation	2.00 (1.15;3.48)
	1	Followup off treatment	Mutation	23.00 (21.51;24.59)
	3		>1 Reported adverse	47.41 (31.02;72.47)
	1		>1 Reported serious AE	1.99 (1.97;2.02)
	4		Abdominal discomfort	8.02 (4.81;13.38)
	1		Abdominal discomfort or pain	15.26 (12.66;18.39)
	1		Abdominal distention	8.00 (7.82;8.20)
	1		Abdominal pain	26.05 (23.00;29.51)
	1		Abnormal ALT/AST	17.99 (17.26;18.76)
	1		Abnormal enzymes (amylase/CPK)	15.96 (15.31;16.64)
	2		Abnormal liver function tests	7.04 (4.30;11.53)
	1		Acne and folliculitis	3.66 (2.79;4.81)
	1		Albumin: 2.0–2.4 g/d	3.00 (2.89;3.12)
	1		Allergic rashes	1.99 (1.92;2.07)
	2		Alopecia	2.51 (1.98;3.19)
	1		ALT > 2× reference value and >5× ULN	5.00 (4.91;5.10)
	1		ALT >2× baseline and >5× ULN	16.95 (16.29;17.62)
	1		ALT »2 times above base-line levels	26.05 (24.09;28.17)
	2		ALT> 2 than at baseline and >500U/l	3.02 (1.57;5.80)
	1		ALT »3 times above base-line levels	15.17 (6.66;34.54)
	1		ALT Grade 3 (>5–10 times the ULN)	2.64 (2.53;2.75)
	1		ALT Grade 4 >10 times the ULN)	15.96 (14.28;17.83)
	1		Amylase >2X upper limit of normal	3.66 (2.79;4.81)
	1		Amylase Grade3 (>2–5 times the ULN)	15.96 (14.28;17.83)
	1		Amylase: value 3.1 to ten times the baseline value and >10 times the baseline value	1.00 (0.98;1.02)
	1		Anorexia	5.00 (4.87;5.14)
	1		Any adverse effect	66.11 (41.30;105.81)
	3		Any adverse event	36.11 (24.98;52.19)
	4		Arthralgia	5.74 (4.53;7.27)
	1		AST Grade3 (>5–10 times the ULN)	5.00 (4.67;5.36)
	1		Asthenia	32.14 (27.98;36.91)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		At least one adverse event	5.00 (4.93;5.07)
	1		At least one adverse effect	68.03 (61.68;75.04)
	2		Back pain	4.77 (3.18;7.15)
	1		Bacterial infection	2.64 (2.53;2.75)
	1		Chest symptoms	2.45 (1.94;3.09)
	2		Constipation	3.83 (2.91;5.05)
	5		Cough	14.63 (10.43;20.53)
	1		CPK >5X upper limit	4.74 (3.21;7.01)
	1		Creatine kinase: value seven to 9.9 times the baseline value and at least ten times the baseline value	7.03 (6.63;7.45)
	1		Decreased appetite	1.99 (1.97;2.02)
	1		Decreased neutrophil count	1.00 (0.98;1.02)
	1		Decreased phosphate level	1.99 (1.92;2.07)
	1		Decreased WBCs	1.00 (0.99;1.01)
	4		Depression	4.02 (2.47;6.53)
	12		Diarrhea	9.44 (7.31;12.18)
	7		Discontinuation due to adverse effect	3.76 (2.61;5.43)
	8		Dizziness	5.16 (4.55;5.87)
	3		Dyspepsia	6.26 (4.98;7.86)
	1		Ear, nose, and throat infection	21.33 (19.20;23.69)
	1		Dose modification due to adverse effects	0.18 (0.18;0.19)
	1		Dose modification due to laboratory abnormality: Alanine aminotransferase elevation, neutropenia, and thrombocytopenia	0.18 (0.18;0.19)
	1		Eczema	3.66 (2.79;4.81)
	1		Events of the hepatobiliary tract and pancreas	4.60 (2.00;10.57)
	4		Fatigue	9.03 (6.36;12.82)
	1		Feeding problems	1.99 (1.97;2.02)
	4		Fever	5.89 (5.16;6.71)
	1		Fever/chills	7.03 (6.74;7.33)
	1		Gastroenteritis	15.96 (14.28;17.83)
	1		Gastrointestinal events	9.58 (7.78;11.81)
	1		Grade III abnormality in ALT	14.14 (7.12;28.07)
	1		Grade III or IV lab abnormalities in alanine aminotransferase	9.97 (9.41;10.58)
	1		Grade III or IV laboratory abnormalities in Albumin	0.70 (0.69;0.72)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Grade III or IV laboratory abnormalities in amylase	0.70 (0.69;0.72)
	1		Grade III or IV laboratory abnormalities in creatine kinase	9.00 (8.94;9.06)
	1		Grade III or IV laboratory abnormalities in lipase	9.00 (8.94;9.06)
	1		Grade III or IV laboratory abnormalities in platelets	0.70 (0.69;0.72)
	1		Grade IV abnormality in ALT	1.46 (0.35;6.03)
	1		Grade 4 (>10 times the ULN)	11.02 (10.00;12.15)
	1		Grade 4 (>30 mg/dL; <500 mg/dL)	2.64 (2.53;2.75)
	1		Grade 4 (4+)	2.64 (2.53;2.75)
	1		Grade 4 (>5 times the ULN)	2.64 (2.53;2.75)
	1		Hair loss	1.99 (1.97;2.02)
	1		Hair loss and alopecia	9.97 (9.57;10.40)
	1		Hair loss or alopecia	1.99 (1.97;2.02)
	13		Headache	11.93 (9.48;15.01)
	1		Hypoglycemia	3.65 (3.06;4.36)
	1		Increased alkaline phosphatase level	2.00 (1.96;2.04)
	1		Increased ALT level	24.00 (23.89;24.11)
	1		Increased cough	15.96 (14.28;17.83)
	2		Increased Creatine phosphokinase level	4.16 (2.49;6.94)
	1		Infection	5.00 (4.67;5.36)
	1		Influenza	20.91 (19.33;22.61)
	3		Influenza-like symptoms	17.27 (14.63;20.40)
	2		Insomnia	6.46 (5.30;7.87)
	1		Leucopenia	5.00 (4.98;5.02)
	1		Lipase: value 2.6-5 times ULNand >5 times the upper limit of normal	3.00 (2.96;3.04)
	1		Liver symptoms	5.00 (4.98;5.02)
	1		Local erythematous reaction	1.00 (0.97;1.03)
	1		Malaise	14.00 (13.91;14.09)
	3		Malaise and fatigue	17.98 (14.62;22.12)
	4		Malaise or fatigue	18.47 (12.74;26.78)
	6		Muscle pain	4.79 (2.87;8.00)
	3		Musculoskeletal pain	4.77 (2.43;9.36)
	2		Nasal signs and symptoms	8.93 (7.83;10.18)
	1		Nasopharyngitis	5.00 (4.76;5.25)
	3		Nausea	3.96 (3.07;5.12)
	4		Nausea and vomiting	8.13 (6.08;10.86)

