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Recommendations change rapidly in HIV care, so the care provider is cautioned that this edition is dated 2005. For the most current and continually updated HIV/AIDS treatment guidelines, contact AIDSinfo at:

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This *Guide* contains information relating to general principles of medical care which should not be construed as specific instructions for individual patients. Some of the information may cite the use of a particular drug in a dosage, for an indication, or in a manner other than recommended. Therefore, the manufacturer's package inserts should be consulted for complete prescribing information.

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FORWARD

A Guide to the Clinical Care of Women with HIV is a comprehensive clinical manual that addresses the primary care needs unique to women with HIV infection. The target audience is clinicians who provide primary care to women as well as those seeking a more in-depth understanding of how to care for women with HIV/AIDS. This 2005 edition of the guide, first published in 2001, has been updated and chapters have been added on international issues and nutrition.

A manual devoted specifically to the care of women with HIV is important. Because women are often challenged by social isolation, poverty, discrimination and lack of access to quality health care, they tend to be diagnosed later and to have poorer health status than men. They must contend with vulnerability related to reproductive and gender issues and domestic violence. Finally, women living with HIV are usually relied upon to meet the care needs of children and other family members, many of whom are also HIV-positive.

DEDICATION

We want to acknowledge the women with HIV/AIDS who have been the inspiration for this Guide. Their strength is celebrated and their struggle is not forgotten. We offer this Guide as a tribute to them, and to the providers who have taken on this struggle and made it their own.

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ABBREVIATIONS

3TC	Lamivudine
5-FU	5-fluorouracil
A-aDO₂	Alveolar to arterial oxygen difference
ABC	Abacavir
ACOG	American College of Obstetricians and Gynecologists
ADC	AIDS dementia complex
ADR	Adverse drug reaction
AFB	Acid-fast bacilli
AFI	Amniotic fluid index
AFP	Alfa fetoprotein
AGC	Atypical glandular cells
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
AP	Antepartum
APAP	Acetaminophen
APV	Amprenavir
ARV	Antiretroviral
ASA	Aspirin (acetylsalicylic acid)
ASC-H	Anal squamous intraepithelial lesions—cannot exclude HSIL
ASCUS	Anal squamous intraepithelial lesions—undetermined significance
ASIL	Anal squamous intraepithelial lesions
ATV	Atazanavir
AUC	Area under the concentration-time curve
AZT	Zidovudine
bDNA	Branched DNA
bid	2 times daily
biw	2 times weekly
BMI	Body mass index
BV	Bacterial vaginosis
bx	Biopsy
CASI	Computer assisted self-interviewing

CBC	Complete blood count
CBV	Combivir
CDC	Centers for Disease Control and Prevention
CEA	Carcinoembryonic antigen
CES-D	Center for Epidemiological Studies Depression scale
CI	Confidence interval
CIN1, -2, -3	Cervical intraepithelial neoplasia, grade 1 (2, 3)
CLIA	Clinical Laboratory Improvements Amendments
C_{max}	Peak serum concentration
C_{min}	Trough serum concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CPK	Creatinine phosphokinase
CrCl	Creatinine clearance
CSF	Cerebrospinal fluid
CST	Contraction stress test
CT	Computed tomography
CVD	Cardiovascular disease
CXR	Chest x-ray
d	Day
d/c	Discontinue
d4T	Stavudine
ddC	Zalcitibine
ddl	Didanosine
DEXA	Dual-energy X-ray absorptiometry
DFA	Direct fluorescent antibody
DLV	Delavirdine
DMPA	Depo-medroxyprogesterone acetate
DOT	Directly observed therapy
DRESS	Drug rash, eosinophilia, systemic symptoms
DS	Double strength
dT	Diphtheria/tetanus toxoid

ABBREVIATIONS *continued*

DVT	Deep venous thrombosis
EBV	Epstein-Barr virus
EC	Enteric coated
EFV	Efavirenz
ELISA	Enzyme-linked immunosorbent assay
EM	Electron microscopy
EMG	Electromyogram
ERCP	Endoscopic retrograde cholangiopancreatography
ESR	Erythrocyte sedimentation rate
ETOH	Ethyl alcohol
FA	Fluorescent antibody
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FTA	Fluorescent treponemal antibody
FTC	Emtricitabine
FUO	Fever of unknown origin
G6PD	Glucose-6-phosphate dehydrogenase
GBS	Group B Streptococci
GBV-C	GB virus type C
GC	Gonorrhea culture
G-CSF	Granulocyte-colony stimulating factor
GI	Gastrointestinal
GTT	Glucose tolerance test
H&E	Hematoxylin and eosin
HAART	Highly active antiretroviral therapy
HAD	HIV-associated dementia
HAV	Hepatitis A virus
HBIG	Hepatitis B immunoglobulin
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin

HCSUS	HIV Cost and Services Utilization Study
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HERS	HIV Epidemiology Research Study
hgc	Hard gel capsule
HLA	Human leukocyte antigen
HPV	Human papillomavirus
hr	Hour
HRT	Hormone replacement therapy
HSIL	High-grade squamous intraepithelial lesion
HSV	Herpes simplex virus
HTLV	Human T-cell lymphotropic virus
IDSA	Infectious Disease Society of America
IDU	Injection drug use/user
IDV	Indinavir
IgA	Immunoglobulin A (E, G, M, etc.)
im	Intramuscularly
INH	Isoniazid
INR	International normalization ratio
IP	Intrapartum
IUD	Intrauterine device
iv	Intravenously
IVP	Intravenous pyelogram
JC virus	(Initials of index case of PML)
KOH	Potassium hydroxide
KS	Kaposi sarcoma
LAAM	L-a-acetyl-methadol
LCR	Ligase chain reaction
LDH	Lactic dehydrogenase
LDL	Low-density lipoprotein
LFT	Liver function test
LIP	Lymphoid interstitial pneumonia

ABBREVIATIONS *continued*

LP	Lumbar puncture
LPV	Lopinavir
LTS	Long-term survival
MAC	Mycobacterium avium complex
MCMD	Minor cognitive-motor disorder
MDD	Major depressive disorder
MDMA	Methylenedioxymethamphetamine (ecstasy)
MMR	Measles, mumps and rubella
mo	Month
MPA	Medroxyprogesterone acetate
MRI	Magnetic resonance imaging
MSM	Men who have sex with men
MTCT	Mother-to-child transmission
MTPA	Methoxy (trifluoromethyl) phenylacetic acid
N/V/D	Nausea/vomiting/diarrhea
N-9	Nonoxynol-9
NASBA	Nucleic acid sequence-based amplification
NFV	Nelfinavir
NIDU	Non-injection drug use
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NOS	Not otherwise specified
NRTI	Nucleoside reverse transcriptase inhibitor
NSAID	Nonsteroidal anti-inflammatory drug
NST	Non-stress test

O&P	Ova and parasites
OC	Oral contraceptive
OI	Opportunistic infection
OR	Odds ratio
PACTG	Pediatric AIDS Clinical Trials Group
PACTS	Perinatal AIDS Collaborative Transmission Study
PaO2	Partial pressure of oxygen
PCN	Penicillin
PCP	Pneumocystis jiroveci (formerly carinii) pneumonia
PCR	Polymerase chain reaction
PEP	Postexposure prophylaxis
PGL	Persistent generalized lymphadenopathy
PI	Protease inhibitor
PID	Pelvic inflammatory disease
PK	Pharmacokinetic
PLWHA	People living with HIV/AIDS
PML	Progressive multifocal leukoencephalopathy
PMTCT	Prevention of mother-to-child transmission
po	By mouth
PP	Postpartum
PPD	Purified protein derivative
PSN	Predominantly sensory neuropathy
PTSD	Post-traumatic stress disorder
PV	Vaginally
qd	1 time daily
qm	1 time monthly
qod	Every other day
qw	1 time weekly

ABBREVIATIONS *continued*

r/o	Rule out
RIBA	Recombinant immunoblot assay
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RT-PCR	Reverse transcriptase polymerase chain reaction
RTV	Ritonavir
sc	Subcutaneously
sgc	Soft gel capsule
SI	Syncytium-inducing
SIL	Squamous intraepithelial lesions
SIV	Simian immunodeficiency virus
SMX	Sulfamethoxazole
SOC	States of Change behavior theory
SP	Sulfadoxone pyrimethamine
sq	Subcutaneous
SQV	Saquinavir
SS	Single strength
SSRI	Selective serotonin reuptake inhibitor
STI	Sexually transmitted infection
sx	Symptom
TAM	Thymidine-associated mutation
TB	Tuberculosis
Td	Tetanus/diphtheria
TDM	Therapeutic drug monitoring

TE	Toxoplasmic encephalitis
TIBC	Total iron binding capacity
tid	3 times daily
tiw	3 times weekly
TMP	Trimethoprim
TSH	Thyroid-stimulating hormone
TSS	Toxic shock syndrome
TST	Tuberculin skin test
UNAIDS	United Nations Program on AIDS
USPHS	United States Public Health Service
VCT	Voluntary counseling and testing
VDRL	Venereal Disease Research Laboratory slide test
VZV	Varicella zoster virus
WBC	White blood cell
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WITS	Women and Infants Transmission Study
yr	Year

I. EPIDEMIOLOGY AND NATURAL HISTORY OF HIV INFECTION IN WOMEN

*Nancy A. Hessel, MSPH, Monica Gandhi, MD, MPH,
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I. INTRODUCTION

The successful introduction and spread of the human immunodeficiency virus (HIV) into the global human population has occurred for many reasons. The discovery and widespread use of penicillin and other antibiotics meant that there was treatment and cure for most sexually transmitted infections. The existence of these new drugs changed how people perceived risks associated with sexual activity. The development of hormonal contraceptives hastened the pace of change in sexual practices, as prevention of pregnancy without barrier methods became a possibility. Lifestyles were also changing: people were moving into regions that were previously uninhabited by man and long-distance travel became easier and much more common, allowing for greater social migration and sexual mixing. Although the virus may have been first introduced to humans earlier in the 20th century (most likely contracted from infected animals), it was in the 1970s that wider dissemination occurred.