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Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	5		Nausea or vomiting	8.77 (5.52;13.94)
	1		Neurological events	6.94 (6.04;7.98)
	2		Pain	4.49 (2.69;7.51)
	1		Paresthesias	3.00 (2.89;3.12)
	1		Pharyngitis	32.14 (27.98;36.91)
	1		Pharyngolaryngeal pain	15.96 (14.76;17.26)
	1		Pigmentary skin disorders	3.66 (2.79;4.81)
	1		Platelets: value of 20 000–49 000/mm3 and less than 20 000/mm3	3.00 (2.96;3.04)
	1		Pruritis	5.00 (4.91;5.10)
	1		Pyrexia	4.02 (3.96;4.07)
	4		Rash	7.45 (6.16;9.01)
	1		Reduced appetite	1.00 (0.98;1.02)
	1		Respiratory infection	35.16 (33.81;36.57)
	1		Rheumatism	5.00 (4.87;5.14)
	1		Rhinitis	26.05 (23.00;29.51)
	1		Severe Myalgia	1.19 (1.14;1.23)
	1		Serum glucose Grade3 (30–39 mg/dL; 251–500 mg/dL)	15.96 (14.28;17.83)
	1		Sinusitis	26.05 (23.00;29.51)
	2		Skin rash	4.84 (3.37;6.97)
	1		Sleep disorder	7.03 (6.63;7.45)
	1		Sleep disturbance	5.00 (4.91;5.10)
	1		Sore throat	7.03 (6.84;7.23)
	1		Temperature regulation disturbance	8.94 (8.11;9.84)
	1		Throat and tonsil discomfort/pain	22.53 (21.82;23.27)
	1		Throat discomfort or pain	14.37 (12.76;16.18)
	2		Upper abdominal pain	5.63 (4.89;6.49)
	1		Upper respiratory tract infection	6.53 (4.72;9.03)
	1		Upper respiratory tract symptoms	38.00 (37.87;38.13)
	1		Upper respiratory viral infection	5.00 (4.98;5.02)
	1		Urine Glucose Grade3 (3+)	21.00 (20.83;21.17)
	1		Vertigo	3.66 (2.79;4.81)
	1		Viral respiratory infection	27.70 (25.30;30.32)
	1		Viral respiratory infections (multiple)	9.48 (3.53;25.46)
	1		Vomiting or diarrhea	6.00 (5.94;6.06)
	1		Weight loss (>10%)	2.00 (1.96;2.04)
	1		Withdrawal due to side effects	1.35 (1.32;1.39)
Peginterferon alfa-2a [56,116]	1	End	HBeAg loss	29.96 (28.74;31.24)
	1	End	HBeAg seroconversion	27.11 (26.01;28.26)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1	End	Normalization ALT	38.86 (37.28;40.51)
	1	End	Combined	9.97 (9.70;10.26)
	1	End	HBV DNA loss	25.03 (24.01;26.09)
	1	End	Flare	5.00 (4.93;5.07)
	1	End	Mutation	0.18 (0.18;0.19)
	2	Follow	HBeAg loss	33.60 (31.77;35.53)
	2	Follow	HBeAg seroconversion	31.98 (29.91;34.20)
	2	Follow	Normalization ALT	37.26 (34.12;40.70)
	2	Follow	Combined	23.88 (21.65;26.34)
	1	Follow	HBV DNA loss	14.01 (13.63;14.41)
	1	Follow	Improved histology	38.09 (36.54;39.71)
	1	Follow	Death	0.18 (0.18;0.19)
	1		Discontinuation due to AE	3.00 (2.96;3.05)
	1		>1 Reported serious AE	4.02 (3.96;4.07)
	2		Cough	8.04 (6.56;9.84)
	1		Dyspepsia	5.00 (4.93;5.07)
	1		Depression	5.00 (4.93;5.07)
	1		Sore throat	5.99 (5.91;6.07)
	1		Gingival bleeding	5.99 (5.91;6.07)
	1		Dose modification due to adverse effects	7.03 (6.84;7.23)
			Dose modification due to laboratory abnormality: Alanine aminotransferase elevation, Neutropenia, and thrombocytopenia	36.97 (35.46;38.54)
	2		Insomnia	12.39 (9.30;16.52)
	1		Rigors	7.03 (6.84;7.23)
	1		Upper abdominal pain	7.03 (6.84;7.23)
	1		Upper respiratory tract infection	13.35 (9.25;19.26)
	1		Anorexia	13.96 (9.68;20.11)
	2		Diarrhea	12.15 (9.75;15.15)
	2		Dizziness	14.19 (11.26;17.89)
	2		Nausea	12.45 (10.30;15.05)
	1		Injection-site reaction	9.03 (8.78;9.28)
	1		Arthralgia	9.03 (8.78;9.28)
	1		Rash	9.97 (9.70;10.26)
	1		Pruritus	9.97 (9.70;10.26)
	1		Decreased appetite	15.03 (14.62;15.45)
	2		Alopecia	26.31 (21.71;31.89)
	2		Fatigue	28.96 (24.23;34.61)
	2		Myalgia	35.59 (30.05;42.15)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	2		Headache	38.55 (32.46;45.78)
	2		Pyrexia	56.61 (50.87;63.00)
	1		>1 reported AE	89.12 (86.69;91.63)
Peginterferon alfa-2a+Lamivudine [56]	1	End	HBeAg seroconversion	24.05 (23.07;25.07)
	1	End	HBeAg loss	27.11 (26.01;28.26)
	1	End	HBV DNA loss	68.72 (65.92;71.64)
	1	End	Normalization ALT	46.06 (44.19;48.02)
	1	End	Combined	15.03 (14.62;15.45)
	1	End	Flare	5.99 (5.91;6.07)
	1	End	Mutation	3.00 (2.96;3.05)
	1	Follow	Death	1.00 (0.99;1.01)
	1	Follow	HBV DNA loss	14.01 (13.63;14.41)
	1	Follow	Combined	20.91 (20.33;21.49)
	1	Follow	HBeAg seroconversion	27.11 (26.01;28.26)
	1	Follow	HBeAg loss	27.94 (26.80;29.12)
	1	Follow	Normalization ALT	38.86 (37.28;40.51)
	1	Follow	Improved histology	40.85 (39.19;42.59)
	1		≥1 Reported adverse event	89.00 (88.96;89.04)
	1		≥1 Reported serious adverse event	6.00 (5.97;6.03)
	1		Alopecia	29.00 (28.95;29.05)
	1		Arthralgia	9.00 (8.97;9.03)
	1		Cough	7.00 (6.97;7.03)
	1		Decreased appetite	13.00 (12.96;13.04)
	1		Depression	6.00 (5.97;6.03)
	1		Diarrhea	10.00 (9.96;10.04)
	1		Discontinuation due to adverse effects	4.00 (3.98;4.02)
	1		Dizziness	12.00 (11.96;12.04)
	1		Dose modification due to adverse effects	8.00 (7.97;8.03)
	1		Dose modification due to Laboratory abnormality: Alanine aminotransferase elevation, Neutropenia, and thrombocytopenia	38.00 (37.94;38.06)
	1		Dyspepsia	2.00 (1.98;2.02)
	1		Fatigue	37.00 (36.94;37.06)
	1		Gingival bleeding	6.00 (5.97;6.03)
	1		Headache	30.00 (29.95;30.05)
	1		Injection-site reaction	6.00 (5.97;6.03)
	1		Insomnia	8.00 (7.97;8.03)
	1		Myalgia	28.00 (27.95;28.05)
	1		Nausea	10.00 (9.96;10.04)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Pruritus	10.00 (9.96;10.04)
	1		Pyrexia	55.00 (54.94;55.06)
	1		Rash	8.00 (7.97;8.03)
	1		Rigors	10.00 (9.96;10.04)
	1		Sore throat	8.00 (7.97;8.03)
	1		Upper abdominal pain	5.00 (4.97;5.03)
	1		Upper respiratory tract infection	6.00 (5.97;6.03)
Peginterferon alfa-2b [81]	1	End	Mutation	0.32 (0.31;0.33)
	1	End	HBeAg seroconversion	8.71 (1.91;39.80)
	1	End	Failure	7.50 (2.20;25.53)
	1	End	HBsAg loss	5.00 (4.81;5.20)
	1	End	Improved histology	20.09 (18.94;21.30)
	1	End	Resistance	14.51 (13.55;15.54)
	1	End	Flare	24.05 (22.67;25.50)
	1	End	HBeAg loss	26.05 (24.56;27.63)
	1	End	Normalization ALT	29.96 (27.71;32.41)
	1	Follow	HBsAg seroconversion	0.44 (0.43;0.45)
	2	Follow	HBeAg seroconversion	14.01 (4.38;44.82)
	2	Follow	HBsAg loss	6.49 (5.55;7.59)
	1	Follow	Improved histology	8.00 (7.70;8.32)
	1	Follow	Combined	16.95 (15.98;17.97)
	2	Follow	HBeAg loss	30.27 (23.96;38.24)
	2	Follow	Normalization ALT	30.88 (25.38;37.56)
	1		Abdominal pain	17.00 (16.94;17.06)
	1		Adverse effects	75.00 (74.92;75.08)
	1		Alopecia	17.00 (16.94;17.06)
	1		Anorexia	14.00 (13.95;14.05)
	1		Arthralgia	14.00 (13.95;14.05)
	1		Depression	19.00 (18.94;19.06)
	1		Diarrhea	10.00 (9.95;10.05)
	1		Discontinuation due to drug-related adverse effects	0.43 (0.42;0.45)
	1		Fatigue	38.00 (37.92;38.08)
	1		Flu-like syndrome	54.00 (53.92;54.08)
	1		Headache	35.00 (34.93;35.07)
	1		Insomnia	7.00 (6.96;7.04)
	1		Local reaction	23.00 (22.93;23.07)
	1		Loss of >10% bodyweight	18.00 (17.94;18.06)
	1		Myalgia	26.00 (25.93;26.07)
	1		Nausea	16.00 (15.94;16.06)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Neutropenia (<1·5*109/L)	19.00 (18.94;19.06)
	1		Pruritus	9.00 (8.96;9.04)
	1		Reduction in dose of Interferon due to adverse events	21.00 (20.94;21.06)
	1		Thrombocytopenia (<75*109/L)	11.00 (10.95;11.05)
Peginterferon alfa-2b + Lamivudine [59,78,117,122]	1	End	Combined	59.74 (52.08;68.53)
	2	End	HBeAg loss	47.53 (30.58;73.87)
	2	End	Failure	12.20 (4.04;36.80)
	2	End	Flare	19.97 (16.41;24.29)
	2	End	HBeAg seroconversion	18.52 (5.02;68.37)
	1	End	HBV DNA loss	9.97 (9.22;10.79)
	2	End	Improved histology	8.00 (3.40;18.87)
	2	End	Mutation	13.45 (6.14;29.45)
	2	End	Normalization ALT	62.18 (58.83;65.72)*
	1	End	Relapse	15.47 (6.53;36.64)
	1	End	Resistance	11.81 (8.47;16.49)
	1	End	HBsAg loss	5.99 (5.76;6.23)
	1	Follow	Combined	23.72 (22.26;25.27)
	1	Follow	Death	1.99 (1.92;2.07)
	1	Follow	Decompensation	1.08 (1.06;1.09)
	2	Follow	HBeAg loss	32.46 (30.71;34.31)
	1	Follow	Flare	14.01 (12.71;15.46)
	2	Follow	HBeAg seroconversion	10.67 (10.35;11.00)
	1	Follow	HBV DNA loss	1.16 (1.14;1.18)
	1	Follow	Improved histology	11.02 (10.39;11.69)
	1	Follow	Normalization ALT	29.96 (27.71;32.41)
	1	Follow	Relapse	1.19 (1.17;1.21)
	2	Follow	HBsAg loss	6.49 (6.31;6.67)
	2		Alopecia	33.19 (16.23;67.87)
	2		Arthralgia	17.60 (9.59;32.31)
	2		Headache	39.63 (37.03;42.43)
	1		Abdominal discomfort	44.00 (43.87;44.13)
	1		Abdominal pain	16.00 (15.94;16.06)
	1		Allergic rashes	18.00 (17.90;18.10)
	1		Anorexia	14.00 (13.95;14.05)
	1		Decreased neutrophil count	2.00 (1.96;2.04)
	1		Decreased phosphate level	4.00 (3.95;4.05)
	1		Depression	18.00 (17.94;18.06)
	1		Diarrhea	9.00 (8.96;9.04)
	1		Dizziness	16.00 (15.90;16.10)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Fatigue	36.00 (35.92;36.08)
	1		Fever	72.00 (71.88;72.12)
	1		Flu-like syndrome	63.00 (62.92;63.08)
	1		Increased alkaline phosphatase level	1.00 (0.97;1.03)
	1		Increased ALT level	16.00 (15.90;16.10)
	1		Increased Creatine kinase level	1.00 (0.97;1.03)
	1		Insomnia	13.00 (12.95;13.05)
	1		Local erythematous reaction	24.00 (23.89;24.11)
	1		Local reaction	25.00 (24.93;25.07)
	1		Loss of >10% bodyweight	16.00 (15.94;16.06)
	1		Malaise	44.00 (43.87;44.13)
	1		Myalgia	26.00 (25.88;26.12)
	1		Myalgia	28.00 (27.93;28.07)
	1		Nausea	9.00 (8.96;9.04)
	1		Neutropenia (<1·5*109/L)	22.00 (21.93;22.07)
	1		Pruritus	12.00 (11.95;12.05)
	1		Reduced appetite	24.00 (23.89;24.11)
	1		Reduction in dose of Interferon due to adverse events	24.00 (23.93;24.07)
	1		Thrombocytopenia (<75*109/L)	9.00 (8.96;9.04)
	1		Upper respiratory tract symptoms	74.00 (73.88;74.12)
	1		Vomiting or diarrhea	14.00 (13.91;14.09)
	1		Weight loss (>10%)	14.00 (13.91;14.09)
Telbivudine [44,72]	2	End	Normalization ALT	82.35 (77.60;87.38)
	2	End	Combined	49.71 (30.50;81.01)
	2	End	HBeAg loss	27.44 (19.93;37.79)
	2	End	HBeAg seroconversion	25.95 (19.72;34.14)
	2	End	HBV DNA loss	55.26 (46.49;65.67)
	2	End	Relapse	5.00 (4.80;5.22)
	2	End	Resistance	1.99 (1.94;2.05)
	1		Abdominal pain	4.02 (3.85;4.19)
	1		Allergic rhinitis	1.12 (1.10;1.13)
	1		Arthralgia	4.02 (3.85;4.19)
	1		At least one adverse event	70.42 (66.40;74.68)
	2		Back pain	4.74 (3.28;6.87)
	2		Cough	5.24 (3.63;7.56)
	1		Depression	2.48 (2.16;2.84)
	2		Diarrhea	7.36 (5.82;9.30)
	2		Dizziness	3.37 (2.61;4.36)
	1		Dyspepsia	3.26 (2.54;4.18)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Epigastric discomfort	4.02 (3.85;4.19)
	2		Fatigue	8.10 (6.03;10.90)
	1		Gastritis	7.03 (6.65;7.43)
	2		Headache	8.92 (6.77;11.75)
	1		Hepatic steatosis	4.02 (3.85;4.19)
	1		Hordeolum	4.02 (3.85;4.19)
	1		Increased Creatine phosphokinase level	5.00 (4.87;5.14)
	2		Influenza	17.16 (14.26;20.64)
	1		Malaise	7.03 (6.65;7.43)
	1		Mouth ulceration	1.12 (1.10;1.13)
	1		Myalgia	1.99 (1.94;2.05)
	2		Nasopharyngitis	4.23 (3.16;5.67)
	2		Nausea	5.10 (4.57;5.68)
	2		Pharyngolaryngeal pain	5.79 (3.88;8.64)
	1		Toothache	4.02 (3.85;4.19)
	1		Total adverse effect	75.94 (69.89;82.53)
	2		Upper abdominal pain	7.00 (5.95;8.24)
	2		Upper respiratory tract infection	6.70 (4.06;11.04)
Telbivudine + Lamivudine[72]	1		Back pain	10.00 (9.88;10.12)
	1		Depression	5.00 (4.91;5.09)
	1		Diarrhea	5.00 (4.91;5.09)
	1		Increased Creatine phosphokinase level	5.00 (4.91;5.09)
	1		Upper respiratory tract infection	10.00 (9.88;10.12)
	1	End	Normalization ALT	78.08 (74.29;82.07)
	1	End	Combined	35.49 (18.71;67.30)
	1	End	HBeAg loss	16.95 (15.59;18.42)
	1	End	HBeAg seroconversion	15.03 (14.02;16.11)
	1	End	HBV DNA loss	48.91 (44.39;53.89)
	1	End	Relapse	11.94 (11.14;12.80)
	1		At least one adverse	70.51 (65.96;75.37)
	1		Cough	7.05 (3.59;13.87)
	1		Dizziness	7.05 (3.59;13.87)
	1		Dyspepsia	2.45 (2.33;2.57)
	1		Fatigue	7.05 (3.59;13.87)
	1		Headache	13.71 (7.32;25.66)
	1		Influenza	23.76 (15.14;37.30)
	1		Nasopharyngitis	7.05 (3.59;13.87)
	1		Nausea	4.88 (1.20;19.80)
	1		Pharyngolaryngeal pain	5.98 (0.99;36.31)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Upper abdominal pain	4.88 (1.20;19.80)
Placebo or no treatment [40,42,47,48,50,53,83,86,87,89,93,94,96,99,100,103-105,108,110,112]	11		HBV DNA loss	7.18 (4.44;11.61)
	7		HBsAg loss	1.73 (1.46;2.06)
	2		Mutation	2.26 (1.50;3.39)
	2		Flare	12.85 (6.00;27.49)
	4		Failure	17.60 (11.63;26.64)
	8		HBeAg loss	10.15 (8.61;11.97)
	8		HBeAg seroconversion	7.33 (6.36;8.44)
	4		Relapse	3.32 (1.53;7.17)
	9		Normalization ALT	12.32 (9.05;16.78)
	6		Improved histology	23.18 (18.44;29.12)
	3		Resistance	32.44 (11.19;94.07)
	7		Combined	4.82 (3.24;7.16)
	2		Death	7.91 (4.73;13.21)
	1		HBsAg seroconversion	5.00 (4.63;5.41)
	1		Cirrhosis	9.97 (8.87;11.22)
	1		Flatulence	5.99 (5.83;6.16)
	6		Headache	17.23 (10.96;27.08)
	1		Respiratory infection	29.08 (27.13;31.17)
	1		Abdominal distention	6.22 (3.08;12.59)
	1		Abnormal ALT/AST	15.96 (14.89;17.10)
	1		ALT> 2 than at baseline	5.31 (3.87;7.29)
	1		Anorexia	5.00 (4.87;5.14)
	1		Back pain	7.03 (6.84;7.23)
	1		Chest symptoms	7.03 (6.74;7.33)
	3		Cough	11.45 (6.74;19.44)
	1		Creatinine mg/dL (>2.0–3.0)	0.30 (0.29;0.31)
	2		Depression	3.32 (2.29;4.82)
	6		Diarrhea	7.11 (3.58;14.09)
	4		Dizziness	7.00 (5.33;9.20)
	1		Ear, nose, and throat	29.58 (27.49;31.82)
	2		Fever	1.64 (0.92;2.94)
	1		Hair loss	5.00 (4.87;5.14)
	2		Leucopenia	4.45 (3.59;5.52)
	2		Malaise and fatigue	22.00 (18.42;26.28)
	2		Muscle pain	8.64 (7.94;9.41)
	2		Musculoskeletal pain	4.16 (3.31;5.23)
	2		Nasal signs and symptoms	6.21 (5.17;7.47)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	2		Nausea and vomiting	2.88 (1.66;5.00)
	1		Nausea/vomiting	20.09 (18.74;21.53)
	2		Pain	9.54 (6.75;13.47)
	2		Rash	5.67 (2.88;11.14)
	1		Rheumatism	4.02 (3.85;4.19)
	1		Throat discomfort	8.00 (7.68;8.34)
	1		Viral respiratory infection	0.90 (0.88;0.91)
	1		>1 treatment-related event	12.00 (11.94;12.06)
	1		»1 adverse event	76.71 (71.57;82.21)
	1		Abdominal discomfort	20.31 (17.65;23.37)
	1		Abdominal pain and discomfort	4.00 (3.96;4.04)
	1		Abnormal enzymes (amylase/CPK)	7.03 (6.74;7.33)
	1		Abnormal liver-function	8.00 (7.68;8.34)
	1		ALT »2 times above base-line levels and bilirubin »2 times above baseline levels	0.84 (0.59;1.19)
	1		Collapse after dizziness	0.00 (0.85;0.90)
	1		Constipation	4.00 (3.96;4.04)
	1		Creatinine mg/dL (>3.0–6.0)	0.30 (0.29;0.31)
	1		Creatinine mg/dL (>6.0)-	0.30 (0.29;0.31)
	1		Creatinine mg/dL (1.5–2.0)	0.30 (0.29;0.31)
	1		Decreased WBCs	0.90 (0.88;0.91)
	1		Developing of IFN neutralizing antibodies	0.00 (1.74;1.83)
	1		Discontinuation due to adverse events	1.00 (0.99;1.01)
	1		Discontinuation due to depression	0.00 (1.74;1.83)
	3		Discontinuation due to adverse effects	1.65 (0.83;3.29)
	1		Discontinuation due to psychosis	0.00 (1.74;1.83)
	1		Dose reduced due to an adverse event or abnormal lab result	1.00 (0.99;1.01)
	1		Dose reduction due to depression, fatigue, hair loss, and headache	0.00 (0.85;0.90)
	3		Fatigue	4.61 (2.91;7.30)
	1		Feeding problems	4.02 (3.85;4.19)
	1		Gastrointestinal events	6.00 (5.96;6.04)
	1		Glycosuria(+1)	3.00 (2.97;3.03)
	1		Glycosuria(+2)	2.00 (1.98;2.02)
	1		Glycosuria(+3)	3.00 (2.97;3.03)
	1		Glycosuria(+4)	0.30 (0.29;0.31)
	1		Grade III or IV lab abnormalities in alanine aminotransferase	13.00 (12.92;13.08)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Grade III or IV laboratory abnormalities in Albumin	3.00 (2.96;3.04)
	1		Grade III or IV laboratory abnormalities in Amylase	1.00 (0.98;1.02)
	1		Grade III or IV laboratory abnormalities in Creatine kinase	4.00 (3.96;4.04)
	1		Grade III or IV laboratory abnormalities in Lipase	7.00 (6.94;7.06)
	1		Grade III or IV laboratory abnormalities in Platelets	3.00 (2.96;3.04)
	1		Grade IV abnormality in ALT	0.84 (0.59;1.19)
	1		Hair loss/alopecia	4.02 (3.85;4.19)
	1		Hematuria Obstructive or Rx required	0.00 (0.29;0.31)
	1		Hematuria<10 RBCs	7.00 (6.96;7.04)
	1		Hematuria>100 RBCs	13.00 (12.95;13.05)
	1		Hematuria10–100 RBCs	10.00 (9.96;10.04)
	1		Hypophosphatemia mg/dL (<1.0)	0.30 (0.29;0.31)
	1		Hypophosphatemia mg/dL (1.0–1.5)	0.30 (0.29;0.31)
	1		Hypophosphatemia mg/dL (1.5–<2.0)	1.00 (0.99;1.01)
	1		Hypophosphatemia mg/dL (2.0–2.2)	1.00 (0.99;1.01)
	1		Incidence of elevation of serum ALT to >5 times the ULN	55.15 (52.17;58.29)
	1		Infections	0.00 (2.22;2.33)
	1		Jaundice	0.00 (2.22;2.33)
	1		Liver symptoms	4.00 (3.96;4.04)
	1		Malaise/fatigue	32.14 (29.57;34.92)
	1		Marrow suppression	0.00 (2.22;2.33)
	1		Muscular or skeletal pain	4.00 (3.96;4.04)
	1		Nasopharyngitis	1.99 (1.97;2.02)
	2		Nausea	7.64 (2.33;25.09)
	1		Paresthesias	7.00 (6.94;7.06)
	1		Proteinuria mg/dL(Nephrotic syndrome)	0.00 (0.29;0.31)
	1		Proteinuria mg/dL(<100)	10.00 (9.96;10.04)
	1		Proteinuria mg/dL(>1000)	0.30 (0.29;0.31)
	1		Proteinuria mg/dL100–1000)	7.00 (6.96;7.04)
	1		Pruritis	4.00 (3.96;4.04)
	1		Sleep disorder	4.00 (3.96;4.04)
	1		Sleep disturbance	4.00 (3.96;4.04)
	1		Temperature regulation disturbance	6.92 (5.88;8.16)