For industrialized countries, the first evidence of the AIDS epidemic was among groups of individuals who shared a common exposure risk. In the United States, sexually active homosexual men were among the first to present with manifestations of HIV disease, followed by recipients of blood or blood products, then injection drug users, and ultimately, children of mothers at risk. Women have represented an increasing proportion of reported AIDS cases in the United States, accounting for 26% of adult cases in 2001 (CDC, 2002). Seventy-eight percent of AIDS cases in women are in African Americans and Hispanics, as compared with 52% of cases in men.

In developing countries, the AIDS epidemic manifested quite differently, both because the signs and symptoms were harder to distinguish from competing causes of morbidity and mortality, and because the epidemic was more generalized, instead of seemingly limited to certain “high-risk” groups. Worldwide, women now represent 50% of all adults living with HIV and AIDS (Table 1-1), and this proportion had been steadily increasing over time (UNAIDS, 2002).

This chapter reviews the epidemiology of HIV/AIDS, beginning with how HIV is transmitted and the variables involved; the natural history of HIV infection in women — both without treatment and in the era of highly active antiretroviral therapy (HAART), and concludes with future issues regarding the HIV/AIDS epidemic.

Table 1-1: Regional HIV/AIDS Statistics and Features, December 2002

<i>Region</i>	<i>Epidemic Started</i>	<i># Persons With Hiv Infection</i>	<i># Persons With New Hiv Infection</i>	<i>Prevalence Among Adults</i>	<i>Percent Of Infected Adults Who Are Women</i>	<i>Main Modes Of Transmission For Adults</i>
Sub-Saharan Africa	Late 1970s-early 1980s	29.4 million	3.5 million	8.8%	58%	Heterosexual contact
North Africa and Mid-East	Late 1980s	550,000	83,000	0.3%	55%	Heterosexual contact, injection drug use,
South, South-East Asia	Late 1980s	6.0 million	700,000	0.6%	36%	Heterosexual contact, injection drug use,
East Asia, Pacific	Late 1980s	1.2 million	270,000	0.1%	24%	Injection drug use, heterosexual contact, male/male sex
Latin America	Late 1970s-early 1980s	1.5 million	150,000	0.6%	30%	Male/male sex, injection drug use, heterosexual contact
Caribbean	Late 1970s-early 1980s	440,000	60,000	2.4%	50%	Heterosexual contact, male/male sex
Eastern Europe, Central Asia	Early 1990s	1.2 million	250,000	0.6%	27%	Injection drug use
Western Europe	Late 1970s-early 1980s	570,000	30,000	0.3%	25%	Male/male sex, injection drug use
North America	Late 1970s-early 1980s	980,000	45,000	0.6%	20%	Male/male sex, injection drug use, heterosexual contact
Australia, New Zealand	Late 1970s-early 1980s	15,000	500	0.1%	7%	Male/male sex
Total		42 million	5 million	1.2%	50%	

Source: Modified from (UNAIDS, 2002).

II. HIV TRANSMISSION

Epidemiologic studies have demonstrated that HIV is transmitted by three primary routes: sexual, parenteral (blood-borne), and perinatal. Virtually all cases of HIV transmission can be attributed to these exposure categories. Transmission rates from the infected host to the uninfected recipient vary by both mode of transmission and the specific circumstances. Because HIV is a relatively large virus, has a short half-life in vitro, and can only live within primates, HIV cannot be transmitted from casual (i.e., hugging or shaking hands) or surface (i.e., toilet seats) contact or from insect bites.

A. MODES OF TRANSMISSION

Sexual transmission of HIV from an infected partner to an uninfected partner can occur through male-to-female, female-to-male, male-to-male, and female-to-female sexual contact. Worldwide, sexual transmission of HIV is the predominant mode of transmission (Quinn, 1996). Among U.S. women with AIDS, sexual transmission constitutes 41% of reported cases as of December 2001 (CDC, 2002). This 41% is probably an underestimate given that a large proportion of the women with AIDS who report no identifiable risk (an additional 17% of AIDS cases in women) are actually also infected via sexual transmission. While receptive anal and vaginal intercourse appear to present the greatest risk of infection (approximately 0.1–3% and 0.1–0.2%, respectively, per episode), insertive intercourse (both anal and vaginal) has also been associated with HIV infection (approximately 0.06% and 0.1%, respectively, per episode) (Mastro, 1996; Vittinghoff, 1999). In addition, there have been a few case reports of male-to-male transmission from receptive oral intercourse with an HIV-infected male partner (approximately 0.04%–0.10% per contact) (Lifson, 1990; Samuel, 1993; Vittinghoff, 1999; Page-Shafer, 2002) and female-to-female transmission from oral-vaginal, oral-anal, sex toy-related, and digital intercourse (Marmor, 1986; Monini, 1996; Monzon, 1987; Perry, 1989; Rich, 1993; Sabatini, 1983; Kwakwa, 2003).

Parenteral transmission of HIV has occurred in recipients of blood and blood products, through transfusion of blood (estimated 95% risk of infection from transfusion of a single unit of HIV-infected whole blood [CDC, 1998a]) or clotting factors, in intravenous or injection drug users through the sharing of needles (approximately 0.67% risk per exposure [Kaplan, 1992]), in health care workers through needlesticks (approximately 0.3–0.4% risk per exposure, depending on the size and location of the inoculum [Tokars, 1993. Updated PHS guidelines, 2001]), and, less commonly, mucous membrane exposure (0.09% risk per exposure [Updated PHS guidelines, 2001, Hessol, 1989]). Among cumulatively reported AIDS cases in U.S. women through December 2001, 39% had injection drug use as their exposure risk and 3% reported receipt of infected blood, blood products, or tissue (CDC, 2002). Parenteral transmission patterns vary by geographic region due to social and economic factors. For instance, in regions where the prevalence of HIV

infection is higher, the risk of occupational or nosocomial transmission of HIV is greater than in regions where there is lower prevalence (Consten, 1995). The transmission risk is therefore related to the prevalence of HIV in the population as well as the frequency of exposure to infected body fluids and organs and the method of exposure (Fraser, 1995). In addition, many developing countries that have a high prevalence of HIV infection also lack the resources to implement universal precautions adequately (Gilks, 1998) and may experience a greater amount of transfusion-associated HIV transmission due to a lack of HIV antibody screening in some areas, a higher residual risk of contamination in blood supplies despite antibody screening (McFarland, 1997), and high rates of transfusion in some groups of patients. Recent data suggests that medical injections may account for a large number of previously unexplained HIV infections in the developing world (Gisselquist, et al. 2002; Gisselquist, 2002; Rosenthal, 2001).

Perinatal transmission can occur in utero, during labor and delivery, or postpartum through breast-feeding (Gwinn, 1996). Perinatal transmission rates average 25–30% (Blanche, 1989) overall in the absence of intervention, but vary by maternal stage of disease, use of antiretroviral therapy, duration of ruptured membranes, practice of breast-feeding, and other factors. In the United States as of December 2001, 91% of cumulative pediatric AIDS cases were attributed to perinatal transmission (CDC, 2002). More information on perinatal transmission can be found in Chapter VII on HIV and Reproduction.

B. FACTORS FACILITATING TRANSMISSION

Transmission of HIV infection can be influenced by several factors, including characteristics of the HIV-infected host and the recipient, as well as the quantity and infectivity of the virus. A summary of factors affecting sexual transmission of HIV is presented in Table 1-2.

INFECTIOUSNESS OF THE HOST

There is an association between the quantity of virus transmitted and the risk of HIV infection (Roques, 1993). Several studies have found that HIV-infected persons may be more likely to transmit the infection when viral replication is high, both during the initial stage of infection (Palasanthiran, 1993) and at more advanced stages of HIV disease (Laga, 1989). People with high blood viral load are more likely to transmit HIV to recipients of blood, their sexual partners, and their offspring (Quinn, 2000; Vernazza, 1999; Gray, 2001). HIV has been quantified in semen (Coombs, 1998; Speck, 1999; Vernazza, 1997) and detected in female genital secretions (Ghys, 1997; Mostad, 1998), and virus in these locations may facilitate transmission. However, the association between infectivity and disease stage is not absolute; HIV-infected women may transmit virus to a first-born child but not to a second-born child (de Martino, 1991), and temporal studies of semen from HIV-infected men demonstrate waxing and waning viral titers over time (Krieger, 1991; Tindall, 1992).