Appendix E. Table 11. Rates of clinical, intermediate, and adverse outcomes after antiviral treatment / no treatment by baseline HBeAg status at the end of treatment and at followup off treatment. (results from individual RCTs and pooled analyses with random effects models. Rates pooled from RCTs that reported outcomes independent of active or control regime)

Antiviral Treatment	Studies	Outcome Assessment	Outcome	95% CI
	1		Throat and tonsil disorder	16.95 (15.83;18.14)
	1		Upper respiratory tract infection	8.00 (7.79;8.23)
	1		Upper respiratory viral infection	4.00 (3.96;4.04)
	1		Viral respiratory infection	27.52 (18.01;42.07)

*- estimates from fixed effects model when the best fit; all estimations were calculated in log odds scale, †- exponentiated estimates were pooled

Appendix E. Table 12. Summary of study IDs meeting eligibility for question 4

Surrogates	Outcomes				
	Decompensation (Liver Failure)	**Cirrhosis**	**HCC**	**Liver-Related Mortality**	**All-Cause Mortality**
ALT normalization during treatment	Di Marco[127]*	Di Marco[127]*	Di Marco[127]*		Di Marco[127]*
HBV DNA detectable end of treatment	Brunetto[128]* and Hui[129]*	Brunetto[128]* and Hui[129]*	Brunetto[128]* and Hui[129]*		
Worsening histology	Hui[129]*	Hui[129]*	Hui[129]*		
Change in HBeAg status	Chan[117]				
HBsAg seroconversion					
Drug Resistance					

* Three studies reported on combined clinical outcome of Decompensation+ Cirrhosis+ HCC

Appendix E. Table 13. Evidence table of the studies that examined the association between changes in intermediate outcomes to predict treatment effectiveness (n=4)

Surrogates	Outcomes				
	Decompensation (Liver failure)	Cirrhosis	HCC	Liver-related mortality	All cause mortality
Chronic hepatitis B Interferon alpha vs. untreated[127]					
ALT normalization during treatment*	RR 0.24 (.10-.59)				RR 0.24 (.08-.69)
HBV DNA detectable end of treatment					
Worsening histology					
Change in HBeAg status					
HBsAg seroconversion					
Drug Resistance					
HBeAg positive chronic hepatitis B Interferon alpha 2a vs. untreated[128]					
ALT normalization during treatment					
HBV DNA detectable during/ end of treatment§	OR 1.58 (1.12- 2.25)				
Worsening histology					
Change in HBeAg status					
HBsAg seroconversion					
Drug resistance					
HBeAg positive chronic hepatitis B All treated with peginterferon alpha 2a or 2b[129] ***Lamivudine plus peginterferon alpha 2b vs. lamivudine***[117]					
ALT normalization during treatment					
HBV DNA detectable at end of treatment#	OR 3.08 (0.44- 22.7)				
Worsening histology&	RR 5.56 (1.12- 27.62)				
Loss of HBeAg end of treatment	OR^ 0.6 (0.03-9.01) O% 0.81 (0.09- 7.64)				
HBsAg seroconversion					
Drug Resistance					

* Adjusted for age, cirrhosis at baseline and interferon alpha treatment. Combined endpoint of decompensation includes ascites, jaundice, encephalopathy, portal hypertensive bleeding and HCC & 2 point increase in modified HAI on serial liver biopsies. Combined clinical outcome of 'Liver complications' reported including decompensated cirrhosis and HCC. Multivariate analysis, adjusted for 'other risk factors.'

§ HBV DNA pattern1 (always or frequently > 10 pg/ml). OR from multivariate analysis adjusted for age, HBeAg at baseline and interferon alpha treatment for composite end point of 'disease progression' defined as progression to cirrhosis, decompensation or HCC.

HBV DNA $\geq 10^4$ copies/ml at 24 weeks after end of treatment. Unadjusted OR; calculated from frequencies reported in table.

^ Unadjusted OR calculated from reported frequencies for cohort of patients treated with lamivudine plus peginterferon alpha-2b

% Unadjusted OR calculated from reported frequencies for cohort of patients treated with lamivudine alone

Appendix E. Table 14. Other baseline factors as predictors of outcomes, and other outcomes (n=3)

Baseline Factors	Outcomes			
	Decompensation, Cirrhosis, HCC (Liver Failure)	Annual Rate of Fibrosis Progression	Liver-Related Mortality	All Cause Mortality
HBeAg-negative chronic hepatitis B				
Lamivudine vs. interferon alpha vs. placebo[130]				
Interferon alpha vs. placebo[131]				
Cirrhosis at baseline			Significant predictor, estimate not reported	Significant predictor, estimate not reported
Fibrosis score at baseline				
Milder fibrosis at baseline (Ishak stage <4)		OR 1.05 (1.0-1.11)		
Worsening necroinflammatory grade (≥2 point increase)		OR 1.05 (1.03-1.08)		
HBeAg-positive chronic hepatitis B -- all treated with Interferon alpha 2b[132]				
Staging score at baseline(0-6) §	HR 1.71 (1.17-2.50)			

§ From multivariate analysis controlling for age and treatment failure. Composite end point of liver-related complications

Appendix E. Table 15. Ongoing interventional randomized studies in patients with chronic hepatitis B (underlined outcomes assessment in patient subpopulations relevant to question 3)

Sponsor	ID	Tested Drug	Design	Outcomes
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); National Institutes of Health Clinical Center (CC)	NCT00023309	Adefovir Dipivoxil	Phase 2, Randomized, Open Label, Parallel Assignment, Safety/Efficacy Study	Maintained combined response (virological, biochemical and histological response). Loss of HBeAg, individual responses (virological, biochemical and histological), antiviral resistance and improvement in symptom scores
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); National Institutes of Health Clinical Center (CC)	NCT00524173	Tenofovir Disoproxil Fumarate Alone vs. Its Combination With Emtricitabine	Phase 2, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	Maintained suppression of HBV DNA below 102 copies/ml (<95 IU/ml, undetectable by current PCR-based assays, Roche Amplicor assay). Normalization of ALT levels and histological improvements which are expected to occur in all patients with full suppression of HBV DNA and in a proportion of those with partial suppression; loss of HBeAg and loss of HBsAg
Foundation for Liver Research	EudraCT: 2004-004736-30	Peginterferon Alfa-2a and Ribavirin Combination (HBeAg-Negative Chronic HBV Infection (PARC Study)	Phase 3, Randomized, Double Blind (Subject, Investigator), Placebo Control, Factorial Assignment, Efficacy Study	The combined presence of HBV DNA level <10E4 copies/ml and ALT normalization at the end of followup ALT normalization; HBV DNA negativity (undetectable by Taqman PCR) HBsAg loss; Improvement liver histology; combined virological, biochemical and histological response
Achillion Pharmaceuticals	NCT00040144	ACH126, 433 (b-L-Fd4C)	Phase 2, Randomized, Double-Blind, Dose Comparison, Parallel Assignment, Safety/Efficacy Study	Not reported
Bristol-Myers Squibb Administration	NCT00065507	Adefovir Entecavir	Phase 3, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	Mean serum HBV DNA PCR adjusted for baseline levels Discontinuation or dose reduction of study drug due to clinical AE or lab abnormality. Confirmed nephrotoxicity (increase in serum creatinine compared w/ baseline)

Appendix E. Table 15. Ongoing interventional randomized studies in patients with chronic hepatitis B (underlined outcomes assessment in patient subpopulations relevant to question 3) (continued)

Sponsor	ID	Tested Drug	Design	Outcomes
Novartis	NCT00076336	Lamivudine	Phase 3, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Dose Comparison, Parallel Assignment, Safety/Efficacy Study	Composite endpoint termed Clinical Response, defined as three efficacy criteria: Serum HBV DNA < 4 log10 copies/mL, Normal ALT level, Improvement or stabilization in CTP score
Novartis	NCT00076336	Telbivudine	Phase 3, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Dose Comparison, Parallel Assignment, Safety/Efficacy Study	Time to Clinical Response; Duration of Clinical Response; Improvement, Stabilization, and Worsening in CTP score; Improvement, Stabilization, and Worsening in a modified (3-component) CTP score
National Institute of Allergy and Infectious Diseases (NIAID); National Institute of Child Health and Human Development (NICHD)	NCT00111943	Tenofovir gel	Phase 2, Prevention, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety Study	Macroscopic evidence of damage to the cervical, vulvar, or vaginal epithelium, including ulceration and other lesions, severe erythema, or severe edema, related or not related to the study gel or applicator Adherence to the study gel regimen, acceptability of the study gel
Gilead	NCT00116805	Adefovir dipivoxil Tenofovir disoproxil fumarate	Phase III, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Active Control, Parallel Assignment, Safety/Efficacy Study	HBV DNA <400 copies/mL and histological improvement (at least a 2 point reduction in the Knodell necroinflammatory score without worsening in fibrosis) HBV DNA <400 copies/mL Histological improvement ALT normalization HBeAg and HBsAg loss/seroconversion Development of resistance mutations safety and tolerability
Gilead Sciences	NCT00117676	Adefovir dipivoxil tenofovir disoproxil fumarate	Phase III, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Parallel Assignment, Safety/Efficacy Study	HBV DNA <400 copies/mL and Histological Improvement (2 point reduction in Knodell Necroinflammatory score without worsening in Knodell fibrosis score) Histological Improvement Development of resistance mutations Safety and Tolerability ALT normalization
Idenix Pharmaceuticals; Novartis	NCT00128544	Telbivudine Valtorcitabine	Phase 2, Randomized, Double-Blind, Active Control, Parallel Assignment, Safety/Efficacy Study	Not reported
University Hospital, Bonn; Hoffmann-La Roche	NCT00221286	Pegylated interferon alfa 2a pegylated interferon alfa 2a + tenofovir + emtricitabine tenofovir + emtricitabine	Phase 3, Randomized, Open Label, Active Control, Factorial Assignment, Safety/Efficacy Study	HBeAg seroconversion Study discontinuation due to adverse events Loss of HBe-Ag; HBV-DNA < $5x10^3$ copies/ml, (COBAS TaqMan HBV Test); decrease of HBV-DNA >2xlog10 compared

Appendix E. Table 15. Ongoing interventional randomized studies in patients with chronic hepatitis B (underlined outcomes assessment in patient subpopulations relevant to question 3) (continued)