<i>Biologic Factor</i>	<i>Host-related Infectivity Factors</i>		
	<i>Hiv Concentration In Genital Secretions</i>	<i>Infectiousness (Transmission)</i>	<i>Susceptibility (Acquisition)</i>
Mutation of chemokine-receptor gene	?	?	▼▼▼
Late stage of HIV infection	▲▲	▲▲▲	Not applicable
Primary HIV infection	▲▲	▲▲	Not applicable
Anti-retroviral therapy	▼	▼▼	▼?
Local infection	▲▲	▲	▲▲
Presence of cervical ectopy*	▲▲	▲?	▲▲
Presence of foreskin*	?	▲▲	▲▲
Method of contraception			
<i>Barrier</i>	Not applicable	▼▼▼	▼▼▼
<i>Hormonal contraceptives</i>	▲▲	◆?	◆
<i>Spermicidal agents</i>	?	▼?	◆
<i>Intrauterine devices</i>	?	?	▲▲
<i>Menstruation</i>	?	▲▲	▲
Factors that lower cervicovaginal pH*	▼?	▼?	▼?
Immune activation	▲?	▲	▲
Genital tract trauma*	▲?	▲▲	▲▲
Pregnancy	▲▲	▲?	▲?

The degrees of positivity (▲ to ▲▲▲) and negativity (▼ to ▼▼▼) of the associations are indicated with arrows, with three arrows indicating a very strong association. The symbol ◆ denotes that there is evidence in support of both a positive and negative association. A question mark (?) indicates an unknown or hypothesized association that is not currently supported by data.

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*More recent data reveal that use of microbicides containing nonoxynol-9 are associated with a higher susceptibility to HIV infection (Roddy, 1998).

Factors that decrease viral titers, including antiretroviral therapy, may decrease but not eliminate the risk of HIV transmission (Hamed, 1993). Zidovudine has been shown to reduce vertical transmission from mothers to their fetus even when administered late in pregnancy or during labor (CDC, 1998b). (See Chapter VII on HIV and Reproduction.) Individuals receiving antiretroviral therapy have also shown reduced rates of HIV transmission to their sex partners (Musicco, 1994). Several studies have suggested that antiretroviral treatment reduces detection of HIV in female genital secretions (Cu Uvin, 1998) and the concentration of HIV

in semen (Gilliam, 1997; Gupta, 1997). Providers counseling patients on treatment should be clear that precautions to prevent transmission of the virus should be maintained because not all treatments reduce infectiousness, and transmissions have been reported among individuals with undetectable HIV RNA levels (European Collaborative Study Group, 1999). The presence of HIV in seminal cells has been documented in some individuals receiving highly active antiretroviral therapy and with undetectable levels of HIV-RNA in plasma (Zhang, 1998).

Factors that increase the risk of exposure to blood, such as genital ulcer disease (Cameron, 1989; Plummer, 1991), trauma during sexual contact (Marmor, 1986), and menstruation of an HIV-infected woman during sexual contact (European Study Group, 1992; Nair, 1993; St Louis, 1993) may all increase the risk of transmission.

Method of contraception also affects the likelihood of HIV transmission (Daly, 1994). There is overwhelming evidence that the correct and consistent use of latex condoms protects both men and women against HIV.

SUSCEPTIBILITY OF THE RECIPIENT

Characteristics of the uninfected individual may increase the likelihood of infection for a given exposure to HIV. Specifically, inflammation or disruption of the genital or rectal mucosa (which can occur with sexually transmitted infections and trauma) and lack of circumcision in heterosexual men may increase the risk of infection (Cameron, 1989; Moses, 1994; Quinn, 2000). Sex during menstruation may increase a woman's risk of acquiring HIV infection (Lazzarin, 1991) as may bleeding during sexual intercourse (Seidlin, 1993). In women, both ulcerative and nonulcerative sexually transmitted infections have been shown to be risk factors for acquiring HIV infection (Laga, 1993; Plummer, 1991). Cervical ectopy has been identified as a risk factor for acquisition of HIV infection in some (Nicolosi, 1994; Plourde, 1994) but not all (Mati, 1994) studies that have evaluated this condition. There is also some evidence that changes in the vaginal flora, as characterized by bacterial vaginosis, may facilitate acquisition of HIV (Sewankambo, 1997; Sturm-Ramirez, 2000).

Nonbarrier contraceptive methods have also been investigated in association with risk of HIV acquisition. The most frequently studied methods of contraception have been oral contraceptives, injectable hormones, intrauterine devices, and nonoxynol-9 (Daly, 1994; Plummer, 1998). (See Chapter III on Prevention of HIV.) Traditional vaginal agents, used in African women for sexual enhancement and self-treatment of vaginal symptoms, have also been investigated as potential cofactors for HIV transmission (Dallabetta, 1995). Use of hormonal contraceptives does not seem to be associated with increased susceptibility to HIV infection after adjustment for behavioral factors (Kiddugavu, 2003). The use of a popular vaginal and rectal microbicide, nonoxynol-9, has been shown to have no protective efficacy against the acquisition

of HIV (Roddy, 1998) and may even increase susceptibility to HIV infection due to mucosal barrier disruption, particularly with frequent use (Stephenson, 2000). The utility of other microbicidal agents for reducing the susceptibility to HIV infection is currently under active investigation.

There is increasing evidence that host genetic or immunologic factors may protect against HIV infection. This has been investigated in cohort studies of Nairobi sex workers (Willerford, 1993) and U.S. homosexual men (Dean, 1996), in which both sets of study subjects remained uninfected despite multiple sexual exposures to HIV. Individuals who are homozygous for a null allele of CCR5 are relatively resistant to sexually transmitted infection with HIV, indicating an important, though not absolute, role for this receptor in viral transmission. However, homozygous CCR5 mutations were not found among 14 hemophiliacs who remained uninfected with HIV after being inoculated repeatedly with HIV-contaminated Factor VIII concentrate from plasma during 1980–1985 (Zagury, 1998). In this study, investigators found an overproduction of β -chemokines in most of the uninfected individuals.

VIRAL PROPERTIES

Several viral factors have been proposed to play a role in the transmissibility of HIV. These include phenotypic characteristics (e.g., envelope proteins required for transmission), genetic factors that control the replicative capacity and “fitness” of the virus, and resistance to antiretroviral drugs (Vernazza, 1999).

Envelope sequences can define viral quasispecies that have been phenotypically arranged according to their ability to induce syncytia formation in infected T-cells (Paxton, 1998). It appears that the most commonly transmitted phenotype is the nonsyncytia-inducing, M-tropic viral strain, which is frequently found in those who have been recently infected. During the course of HIV infection the development of a more cytopathic, syncytia-inducing, T-tropic viral phenotype can be found and this is often a precursor to the development of AIDS. While some researchers have suggested that nonsyncytia-inducing isolates of HIV are preferentially transmitted (Roos, 1992), others have not been able to show preferential transmission of this isolate (Albert, 1995).

Envelope sequences can also be used to define viral subtypes, or clades, and these subtypes may also influence the transmissibility of HIV. The distribution of HIV subtypes differs according to geographic region, with A, C, D, and E predominant in Sub-Saharan Africa and Asia and B predominant in the United States, the Caribbean, South America, and Western Europe (Hu, 1996). In one study, subtype E is reported to have greater tropism for Langerhans cells than subtype B (Soto-Ramirez, 1996) and may have a greater per-contact transmissibility.

The transmission characteristics of a viral strain that is resistant to certain antiretroviral agents may differ from transmission of wild-type virus. Recent data indicates that resistant virus may be transmitted less efficiently than wild-type virus (Leigh Brown, 2003), but further research on the characteristics of drug-resistant virus is underway.

III. NATURAL HISTORY AND HIV DISEASE PROGRESSION

The natural history of HIV infection in adults has been extensively documented in the medical literature. The impact of sex on the manifestations and progression of HIV disease is still being investigated.

HIV infects and induces cell death in a variety of human cell lines. T-helper lymphocytes (also known as CD4 cells) are a major target of viral infection, and circulating CD4 cells become steadily depleted from peripheral blood in most untreated infected persons. Thus quantification of CD4 cells in blood is a rather simple way of determining cumulative immunologic damage due to HIV. Profound CD4 cell depletion is unusual in persons who do not have HIV infection and is usually iatrogenic or associated with severe illnesses, such as chemotherapy-induced leukopenia (Aldrich, 2000). Other immunologic parameters become altered with HIV disease progression, and though often used for research purposes, they tend to be more difficult to measure and less reliable or more costly. The plasma HIV-RNA level or viral load quantifies the amount of virus circulating in the bloodstream and reflects the level of HIV replication.

Untreated HIV infection is a chronic illness that progresses through characteristic clinical stages; AIDS is an endpoint of HIV infection, resulting from severe immunologic damage, loss of an effective immune response to specific opportunistic pathogens, and tumors. AIDS is diagnosed by the occurrence of these specific infections and cancers or by CD4 cell depletion to less than 200/mm³.

A. STAGING

HIV can cause a wide range of symptoms and clinical conditions that reflect the level of immunologic injury and different predisposing factors. Certain conditions tend to occur in association with each other and at specific CD4 cell counts. Staging systems for HIV disease facilitate clinical evaluation and therapeutic interventions, help determine the individual level of infirmity, and give prognostic information. Untreated HIV infection is a chronic illness that progresses through characteristic clinical stages that can be used to describe infirmity. Several groups have produced organized staging systems to facilitate clinical evaluation and planning therapeutic interventions. In industrialized countries, the most widely used system for classifying HIV infection and AIDS in adults and adolescents was published by the United States Centers for Disease Control and Prevention in 1992 (CDC, 1992).