Sponsor	ID	Tested Drug	Design	Outcomes
				to baseline; normalization of ALT; Viral kinetics of HBV-DNA; Paired liver biopsy comparison according to METAVIR-activity and fibrosis score. HIV-RNA <50 copies/ml and CD4-cell increase Safety: number of adverse events, according to type and severity.
MTmedical Institute of Health The University of Texas Health Science Center at San Antonio BioMonde Preparations Limited	NCT00225537	4-Methylumbelliferone (Heparvit®)	Phase 2, Randomized, Double-Blind, Placebo Control, Single Group Assignment, Safety/Efficacy Study	Reduction of virus in blood to undetectable levels; Normalization of serum ALT and AST. Reduced viral loads; Improvement of serum ALT and AST; Improvement in general health status; Improvement in serum marker of hepatic fibrosis; Loss of HBeAg/seroconversion to HBeAb (for HBV patients).
Chinese University of Hong Kong; GlaxoSmithKline	NCT00226447	Lamivudine Pegylated Interferon	Phase 2, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study	HBV DNA reduction Normalization of ALT and negative HBV DNA at EOT, negative HBV DNA at EOT; Safety of treatment
PowderMed	NCT00277576	HBV DNA Vaccine ppdpSC18	Phase 1, Randomized, Double-Blind, Placebo Control, Single Group Assignment, Safety Study	Adverse events at all visits, vaccine site evaluations, laboratory parameters pre and post vaccination
Seoul National University Hospital; Hoffmann-La Roche	NCT00291616	Pegylated Interferon-alpha 2a Thymosin alpha 1	Phase 4, Randomized, Open Label, Historical Control, Parallel Assignment, Safety/Efficacy Study	HBeAg seroconversion, HBV DNA titer <20,000 IU/mL Normalization of serum ALT, loss of HBeAg and HBsAg, production of anti-HBs
Gilead Sciences	NCT00298363	Emtricitabine Entecavir tenofovir disoproxil fumarate	Phase 2, Randomized, Double Blind (Subject, Investigator, Outcomes Assessor), Active Control, Parallel Assignment, Safety/Efficacy Study	Safety (adverse events and laboratory tests, discontinuations due to adverse events)
Thomas Jefferson University	NCT00307242	Adefovir Dipivoxil	Phase 4, Randomized, Open Label, Active Control, Parallel Assignment, Safety Study	ALT elevations (>10 x ULN); serum HBV DNA levels over time; serum ALT levels; YMDD variants; safety
Gilead Sciences	NCT00307489	Emtricitabine Tenofovir DF	Phase 2, Randomized, Double Blind (Subject, Investigator, Outcomes Assessor), Active Control, Single Group Assignment, Safety/Efficacy Study	HBV DNA <169 copies/mL

Appendix E. Table 15. Ongoing interventional randomized studies in patients with chronic hepatitis B (underlined outcomes assessment in patient subpopulations relevant to question 3) (continued)

Sponsor	ID	Tested Drug	Design	Outcomes
Bukwang Pharmaceutical; Hong Kong: Department of Health	NCT00362635	Clevudine	Phase 3, Randomized, Double-Blind, Active Control, Parallel Assignment, Safety/Efficacy Study	HBV DNA negativity (i.e., <300 copies/ml) by PCR Safety: Laboratory tests, Adverse Events, Physical examination Viral kinetics of HBV DNA suppression
Bristol-Myers Squibb; Korea: Food and Drug Administration	NCT00393484	Entecavir + Lamivudine Placebo	Phase 4, Randomized, Double Blind (Subject, Investigator), Active Control, Parallel Assignment, Efficacy Study	Undetectable HBV DNA, <300 copies/mL, by Roche COBAS Amplicor PCR assay Mean log10 reduction from baseline in HBV DNA; normalization of serum ALT (≤1 x ULN); HBV DNA < 103, <104 or <105 copies/mL
Novartis	NCT00409019	Adefovir Telbivudine Tenofovir	Phase IV, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study	Not reported
Bristol-Myers Squibb	NCT00410072	Entecavir Entecavir + Tenofovir	Phase 3, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	HBV DNA <50 IU/mL (approximately 300 copies/mL) HBV DNA <50 IU/mL (300 copies/mL); Mean Log 10 reduction from baseline in HBV DNA by PCR; ALT Normalization (≤1 x upper limit of normal); HBeAg loss; HBe seroconversion; HBs seroconversion Frequency of adverse events, serious adverse events, and discontinuations from study drug due to adverse events or laboratory abnormalities
Bristol-Myers Squibb	NCT00410202	Entecavir vs. Adefovir Plus Lamivudine vs. Combination Entecavir Plus Adefovir in Lamivudine-Resistant Chronic Hepatitis B Subjects: The DEFINE Study	Phase 3, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	HBV DNA <50 IU/mL (approximately 300 copies/mL) Mean Log10 reduction from baseline in HBV DNA; ALT normalization (≤1 x upper limit of normal); HBeAg loss; HBe seroconversion; HBs seroconversion; virologic rebound due to genotypic resistance Frequency of adverse events, serious adverse events, and discontinuations from study drug due to adverse events or laboratory abnormalities
Novartis; Idenix Pharmaceuticals	NCT00412529	Entecavir Telbivudine	Phase 3, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	Change in mean hepatitis B virus (HBV) DNA level from baseline; early viral kinetics through estimation of various parameters; change in ALT levels; the area under the curve (AUC) of HBV DNA change from baseline to week 12; polymerase chain reaction (PCR) negative;

Appendix E. Table 15. Ongoing interventional randomized studies in patients with chronic hepatitis B (underlined outcomes assessment in patient subpopulations relevant to question 3) (continued)

Sponsor	ID	Tested Drug	Design	Outcomes
				Safety assessed by adverse events and laboratory values
Hoffmann-La Roche	NCT00435825	Peginterferon alfa 2a	Phase 4, Randomized, Double Blind (Subject, Investigator), Active Control, Parallel Assignment, Safety/Efficacy Study	HBeAg seroconversion Loss of HBeAg, HBsAg seroconversion, loss of HBsAg, ALT, HBV-DNA AEs, laboratory parameters
Hoffmann-La Roche; Bulgaria: Bulgarian Drug Agency	NCT00442572	Peginterferon alfa 2a	Phase 2, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	Serum HBV DNA <100,000 copies/mL Loss of HBsAg and seroconversion Changes in liver fibrosis, AEs, lab parameters
Gilead Sciences; United States: Food and Drug Administration	NCT00507507	Tenofovir disoproxil fumarate	Phase 2, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Active Control, Parallel Assignment, Safety/Efficacy Study	Suppression of HBV DNA <169 copies/mL
Gilead Sciences	NCT00507689	Emtricitabine/tenofovir disoproxil fumarate Emtricitabine/tenofovir disoproxil fumarate + Hepatitis B Immunoglobulin	Phase 2, Prevention, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	Recurrence of Chronic Hepatitis B virus post liver transplant
Genexine Co., Ltd.; Korea: Food and Drug Administration	NCT00513968	Adefovir	Phase 1, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	Adverse events and clinical laboratory abnormalities; HBeAg/HBsAg seroconversion rate, HBV Ag specific T cell immunity
Korea University; GlaxoSmithKline	NCT00531167	Entecavir Lamivudine + Adefovir	Phase 4, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study	PCR negativity (<60 IU/ml) of HBV DNA 1. PCR negativity (<60 IU/ml) of HBV DNA at year 1 (interim analysis) 2. Degrees of HBV DNA reduction 3. ALT normalization 4. HBeAg seroconversion 5. Development of resistant mutation 6. Virologic breakthrough 7. Biochemical breakthrough
Schering-Plough; China: State Food and Drug Administration	NCT00536263	Pegylated interferon alpha-2b	Phase 3, Randomized, Open Label, Active Control, Crossover Assignment	HBeAg Loss; HBe seroconversion; HBV-DNA decrease; ALT normalization Combined Response (defined as HBV DNA (PCR) <20,000 IUs/ml and HBe seroconversion and ALT normalization) HBsAg Loss; HBs seroconversion
French National Agency for Research on AIDS and Viral Hepatitis	NCT00536627	Naked DNA vaccine pCMVS2.S	Phase 1/Phase 2, Randomized, Open Label, Parallel Assignment, Safety/Efficacy Study	Virologic failure defined by 1) reactivation after analogs' treatment interruption, 2) virologic breakthrough during treatment with analogs, 3) the impossibility for the patients to interrupt treatment at week 48

Appendix E. Table 15. Ongoing interventional randomized studies in patients with chronic hepatitis B (underlined outcomes assessment in patient subpopulations relevant to question 3) (continued)