The case definition (Table 1-3) begins first with confirmation of HIV infection via either serologic testing (combination of a screening method such as enzyme immunoassay and a more specific confirmatory test such as Western blot), or direct detection of HIV in patient tissue by viral culture, antigen detection, or other test such as polymerase chain reaction (PCR). The definition of each stage of illness is then based on two types of information: peripheral blood CD4 cell counts and clinical manifestations. CD4 cell counts are placed in three strata, ranging from relatively normal (>500 cells/mm³) to severe CD4 depletion (<200 cells/mm³).

The clinical manifestations of HIV infection are also placed in three strata, generally in accordance with the level of immunologic dysfunction associated with the various conditions (Table 1-3). Category A includes persons who have minimal clinical findings, clinical findings that do not indicate immune injury (including absence of symptoms), generalized lymphadenopathy, or resolved acute HIV infection. Category B includes conditions that indicate the presence of a defect in cell-mediated immunity or conditions that appear to be worsened by HIV infection. Category C includes conditions that are considered AIDS defining, even in the absence of a CD4 cell count less than 200 cells/mm³ (CDC, 1992). The addition of specific laboratory measures, such as plasma HIV RNA level, improves prognostic value even after the occurrence of Category C conditions (Lyles, 1999).

DEVELOPING WORLD

The CDC criteria require diagnostic testing and case confirmation methods that may not be available in developing countries, so several other sets of criteria have been proposed for these regions. Because lymphocyte subset quantitation is not widely available in many countries, the Global Program on AIDS of the World Health Organization (WHO) proposed a clinically based staging system that is more broadly applicable than the CDC system (WHO, 1993). The system uses clinical historical data, laboratory measures (optional), and indices of physical activity to assess level of infirmity to establish four clinical stages, summarized in Table 1-4. Laboratory measures include a single-assessment absolute CD4 cell count, with the option of replacing this test with total lymphocyte count, both of which are placed in three strata. CD4 cell count is a better prognostic indicator than total lymphocyte count, but the two results correlate well (Brettle, 1993; Jacobson, 2003; Badri, 2003).

Clinical history and functional measures are placed in four categories that range from asymptomatic to severe disease. In general, when compared with the CDC stages, the WHO system requires fewer diagnostic test data and fewer direct observations. The definition includes broader categories for conditions that may vary by region (e.g., disseminated infections with endemic mycoses, which are common in Southeast Asian AIDS patients but not in the United States or Europe). The inclusion of performance scale measures permits quantitative clinical assessment that is not dependent on laboratory resources.

Table 1-3: 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adults And Adolescents

<i>Cd4 Cell Category</i>	<i>Clinical Category A</i>	<i>Clinical Category B</i>	<i>Clinical Category C</i>
1. 500 cells/mm³	A1	B1	C1
2. 200-499 cells/mm³	A2	B2	C2
3. < 200 cells/mm³	A3	B3	C3

<i>Category A Conditions</i>	<i>Category B Conditions</i>	<i>Category C Conditions</i>
<ul style="list-style-type: none"> • No symptoms • Acute HIV infection (resolves) • Generalized lymphadenopathy 	<ul style="list-style-type: none"> • Bacillary angiomatosis • Oropharyngeal candidiasis • Vulvovaginal candidiasis: persistent, frequent, or poorly responsive to therapy • Cervical intraepithelial neoplasia II or III • Constitutional symptoms: fever, diarrhea > 1 month • Oral hairy leukoplakia • <i>Herpes zoster</i>: multiple episodes or involving > 1 dermatome • Idiopathic thrombocytopenic purpura • Listeriosis • Pelvic inflammatory disease: particularly if complicated by tubo-ovarian abscess • Peripheral neuropathy 	<ul style="list-style-type: none"> • Candidiasis of bronchi, trachea, lungs, or esophagus • Invasive cervical cancer • Coccidioidomycosis, disseminated or extrapulmonary • Cryptococcosis, extrapulmonary • Cryptosporidiosis (intestinal infection > 1 mo duration) • Cytomegalovirus disease (excluding liver, spleen or lymph nodes) • HIV-related encephalopathy • <i>Herpes simplex</i>: chronic ulcer > 1 mo duration, or bronchitis, pneumonitis, or esophagitis • Histoplasmosis: disseminated or extrapulmonary • Isosporiasis: > 1 mo duration • Kaposi's sarcoma • Burkitt's lymphoma • Immunoblastic lymphoma • Primary lymphoma of the brain • <i>Mycobacterium avium complex</i> or <i>M. kansasii</i>: disseminated or extrapulmonary • <i>M. tuberculosis</i>: any site • <i>Mycobacterium</i>: other species or unknown species, disseminated or extrapulmonary • <i>Pneumocystis carinii</i> pneumonia • Recurrent pneumonia • Progressive multifocal leukoencephalopathy • <i>Salmonella</i> septicemia, recurrent • Toxoplasmosis of the brain • Wasting syndrome due to HIV

Source: CDC, 1992.

Table 1-4: The World Health Organization Clinical HIV Staging System and Proposed Modifications

	<i>Laboratory Component</i>		<i>Clinical Group</i>			
	<i>Cd4 Cell Count</i>	<i>Total Lymphocyte Count</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>
<i>A</i>	<i>> = 500</i>	<i>> = 2000</i>	<i>A1</i>	<i>A2</i>	<i>A3</i>	<i>A4</i>
<i>B</i>	<i>200-499</i>	<i>1000-1999</i>	<i>B1</i>	<i>B2</i>	<i>B3</i>	<i>B4</i>
<i>C</i>	<i>< 200</i>	<i>< 1000</i>	<i>C1</i>	<i>C2</i>	<i>C3</i>	<i>C4</i>

<i>Clinical Stage</i>	<i>Clinical History</i>	<i>Performance Scale Criteria</i>	<i>Proposed Modifications</i>
One: Asymptomatic	<ol style="list-style-type: none"> 1. Asymptomatic infection 2. Persistent generalized lymphadenopathy 3. Acute retroviral infection 	Normal functional level in performance scales	None
Two: Mild Disease	<ol style="list-style-type: none"> 1. Unintentional weight loss less than 10% of body weight 2. Minor mucocutaneous manifestations 3. Herpes zoster within the previous 5 years 4. Recurrent upper respiratory infections 	Performance scale level at which symptoms are present but patients are almost fully ambulatory	<ol style="list-style-type: none"> 1. Substitution of weight loss with BMI 19–21 kg/m²* 2. Specify addition of acute oral or genital ulcers as one of the minor mucocutaneous manifestations* 3. ESR ≤ 65 mm/hr defines Kigali stage II 4. ESR > 65 mm/hr defines Kigali stage III
Three: Moderate Disease	<ol style="list-style-type: none"> 1. Unintentional weight loss greater than 10% of body weight 2. Chronic diarrhea† 3. Prolonged intermittent or constant fever† 4. Oral candidiasis 5. Oral hairy leukoplakia 6. Pulmonary tuberculosis developing within the previous year 7. Severe bacterial infections 8. Chronic vulvovaginal candidiasis† or poorly responsive to therapy 	Performance scale level at which patients remain in bed <50% of daytime, but more than normal	<ol style="list-style-type: none"> 1. Suggest exclusion of oral candidiasis and pulmonary tuberculosis* 2. Recommend substitution of weight loss with BMI ≤ 19 kg/m²* 3. Differentiation of ambulatory vs. hospitalized patients improved correlation with laboratory markers (Kassa, 1999) 4. ESR ≤ 65 mm/hr defines Kigali stage II 5. ESR > 65 mm/hr defines Kigali stage III

Table 1-4 (continued)

Clinical Stage	Clinical History	Performance Scale Criteria	Proposed Modifications
Four: Severe Disease	<ol style="list-style-type: none"> 1. HIV wasting syndrome defined as unexplained weight loss > 10% and either chronic diarrhea† or chronic weakness† and unexplained fever 2. <i>Pneumocystis carinii</i> pneumonia 3. CNS toxoplasmosis 4. Chronic cryptosporidial diarrhea† 5. Chronic isosporiasis with diarrhea† 6. Extrapulmonary cryptococcosis 7. Cytomegalovirus disease affecting organs other than the liver, spleen, or lymph nodes 8. Visceral or chronic† mucocutaneous <i>Herpes simplex</i> virus infection 9. Progressive multifocal leukoencephalopathy 10. Any disseminated endemic mycosis 11. Candidiasis of the esophagus, trachea, bronchi, or lungs 12. Disseminated atypical <i>Mycobacterium</i> spp. infection 13. Nontyphoidal <i>Salmonella</i> septicemia 14. Extrapulmonary tuberculosis 15. Lymphoma 16. Kaposi's sarcoma 17. HIV-related encephalopathy 	Performance scale level at which patients remain in bed > 50% of daytime	<ol style="list-style-type: none"> 1. Addition of oral candidiasis 2. Substitution of weight loss with BMI \leq 19 kg/m²* 3. Addition of chronic† oral or genital ulcer 4. Addition of pulmonary tuberculosis 5. ESR > 65 mm/hr defines Kigali stage III 6. Addition of positive HIV serology‡ 7. Addition of invasive cervical cancer‡

* Lifson, 1995.
 † >1 mo duration.
 ‡ De Cock, 1993.
 Source: WHO, 1993.

The four clinical stages in the WHO system correlated well with CD4 cell counts and HIV RNA levels in a study of 750 Ethiopians (including 336 women) by Kassa and others (Kassa, 1999). Other studies of patient populations have also demonstrated correlation of WHO clinical stage with CD4 cell count and clinical outcome (Morgan, 1997; 1998; Schechter, 1995). When compared with the CDC staging, the WHO clinical stages demonstrated a high degree of specificity, but a lower level of sensitivity (35–65%) for HIV infection (Gallant, 1992; 1993). In particular all of the systems for disease staging are not perfectly sensitive and specific for HIV infection, but can be improved by the addition of HIV serologies (Ankrah, 1994; De Cock, 1991). Modifications (Table 1-4) have been

proposed that improve the prognostic accuracy of the WHO system. Based on observations made in a study of AIDS mortality among Rwandan women, Lifson and colleagues proposed minor modifications of clinical history definitions, replacement of body mass index (weight (kg) divided by height (m²)) for weight loss and use of erythrocyte sedimentation rate as a laboratory indicator of infirmity (Lifson, 1995). Body mass index was significantly better than percentage of body weight lost over two measurements taken in 1 year at predicting mortality. Both erythrocyte sedimentation rate and hematocrit were highly predictive of mortality over a 36-mo period of observation (Lifson, 1995).

Other HIV-disease classifications, such as the Caracas definition proposed by the Pan American Health Organization (Rabeneck, 1996; Weniger, 1992), have been proposed but have not been evaluated as extensively as the CDC and WHO systems.

B. UNTREATED NATURAL HISTORY

PRIMARY OR ACUTE INFECTION

Acute HIV infection is a transient symptomatic illness that can be identified in 40–90% of cases of new HIV infection. It is characterized by a high rate of HIV replication, high titers of virus in blood and lymphoid organs (up to several million copies of HIV RNA per cubic millimeter of plasma), and initiation of an HIV-specific immune response. The amount of virus present in blood and tissues begins to fall after the appearance of cytotoxic (“killer”) lymphocytes that specifically react with HIV antigens; the vigor of this response varies among individuals and is associated with subsequent rate of disease progression (Cao, 1995). A pool of persistently infected CD4 cells (“latent reservoirs”) emerges early in the course of HIV infection and persists indefinitely (Chun, 1998).

Symptoms have been identified 5–30 days after a recognized exposure to HIV (Schacker, 1998). The signs and symptoms of acute HIV infection are not specific; fever, fatigue, rash, headache, lymphadenopathy, pharyngitis, mild gastrointestinal upset, night sweats, aseptic meningitis, and oral ulcerations are most frequently reported. Because the clinical signs of acute HIV infection resemble those of many acute viral illnesses, the correct diagnosis is often missed. Because early treatment at the time of acute infection is actively being investigated (Rosenberg, 2000) (see Chapter IV on Primary Medical Care), early suspicion of and evaluation for HIV infection should be encouraged (Kahn, 1998).

ESTABLISHED INFECTION

Regardless of whether the syndrome of acute HIV infection is recognized or not, after the HIV-specific immunological response begins to control the intensity of viremia, a so-called “viral set point” is established, which varies by individual. With exceedingly rare exceptions, the immunological response to HIV does not eliminate infection, but rather establishes

a steady state between viral replication and elimination (Henrad, 1995). A variable level of viremia is attained that can be measured via quantification of the number of copies of HIV RNA present in blood (viral load). Although the viral load within the first 120 days of HIV infection is not of prognostic value (Schacker, 1998), most patients establish a relatively stable viral load after recovering from acute infection, and this viral set point is highly predictive of the rate of future progression of illness. In the case of a high viral load set point (i.e., values ranging up from 40000 copies/mm³), more rapid decline in CD4 cell counts and more rapid occurrence of Clinical Class B and C conditions will occur. Some patients have low viral load set points (below 500 copies/mm³), which indicates a better prognosis; no evidence of progression (CD4 cell depletion or HIV diseases) is seen for long periods of time in a small subset of patients (see section on long-term progression, below). The viral set point is likely influenced by several factors such as presence of other infections at the time of HIV exposure, genetic characteristics (particularly the type of HIV binding receptors present on lymphocytes), viral characteristics, age, and perhaps sex (see below) (Kahn, 1998).

During the period of clinical stability, acute illnesses and other events that can stimulate the immune system, such as influenza, *Herpes simplex* outbreaks, tuberculosis, and even routine vaccinations, have resulted in 10–1000-fold increases in viral load; these increases are transient and most often resolve within 2 months (Stanley, 1996; Staprans, 1995). Thus, determination of viral load for prognostic purposes should not be done during or shortly after an acute illness.

For most HIV-infected persons, viral quasispecies evolve over time. Transition for the nonsyncytia-inducing macrophage-tropic viral strains that are commonly present after transmission to syncytia-inducing T-lymphocyte tropic strains occurs in many hosts. While variation of viral quasispecies with time is usual, the mechanism by which this process occurs has not been defined. However, transitions in viral quasispecies and cellular tropism have been observed to coincide with key clinical events such as CD4 cell depletion and development of symptomatic illness. These virologic changes may reflect evolution of a virus that is tailored to an individual's immune response or other genetic characteristics. Interventions that prevent evolution of quasispecies in a host may yield effective therapies in the future.

The HIV RNA level in tissues does not correlate in a linear fashion with blood levels, so even in patients with undetectable plasma HIV RNA, intracellular and tissue HIV RNA can still be detected with more sophisticated techniques (Hockett, 1999). Thus HIV replication continues at varying pace among infected persons, even those who control viremia well.

HIV is also frequently present in the genital tract (Fiore, 1999; Iversen, 1998), where expression of inflammatory mediators and lymphocyte receptors differ from blood and may influence the rate of viral replication and numbers of virions present (Anderson, 1998; Hladik, 1999). While the quantities of HIV present in cervicovaginal fluid are generally similar to those in blood (Hart, 1999; Shaheen, 1999), they differ in some individuals. The finding that HIV isolates from the lower genital tract can have different genotypic markers than blood isolates from a single host (Di Stefano, 1999; Shaheen, 1999) supports the concept that the lower genital tract sometimes functions as a separate virologic compartment.

TIME COURSE

In most studies of seroconverters (persons for whom the date of the HIV infection can be estimated), 50–60% of adults will be diagnosed with an AIDS-defining condition within 10 years of infection (for the pre-HAART treatment era). Almost half of seroconverters will die (due to any cause) after 10 years of infection if the disease is left untreated (Vella, 1992). Increasing age is the factor most consistently associated with rate of progression and death in most groups of patients studied to date (Alioum, 1998; UK Register of HIV Seroconverters Steering Committee, 1998; Pezzotti, 1999b; Prins, 1999). Date of infection also influences time from infection to an AIDS diagnosis, at least in some locations, demonstrating that even in the pre-HAART era, improvements in treatment have resulted in tangible benefits (Webber, 1998).

LABORATORY INDICATORS AND PREDICTORS

A large number of laboratory tests have been evaluated as prognostic indicators in HIV infection. For the most part, the tests can be divided into three groups: A, measures of HIV replication; B, measures of immune function; and C, measures of inflammation. Group A is specific to HIV infection; Group B, when indicating severe CD4 cell depletion, is relatively specific to HIV infection; and Group C is generally not specific to HIV infection. Table 1-5 summarizes these laboratory measures, their outcomes, and their advantages and disadvantages. HIV RNA quantitation, performed on fresh or fresh-frozen plasma or serum, is a powerful and accurate prognostic indicator in HIV infection and is uniquely useful in determining response to antiretroviral therapy (Saag, 1996). In general the best measures of prognosis and staging include combinations of HIV RNA level, CD4 cell count, and perhaps lymphocyte function (cytotoxic lymphocyte response to HIV) (Spijkerman, 1997; Vlahov, 1998).