Sponsor	ID	Tested Drug	Design	Outcomes
National Taiwan University Hospital; Bristol-Myers Squibb	NCT00597259	Entecavir Pegasys plus Entecavir	Phase 4, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study	HBeAg seroconversion Serum ALT normalization, HBeAg loss, serum HBV DNA disappearance, HBsAg disappearance, histological change, Entecavir resistance
Bristol-Myers Squibb	NCT00605384	Adefovir +Lamivudine Entecavir + Tenofovir	Phase 3, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	HBV DNA level <50 IU/mL
Hoffmann-La Roche; China: State Food and Drug Administration	NCT00614471	Entecavir peginterferon alfa-2a	Phase 4, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	Log change in quantitative HBeAg from baseline HBeAg seroconversion, HBV-DNA <1000 copies/mL, loss of HBeAg, HBV DNA reduction, ALT normalization, loss of HBsAg seroconversion, reduction of HBsAg 24 weeks after end of treatment; AEs, laboratory parameters
Pusan National University Hospital; Yonsei University	NCT00625339	Entecavir Lamivudine	Phase 4, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	HBV DNA <60 IU/mL (Undetectable serum HBV DNA by PCR method); drug resistant mutations; ALT normalization, HBeAg loss, HBe seroconversion, HBsAg loss and HBs seroconversion Cumulative discontinuation rates due to lamivudine or entecavir resistance mutations and clinical breakthrough, Safety assessment
Yonsei University; Pusan National University Hospital; Yonsei University	NCT00625560	Entecavir Lamivudine	Phase 4, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	HBV DNA < 60 IU/mL Drug resistant mutations; change from baseline in mean HBV DNA; ALT normalization, HBeAg loss, HBe seroconversion, HBsAg loss and HBs seroconversion Cumulative discontinuation rates due to lamivudine or entecavir resistance mutations and clinical breakthrough Safety assessment
Yonsei University; Pusan National University Hospital	NCT00637663	Entecavir Lamivudine	Phase 4, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	HBV DNA <60 IU/mL (Undetectable serum HBV DNA by PCR method); ALT normalization, HBeAg loss, HBe seroconversion, HBsAg loss and HBs seroconversion Cumulative discontinuation rates due to lamivudine or Entecavir resistance mutations and clinical breakthrough, Safety assessment

Appendix E. Table 15. Ongoing interventional randomized studies in patients with chronic hepatitis B (underlined outcomes assessment in patient subpopulations relevant to question 3) (continued)

Sponsor	ID	Tested Drug	Design	Outcomes
Bukwang Pharmaceutical; South Korea: Korea Food and Drug Administration (KFDA)	NCT00641082	Adefovir Clevudine	Phase 4, Randomized, Double-Blind, Parallel Assignment, Safety/Efficacy Study	HBV DNA below 300copies/mL The change of HBV DNA from the baseline; HBV DNA below LOD of RT-PCR; ALT normalization rate; viral breakthrough
Hoffmann-La Roche; Turkey: Ministry of Health	NCT00661076	Adefovir dipivoxil Peginterferon alfa-2a	Phase 3, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	Normalization of ALT, and HBV-DNA <400 copies/mL HBsAg quantitative loss and anti-HBs seroconversion; AEs, lab parameters, vital signs
University of Ulm; Novartis	NCT00710216	Lamivudine Telbivudine	Phase 4, Randomized, Open Label, Active Control, Parallel Assignment, Pharmacokinetics/Dynamics Study	Decrease in viral load after 2 weeks of therapy measured in serum HBV-DNA concentration (Copies/ml or IU/ml) Influence of HBeAg status to the decrease in viral load Influence of HBV genotype to the decrease in viral load Change in ALT and AST levels from baseline to week 12 Development of viral resistance and treatment failure during the study and subsequent course of observation Safety assessed by adverse events and laboratory values
Maimonides Medical Center	NCT00715715	Prednisone Priming	Randomized, Single Blind (Subject), Placebo Control, Parallel Assignment, Safety/Efficacy Study	Reduction in HBV DNA, HBeAg seroconversion, normalization of ALT; histological improvement
Bristol-Myers Squibb; China: State Food and Drug Administration	NCT00718887	Adefovir, then Entecavir Entecavir	Phase 4, Randomized, Open Label, Active Control, Crossover Assignment, Safety/Efficacy Study	HBV DNA <50 IU/mL Mean reduction of HBV DNA; ALT normalization; HBeAg loss, seroconversion, HBsAg loss and seroconversion Safety Resistance
Gilead Sciences	NCT00734162	Tenofovir disoproxil fumarate	Phase 2/Phase 3, Randomized, Double Blind (Subject, Investigator), Placebo Control, Parallel Assignment, Safety/Efficacy Study	Composite endpoint of HBV DNA <400 copies/mL and ALT normal Adverse events and clinical laboratory tests
Gilead Sciences	NCT00737568	Emtricitabine/tenofovir DF Tenofovir DF	Phase 4, Randomized, Double Blind (Subject, Investigator), Active Control, Parallel Assignment, Safety/Efficacy Study	Antiviral efficacy against HBV; safety and tolerability

Appendix E. Table 16. Completed unpublished RCTs in patients with chronic hepatitis B

Sponsor	ID	Tested Drug	Phase	Design	Outcomes
Mayo Clinic; Idenix Pharmaceuticals	NCT00275652	LdT (Telbivudine) and lamivudine	Phase 3	Randomized, Double-Blind, Active Control, Parallel Assignment, Safety/Efficacy Study	A composite endpoint called "clinical response" which is defined as HBV DNA <10 4 copies/ml and normal ALT and improvement, or stabilization in CTP score. Improvement, stabilization, and worsening in CTP score; normal ALT; improvements in serum albumin levels, in patients with hypoalbuminemia pre-treatment
GlaxoSmithKline	NCT00316719	Adefovir dipivoxil	Phase 3	Randomized, Double-Blind, Active Control, Parallel Assignment, Safety/Efficacy Study	Change in serum HBV-DNA level from baseline to week 52 HBV-DNA level ; ALT level and proportion of patients achieving ALT normalization; Emergence rate of resistant virus
Idenix Pharmaceuticals; Novartis	NCT00124241	Telbivudine lamivudine	Phase 2	Randomized, Double-Blind, Active Control, Parallel Assignment, Safety/Efficacy Study	Not reported
Bristol-Myers Squibb; Bristol-Myers Squibb	NCT00096785	Entecavir adefovir	Phase 3	Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study	Antiviral efficacy, as measured by the mean reduction in serum HBV DNA levels by PCR(log10 copies/mL) Exploratory viral kinetics: HBV DNA by PCR<LOQ and normalization of ALT (<1xULM). Relapse during 24-week post-dosing phase for those who achieve Response. Safety: Number and percentage of subjects with AEs, lab abnormalities and discontinuations due to AEs
Valeant Pharmaceuticals North America; Valeant Pharmaceuticals North America	NCT00230503	Pradefovir mesylate adefovir dipivoxyl	Phase 2	Randomized, Open Label, Active Control, Parallel Assignment, Safety Study	Safety :Clinical examinations of laboratory tests Change in viral load over time Undetectable viral load

Appendix E. Table 16. Completed unpublished RCTs in patients with chronic hepatitis B (continued)

Sponsor	ID	Tested Drug	Phase	Design	Outcomes
University of Washington; Gilead Sciences; GlaxoSmithKline	NCT00230477	Hepsera Hepsera and lamivudine	Phase 4	Randomized, Open Label, Dose Comparison, Parallel Assignment, Efficacy Study	Decrease in the viral DNA HBeAg conversion
National Taiwan University Hospital; Schering-Plough	NCT00275938	Interferon alpha 2b plus ribavirin interferon alpha 2b plus placebo	Phase 2/Phase 3	Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study	Undetected serum HBV DNA level (i.e., less than 2.5 pg/ml) at the end of the 24-week followup period HBV DNA level at the end of treatment Clearance of HBeAg and rate of ALT normalization both at the end of the 32-week treatment period and at the end of the 24-week followup
GlaxoSmithKline; Schering-Plough	NCT00140725	Lamivudine plus Polyethylene glyco-interferon alfa 2b Lamivudine	Phase 3	Randomized, Open Label, Uncontrolled, Parallel Assignment, Safety/Efficacy Study	HBeAg seroconversion to anti-HBe Normalization of ALT Undetectable HBV DNA Histologic improvement Tyrosine, methionine, aspartate, aspartate (YMDD) mutants among the viremic relapsers at the end of therapy and safety of treatment
Achillion Pharmaceuticals	NCT00034359	ACH-126, 443 (beta-L-Fd4C)	Phase 2	Randomized, Double-Blind, Dose Comparison, Parallel Assignment, Safety/Efficacy Study	Not reported
Idenix Pharmaceuticals; Novartis	NCT00132652	Lamivudine Telbivudine	Phase 3	Randomized, Double-Blind, Active Control, Parallel Assignment, Safety/Efficacy Study	Not reported
Chinese University of Hong Kong; GlaxoSmithKline	NCT00338780	Lamivudine/Placebo 100mg daily	Phase 4	Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study	Complete response (ALT<1xULN and disappearance of HBV DNA, lower limit of detection) Histological improvement at month 24 Progression of fibrosis Progression of fibrosis to cirrhosis HBsAg seroconversion Safety of treatment

References for Appendix E

(Note that there is a separate set of references at the end of the report and reference numbers are different than those in Appendix E)