Group	Test	Interpretation in HIV	Advantages	Disadvantages
A	HIV RNA level	Higher level, greater rate of viral replication, poorer prognosis	Direct measure of current viral activity, excellent prognostic indicator. Useful as indicator of treatment response.	Requires freshly frozen and separated sample, expensive and technically demanding. (O'Brien, 1996; Saag, 1996)
A	P24 antigen level	Higher level indicates greater level of viremia, poorer prognosis	Simple and relatively inexpensive	Of less prognostic value than most other assays (Coombs, 1989; Fahey, 1990)
A	Syncytium-inducing (SI) HIV phenotype	Emergence of SI strains is an independent predictor of progression to AIDS	An indicator of viral virulence for CD4 cells, adds to prognostic information provided by CD4 and HIV RNA level	Requires viral culture or DNA assay, which is cumbersome and costly. (Koot, 1993)
B	Lymphocyte count	Lymphopenia suggests greater immune injury	Indicates current status, cumulative over variable time	Nonspecific, can be influenced by large number of concurrent conditions and treatments
B	CD4 subset (absolute count, % or CD8 ratio)	Depletion of CD4 cells suggests immune injury and poorer prognosis, excellent prognostic indicator.	Indicates current status, cumulative over variable time, severe depletion relatively specific for HIV	Large range of variation (some introduced by differences among labs) expensive, must be performed on fresh (not frozen) specimen
B	Lymphocyte markers of immunologic activation	Presence of specific sets of activation markers on lymphocytes, depending on type, indicates favorable or unfavorable prognosis. Excellent prognostic indicators.	Highly specific marker of long term stability or decline.	Methods not standardized, costly and has limited availability. (Giorgi, 1994)
B	HIV-specific cytotoxic lymphocytes	Strong cytotoxic responses to HIV indicate favorable prognosis.	Highly specific marker of long term stability.	Methods not standardized, costly and has limited availability. (Harrer, 1996)
C	B-2 microglobulin	Higher B-2 microglobulin levels associated with risk of progression	Simple to perform	General marker of inflammation, nonspecific. (Planella, 1998)
C	Neopterin	Higher neopterin levels associated with risk of progression	Perhaps best prognostic indicator among group C. Simple to perform assay.	Not as good a prognostic indicator as CD4 cell count. (Fahey, 1990)

LONG-TERM NONPROGRESSORS

In untreated adults the median time from HIV infection to AIDS in developed countries is 8-10 years. However, approximately 8–15% of HIV-infected persons (most studies focus on men) remain symptom-free for much longer periods of time (Buchbinder, 1994; Munoz, 1995), a phenomenon that has been named long-term survival (LTS). These individuals are often called long-term nonprogressors. Among these individuals who remain clinically stable without treatment for 5–8 years, two groups can be discerned, those who have stable CD4 cell counts and those who have low CD4 cell counts but no AIDS-defining conditions (Schrager, 1994). Several factors have been found to be associated with long-term survival including host characteristics such as the presence of specific anti-HIV cytotoxic lymphocyte responses and viral characteristics such as defective genes and gene products (Kirchhoff, 1995). LTS patients tend to have consistently lower levels of HIV RNA after the period of acute infection, suggesting better control of viral replication (Vesanen, 1996). For example, viral growth in peripheral mononuclear cells taken from LTS patients was markedly less than in peripheral blood mononuclear cells taken from healthy HIV-uninfected donors (Cao, 1995).

SEX EFFECTS

Concerns about sex-based differences in the course of HIV infection were expressed early in the epidemic. Women appeared to have more rapid progression of illness than men and to present with a different constellation of opportunistic conditions than men. However, current data suggests that the incidence and distribution of HIV-related illnesses are similar by sex, with the exception of Kaposi's sarcoma, which is uncommon in women, and gynecologic manifestations of HIV. When sophisticated statistical methods were applied that controlled for the tendency of women to receive less care and to present with more advanced disease, sex-based differences in HIV disease course appeared to be eliminated. In general the predictors of the rate of HIV disease progression and survival among women are the same as in men. CD4 cell count depletion and higher HIV RNA level are strong predictors of progression and survival in women (Anastos, 1999b). Several recent reports, however, describe sex-based differences in HIV RNA level and in rate of CD4 cell depletion; women had HIV RNA levels 30–50% lower than men who had comparable CD4 cell counts (Bush, 1996; Evans, 1997; Farzadegan, 1998). Similar results occurred when analysis was restricted to seroconverters or when HIV culture was used to quantify viremia rather than RNA assays (Lyles, 1998; Sterling, 1999; Sterling, 2001). A recent epidemiologic review of 13 studies, 4 of which were longitudinal, confirmed these findings, which were unchanged after adjustment for potential confounding variables, such as age, race, mode of transmission, and antiretroviral treatment (Gandhi, 2002). Intuitively, lower levels of circulating HIV RNA, which suggest lower steady-state levels of viremia, should be associated with better outcome. However, the lower HIV RNA

level seen in women does not appear to provide benefit in terms of disease progression or survival. Viral load differences tend to dissipate several years after seroconversion and rates of progression to AIDS are similar by sex (Sterling, 1999; Sterling, 2001) when examined in men and women followed from seroconversion. [Studies have also suggested that CD4 cell counts are higher in women at onset of AIDS (Prins, 1999) but that CD4 cell depletion may occur more rapidly in women as compared to men (Anastos, 2000).]

Determination of the effect of sex on the rate of progression, time until occurrence of an AIDS-defining condition, and death is a complicated process. Unless the date of HIV infection can be established, duration of infection becomes a significant unknown factor in studies. In addition, particularly in developed countries, HIV-infected women and men differ by more than just their biologic sex. Women tend to have lower income, be un- or underinsured for health care, be members of minority ethnic groups, have been born in Africa, have used injection drugs or cocaine, or to have a sexual partner who has done so, all of which are risk factors for poor health in general. In most studies women have shorter duration of infection prior to AIDS and death than men, but these differences tend to disappear when CD4 cell count and drug use are taken into consideration (Alioum, 1998; UK Register of HIV Seroconverters Steering Committee, 1998; Pezzotti, 1999a; Santoro-Lopes, 1998). Several studies have reported an excess proportion of infections or deaths due to bacterial infection, often pneumonia (Feldman, 1999), among women compared with men (Melnick, 1994; Weisser, 1998).

Factors that influence disease progression are summarized in Table 1-6.

<i>Host Factors</i>	<i>Effect</i>	<i>Notes</i>	<i>Reference</i>
Age	Increasing age associated with more rapid progression	Increasing age at the time of infection is consistently associated with rate of progression to AIDS and survival after AIDS diagnosis	(UK, 1998; Del Amo, 1998; van Benthem, 1998)
Sex	Lower HIV RNA level among women, without progression benefit (Sterling 2001).		(Sterling, 2001)
Race	No consistent effect in various studies		(Del Amo, 1998)
Chemokine receptor and ligand mutations: CCR5, CCR2, SDF-1	Homozygous mutation protective versus primary infection, heterozygotes appear to have slower progression	These mutations are much more common among Caucasians	(Winkler, 1998; Zimmerman, 1997; Martin, 1998)

Table 1-6 Factors that influence rate of HIV-disease progression (continued)			
Host Factors	Effect	Notes	Reference
HLA Type	HLA differences associated with differing HIV RNA levels and rate of progression	Not currently of clinical utility, may provide clues to immunopathogenesis	(Saah, 1998)
HIV risk behavior	Higher CD4 cell counts in persons with a history of IDU	This effect seen in several studies	(Brettle, 1995)
Viral Factors	Effect	Notes	Reference
Clade/location	Mixed evidence, possible impact of viral subtype (or clade) on rate of progression	No clinical application currently	(Prins, 1999; (Kanki, 1999)
Mutations	Mutation of viral genes can produce attenuated viral strains that are associated with slowed disease progression	Mutation resulting in attenuation appears relatively rare.	(Deacon, 1995; Learmont, 1999)
Clinical Indicators	Effect	Notes	Reference
Oral candidiasis and hairy leukoplakia	The presence of oral candidiasis or hairy leukoplakia suggests HIV infection and progression to impaired immunological function. Oral candidiasis adds to the predictive value of HIV RNA in persons with low CD4 cell counts	Accuracy of diagnosis varies with clinician experience, but oral manifestations are particularly useful prognostic indicators in resource-poor environments and important points of HIV recognition world-wide	(Carre, 1998; Greenspan, 1996)

C. NATURAL HISTORY IN HAART ERA

INDUSTRIALIZED COUNTRIES

In countries that are able to provide highly active antiretroviral therapy (HAART), HIV-associated morbidity and mortality have declined significantly (Michaels, 1998; Miller, 1999a; Miller 1999b; Palella, 1998; Pezzotti, 1999b). (See Primary Medical Care in Chapter IV for more information.) These population findings, based on regional surveillance systems, were preceded by a multitude of clinical trials that demonstrated clinical and virologic benefits of HAART (Bartlett, 1996; Collier, 1996; Deeks, 1997; Hammer, 1997). Despite the promise and documented benefits of HAART, clinical progression continues to occur among recipients, particularly among persons who received antiretroviral

treatment before initiation of HAART (Ledergerber, 1999). Viral resistance to HAART components can occur via several mechanisms, which for the most part involve mutation of viral target proteins (Richman, 1996; Schapiro, 1999). The emergence of antiretroviral resistance is a function of several factors: prior treatment, pre-treatment level of viremia, drug levels (adherence to medication regimens, bioavailability of medications, adequate dosing), and specifics of the regimen (Gulick, 1998; Ledergerber, 1999; Shafer, 1998). Multiple daily doses, side effects, and, in some cases, dietary restrictions aggravate the problem of achieving optimal drug levels because protease inhibitor agents are relatively poorly bioavailable. Suppression of viral replication and prevention of resistance are directly related to the levels of antiretroviral medications. Persistent viral replication provides an opportunity for resistant mutations to occur, and selective pressure to support the continued presence of such mutants (Condra, 1998; Feinberg, 1997; Wong, 1997). Besides clinical treatment failure, emergence of antiretroviral resistance is now associated with transmission of resistant virus to previously uninfected persons, a finding that could portend significant limits to the effectiveness of these treatments in populations over long periods of time (Boden, 1999; Brodine, 1999; Yerly, 1999; Grant, 2002).

DEVELOPING COUNTRIES

The high cost of antiretroviral drugs and the need for clinical and laboratory services for monitoring response to and efficacy of these treatments has greatly restricted provision of HAART in the developing world. Thus the reductions in morbidity and gains in survival in HIV patients that have been demonstrated in many industrialized countries do not consistently extend to developing countries in which the majority of HIV cases occur worldwide. A consensus statement regarding provision of these therapies has been released based on meetings held in Dakar and Abidjan during 1997. The key recommendations of conference participants include: efforts must be made to expand provision of antiretroviral therapy; antiretroviral therapy only makes sense in the setting of effective AIDS control programs; funding must be sustained to provide uninterrupted treatment and continuity of care; care providers must be trained in use of the treatments and basic patient rights; resources for assessment of efficacy and tolerance must be available; sentinel monitoring for resistance pattern determination should be available; 3-drug combination regimens should be used when possible; treatment of pregnant women to prevent perinatal transmission must be a priority; and new drug development should focus on less costly medications (International AIDS Society, 1999). In December 2002, the World Health Organization launched a new initiative called "A Commitment to Action for Expanded Access to HIV/AIDS Treatment" to promote international cooperation in expanding access to HIV treatments to resource-poor settings.

IV. FUTURE ISSUES

A. GLOBAL IMPACT

The HIV/AIDS epidemic continues to spread without full control in any country. Over 58 million people have been infected worldwide. By the end of 2002, the United Nations Program on AIDS (UNAIDS) estimated that 42 million people were living with HIV, a figure that includes 19.2 million adult women (UNAIDS, 2002) (Table 1-1). In 2002 it is estimated that 5 million new HIV infections occurred, with 2 million of these occurring in women. After steady increases of the prevalence of disease among women during the 1990s, currently 46% of all persons over the age of 15 living with HIV are women. Globally, AIDS is now the fourth leading cause of mortality; 3.1 million deaths have been attributable to AIDS in 2002 alone, of which 1.2 million occurred in women. The notable improvements in AIDS mortality reported in North America and Europe, in association with the introduction of highly active combination antiretroviral therapies, do not extend to most of the world's cases, which occur in regions where this expensive type of treatment is not available.

More than 95% of HIV-infected people live in the developing world, most in Sub-Saharan Africa. Seventy percent of infections that occurred during 2002 took place in this epicenter. The region has also experienced 83% of all AIDS deaths. Unfortunately, prior projections of the epidemic course in southern Africa underestimated the incidence of infection by half (Balter, 1998). Improved data have revealed that the prevalence rates in southern Africa are staggering: 20–26% of adults (aged 15–49 yr) are infected; in some regions 20–50% of pregnant women are infected and are likely to transmit infection to one third of their offspring. In four southern African countries, HIV prevalence in adults now exceeds 30%: Botswana (38.8%), Lesotho (31%), Swaziland (33.4%), and Zimbabwe (33.7%). The declining mortality rate and population growth taking place in other regions cannot be extended to Sub-Saharan Africa, because of the extent of AIDS mortality (Bongaarts, 1998). AIDS has now surpassed malaria as the leading cause of death in this region (Balter, 1999). Life expectancy will fall from 64 to 47 yr by 2015. AIDS will cost, on an average, 17 yr of life expectancy in the 9 Sub-Saharan countries with a >10% prevalence of HIV infection among adults. The child mortality rates in this region are also elevated by AIDS; rates are approximately double that expected without the HIV epidemic (UNAIDS, 2002). Within 1 yr, 2400 Zimbabweans will succumb to AIDS per week, many in the prime of life, many leaving dependent children as orphans (up to 1 in 5 children are likely to become orphans). The former United States Surgeon General, David Satcher, notes that “the progress of decades of work immunizing children, controlling diseases, and improving nutrition is being negated by HIV” (Satcher, 1999).

In Asia, the epidemic has a mixed pattern that includes countries with slow growth in HIV prevalence, countries with some success in control efforts, and regions that appear to be experiencing explosive epidemics.

Currently 7.2 million Asians are infected with HIV. Rapidly accelerating epidemics are occurring in China, Cambodia, Vietnam, and India. For instance, the US Intelligence Council estimates that 20 to 25 million people in India will be infected by the year 2010. Whereas urban areas were initially of greatest concern in many countries, recent information has revealed very active epidemics in specific rural areas (up to 2% of the general population), which are hosts to large proportions of the region's population.

Although the outlook for AIDS in Asia is bleak, there is also cause for hope. Growth of the epidemic in the Philippines is notably slow (Jacobs, 1999). Thailand has been successful in reducing the incidence of infection in sentinel population groups (such as members of the military and pregnant women) using a combination of good surveillance, effective policy response, and implementation of educational and condom promotion programs. The incidence of HIV infection among pregnant women in Thailand has dropped from a peak of 2.4% in 1995 to 1.7% in 1997 (Phoolchareon, 1998). However, ongoing political upheaval and cuts to the national HIV prevention budget may modify this pattern of success in the near future.

In the Americas the epidemic continues to grow in specific subgroups. In the United States, as summarized earlier in this chapter, the highest incidence of infection is occurring among poor women, particularly among women of color. Increasing rates of HIV incidence in men who have sex with men have been reported from large urban centers in the US over the past several years [Chen, 2002; Koblin, 2003]. In Mexico the incidence of infection among men who have sex with men continues to be high, whereas in Brazil and the Caribbean heterosexual transmission is increasing. At surveillance sites in the Dominican Republic and Haiti the prevalence of HIV infection among pregnant women has reached 8% (UNAIDS, 2002).

Rapid spread of infection among injection drug users in Eastern Europe and Central Asia is likely to foreshadow a large number of cases among women and increasing prevalence of perinatal transmission. The introduction of HIV into these high-risk populations has been paralleled by tremendous increases in the incidence of syphilis and other sexually transmitted infections.

B. CONTAINING THE EPIDEMIC

Control of the HIV epidemic should be a worldwide health priority. Complex interactions of social, economic, and cultural factors have preceded AIDS with epidemics of other sexually transmitted infections, and now hinder control of HIV itself. Global disparities in economic status have limited efforts to control sexually transmitted infections that are much simpler to diagnose and treat than HIV. The effect of limited monetary resources is compounded by stigmatization of HIV and sexually transmitted infections that affect willingness to seek care, social support of afflicted individuals,

and health policy decision making. Traditional cultural values regarding the role of women also tend to intensify the problems. Lack of acceptance of the right of women to make decisions about childbearing and work outside the home limits options for individuals who wish to reduce the risk of infection via sexual exposures. Economic independence is a crucial factor enabling women to make decisions for themselves. The options for employment outside of sex work, for divorced or widowed women, in many societies are quite restricted. These fundamental values may directly conflict with efforts to empower women to avoid the risk of HIV and other sexually transmitted infections (Gollub, 1999).

To control the HIV epidemic, societies need to make commitments that may require an uncomfortable loss of highly valued cultural norms. Without social acceptance and encouragement, behaviorally mediated risk reduction strategies may not assume full efficacy. Vaccination is, at present, an optimal but unavailable solution. The prospects for development of an effective vaccine in the near future are not promising. Thus we have good cause to fear for the effects of HIV on women worldwide, and to increase our attention to this enormous problem as we enter the 21st century and the third decade of the HIV pandemic.

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II. APPROACH TO THE PATIENT

Jean R. Anderson, MD

The woman with HIV infection is indistinguishable from most women seen in primary care today. Women with HIV cover the spectrum of age, color, geography, education, cultural background, and income level, and have all of the health and lifestyle concerns any other woman has, in addition to those related to HIV. She is often asymptomatic, and may not know she is infected. She is frequently a mother and a caretaker for other family members. The issues most important to her will be those shaped by her personal circumstances — HIV is part of these circumstances, but her own perception of how big a part will vary from woman to woman and from time to time. The health care provider–patient relationship begins with where the individual woman is. To be most effective, it must become a partnership based on mutual trust and respect.

This chapter reviews general guidelines for interaction with all patients, highlighting points that are particularly relevant to women with HIV infection, and provides an overview of the initial and ongoing medical and psychosocial evaluation.

I. GENERAL GUIDELINES

A. COMMUNICATION

The initial interaction of patient and provider should begin with introductions and from there, it should be highlighted with clear and nonjudgmental communication. Language and terminology used should be sensitive, inoffensive, and easily understood by the patient. This will vary depending on the patient's age, cultural background, and level of education. Translation will be needed for women unable to adequately understand or express themselves in the language of the medical provider.

Whenever possible, questions should be asked in an open-ended manner, including questions about behavior and treatment adherence, and the woman should be given permission to be honest and to acknowledge failure in terms of relapse or nonadherence. She should be given adequate time and opportunity to ask questions and express concerns.

Women undergoing gynecologic exams often feel special anxiety, vulnerability, embarrassment, or simply fear of discomfort or the discovery of pathology. This anxiety and vulnerability may be particularly pronounced in women with history of sexual abuse, rates of which are increased in some populations of women living with HIV. It is important

to adequately prepare each woman verbally for the exam, and visually as well, if possible, showing her charts, models, or equipment (such as specula), which may demystify the whole process. Explain what will be done and why, as well as the degree of discomfort to be expected. During the exam tell her what you are going to do before doing it, describe what you see or feel, and reassure her when findings are normal.