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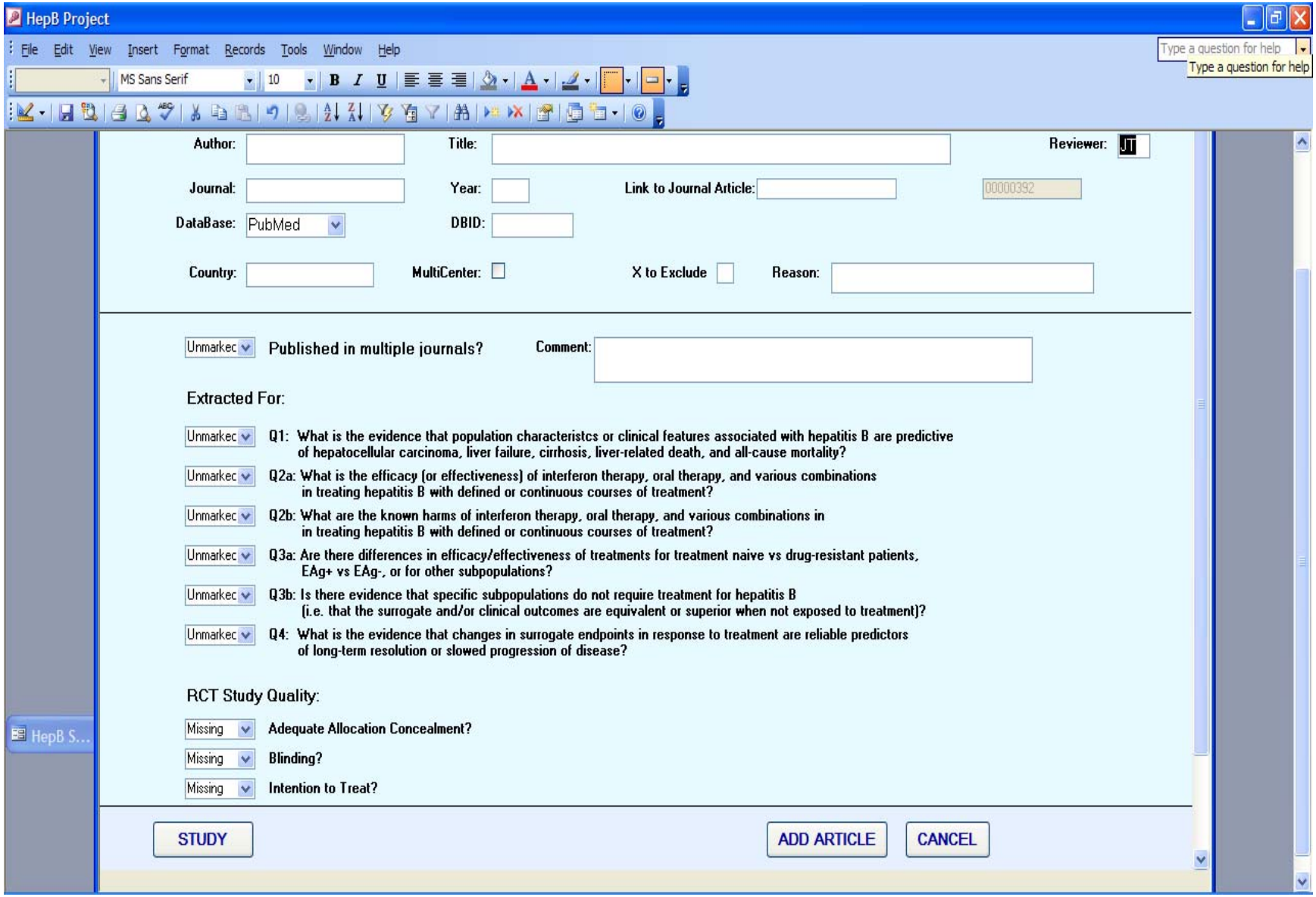
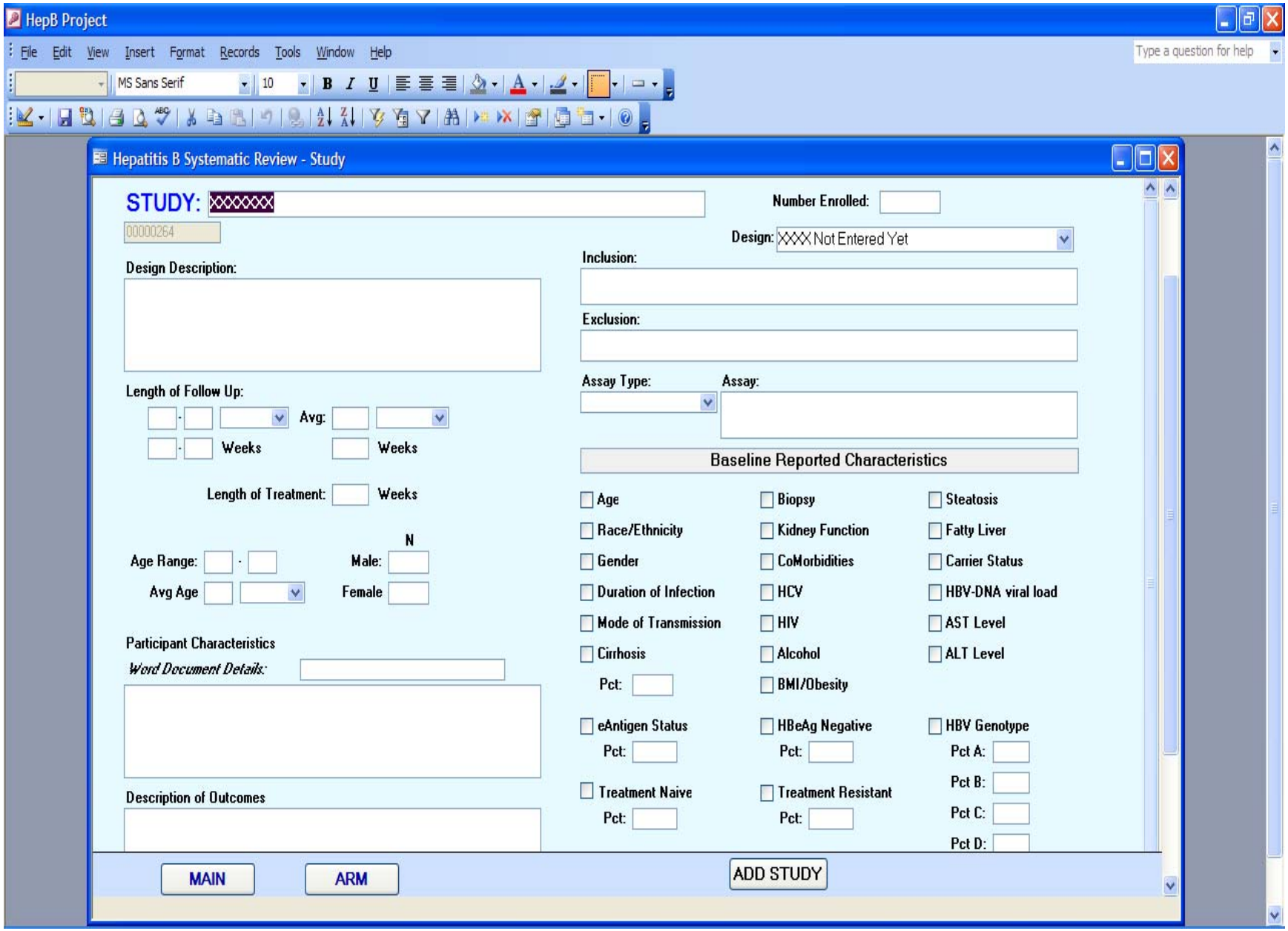
Appendix F: Data Abstraction Form




HepB Project
File Edit View Insert Format Records Tools Window Help
Type a question for help
MS Sans Serif
10
Hepatitis B Systematic Review - Study
STUDY:
Number Enrolled:
00000264
Design: XXXX Not Entered Yet
Design Description:
Inclusion:
Exclusion:
Length of Follow Up:
Avg:
Weeks
Weeks
Length of Treatment:
Weeks
Assay Type:
Assay:
Baseline Reported Characteristics
Age
Race/Ethnicity
Gender
Duration of Infection
Mode of Transmission
Cirrhosis
Pct:
eAntigen Status
Pct:
Treatment Naive
Pct:
Biopsy
Kidney Function
CoMorbidities
HCV
HIV
Alcohol
BMI/Obesity
HBeAg Negative
Pct:
Treatment Resistant
Pct:
Steatosis
Fatty Liver
Carrier Status
HBV-DNA viral load
AST Level
ALT Level
HBV Genotype
Pct A:
Pct B:
Pct C:
Pct D:
N
Age Range:
Male:
Avg Age
Female
Participant Characteristics
Word Document Details:
Description of Outcomes
MAIN
ARM
ADD STUDY