Do not underestimate the importance of nonverbal communication. Facial expression and body posture are often far more articulate than words, and the most effective providers are sensitive to these cues and use their own body language with care. Maintaining frequent eye contact encourages the patient's candor, builds rapport and trust, helps allay embarrassment and fear, and conveys your interest and attention. The gynecologic exam may need to be postponed until a subsequent visit in some women in order to develop trust and to ensure there is adequate time for those with special anxiety about the exam.

Patients should be given written instructions on how to reach their providers when there are problems or questions and how to make appointments. Whenever possible, written information about HIV and its treatment, and other health issues, should be available to supplement face-to-face discussions.

B. RESPECT

Every person deserves respect. Do not be condescending, patronizing, or judgemental. Under no circumstances should a patient ever be treated as a sexual object, particularly when assessing risk behaviors or performing the pelvic exam. Although different circumstances may dictate different levels of formality, addressing the patient by her first name (without her express consent) or, especially, by terms of familiarity (e.g., "honey" or "dear") is usually inappropriate and often offensive.

Respect for the individual includes respect for her beliefs and values. The use of complementary therapies among HIV-infected individuals is common and should be respected, not ridiculed, even while discouraging potentially harmful remedies and emphasizing the proven effectiveness of currently recommended regimens.

C. SENSITIVITY

Sensitivity is essential to gather and impart important information, to foster trust, and to ensure ongoing follow-up. It requires attention to how words are used and questions are asked, and to a great deal that is unspoken. Responding to a patient's fear, anxiety, denial, or anger is inevitably part of the health provider's role and requires consideration of more than a disease process, but of a whole person and the entire context of her life. Any chronic and life-threatening disease carries with it an enormous burden of vulnerability and loss of control. Anything the

provider can do to give back some control to the woman will help ease that burden. The importance of adherence to antiretroviral regimens for optimal effectiveness and to reduce the development of drug resistance has been well established. Allowing the patient to be involved in choosing her treatment regimen when possible will allow her values and lifestyle (job schedule, etc.) to be considered and is believed to enhance adherence. Understanding her cultural background enhances your sensitivity. For example, involvement of the patient's spouse or mother during visits may be particularly important and reassuring for Hispanic women.

D. CONFIDENTIALITY

Confidentiality is a major cornerstone of the therapeutic relationship. It carries special meaning for HIV-infected individuals who have experienced discrimination in the workplace and other settings, stigmatization, and occasional abandonment by friends or family. HIV-positive women may be particularly vulnerable to these effects because of lower economic status, cultural traditions and general societal beliefs about the role of women, minority status, and child care or other caretaking responsibilities. Information about a patient's HIV status or details about her medical condition should be kept strictly confidential by providers and shared only with the express permission of the woman herself. At the same time she should be encouraged and assisted in disclosing her status to others who need to know, i.e., sexual partners and health care providers. It is important to note that all states are required to report cases of AIDS and some also have mandatory HIV reporting. The need to report and the safeguards (such as anonymous reporting in some states) which are in place should be discussed with each woman.

II. EVALUATION OF THE HIV-INFECTED WOMAN

A. TEAM APPROACH

Because of the medical and social complexity of HIV disease, a team approach to the care of women with HIV is essential and care should be both coordinated and integrated with different members of the team. Furthermore, as the time available for the primary care provider to spend with each patient becomes increasingly limited, the role of other team members in assistance with education and support becomes even more important. Expertise needed includes HIV medical expertise (including management of antiretroviral regimens), gynecology, nursing, counseling, and social service assistance/case management. Throughout the course of HIV infection, multidisciplinary medical collaborations should be available for evaluation and management of the varied medical problems associated with HIV. The use of peer

counselors may be especially helpful as women deal with negotiating safer sexual practices, contraception and other reproductive concerns, medication adherence, and other issues where similar cultural background and personal experience with HIV may facilitate education and candid discussion.

B. HIV EXPERIENCE

Care by a medical provider with HIV experience is one of the few specific provider or health care system-related factors that has been shown to prolong the life of HIV-infected individuals (Kitahata, 1996; Laine, 1998). This is increasingly important as antiretroviral treatment becomes steadily more complicated and recommendations change almost monthly. Awareness of drug interactions and strategies to avoid the development of antiretroviral resistance are but two issues that have a significant impact on both the short- and long-term health of the HIV-positive individual. Primary providers with little or no HIV experience should link with providers with HIV expertise to provide optimal care by referral or regular consultation. If a woman requires referral to an HIV expert, it is important that the primary care provider assure the woman that she is not being abandoned; furthermore, as women live longer with HIV, the primary care provider's involvement in caring for other medical conditions remains critical for the overall health of the woman. Current U.S. Public Health Service treatment guidelines, several as living documents with regular online updating, can be accessed at <http://www.aidsinfo.nih.gov>. The Health Resources and Services Administration also supports the AIDS Education and Training Centers warmline (1-800-933-3413), which is a resource for clinical providers needing expert consultation.

C. CULTURAL SETTING AND BACKGROUND

The ability to give optimal patient care depends on an understanding of where the patient "begins," her traditions and beliefs. These affect her understanding of health and disease and her acceptance of conventional medical treatment, as well as possible reliance on alternative or complementary therapies. These also affect her view of herself as a woman, her role and responsibilities in society, and issues related to childbearing and contraception. Potential barriers to care that may be encountered include difficulties in speaking, understanding, or reading English, culturally based fears and mistrust of the health care system, and undocumented immigration status. The role of cultural sensitivity in the care of HIV-positive women will be more fully addressed in Chapter VIII on Psychosocial and Cultural Considerations.

D. SPECIAL POPULATIONS

In addition to cultural setting or background, women living with HIV/AIDS may have other life circumstances that require special approaches to care and unique sensitivity. These include incarcerated women; women with alcohol or drug addiction; women with psychiatric illness; lesbians and transgendered women; women who are victims of domestic violence; and others. Certain circumstances may arouse strong emotions in care providers because of the provider's own background or beliefs. It is essential that the provider be willing and able to separate themselves from whatever personal connotations or associations they may assign to certain lifestyles or life circumstances, and provide care that is unbiased, sensitive, kind, and empathetic. If this is not possible, the patient should be referred to another provider who can give such care.

E. SPIRITUALITY

The spiritual dimension of a person's life encompasses her beliefs and values and what gives her life meaning and a sense of wholeness (Puchalski, 2000). Spirituality is important throughout life, during both health and illness, and an individual's beliefs and values can have a profound effect on the way she views illness and its treatment. Some women may view HIV as a punishment and this belief may lessen their acceptance of treatment or may put them at risk of nonadherence. Major spiritual questions that often arise during illness are:

- What gives my life meaning?
- Why is this thing happening to me?
- How will I survive this loss?
- What will happen to me when life ends?

It is important that the health care provider consider spirituality as an important component of physical, emotional, and mental health, assess the woman's beliefs, and learn what is important to her. The spiritual history should include specific questions about the patient's faith or beliefs, the importance and influence of these in her life, her involvement in a spiritual or religious community and its importance to her, and how the health care provider can help address these issues as part of her health care. Spirituality should be addressed as an ongoing issue, and referrals to ministers, priests, rabbis, other spiritual guides, or similar community resources can be an important component of care. The provider's own spiritual beliefs can be a source of strength personally and can enhance the patient-provider relationship, but should not be imposed on the patient — her own beliefs should be respected.

F. IDENTIFYING SUPPORT SYSTEMS AND DISCLOSURE

During the initial evaluation, the HIV-infected woman's social and emotional support system should be identified and reinforced, and updated information about this support system should be obtained at each visit. To whom has she disclosed her HIV status and what was the response? Many

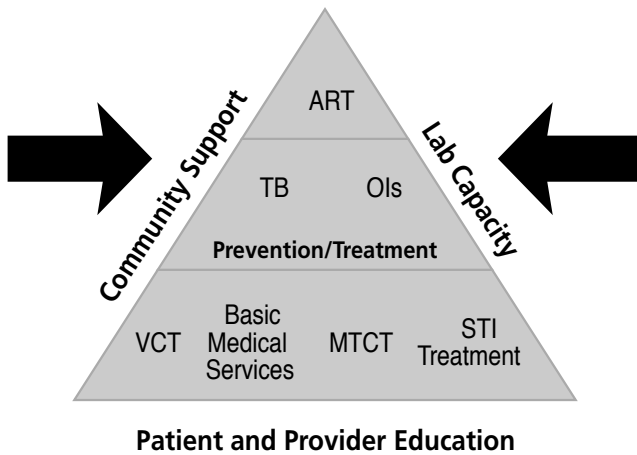
HIV-positive women experience feelings of guilt and shame, or are fearful of violence or abandonment, and so are reluctant to trust anyone with knowledge of their infection or their feelings about it. Many communities still attach enormous stigma to HIV and the individual woman's fears about ostracism and abandonment should be openly addressed. Their sense of isolation is harmful to both their physical and emotional well-being, and may result in avoiding clinic visits and nonadherence to drug therapy. The use of peer advocates or support groups may offer additional support for many women with HIV.

Special issues involve disclosure to sexual partners, children, and other health care providers. Disclosure to those individuals who may be at risk for transmission of HIV from the patient should be encouraged and barriers to disclosure, such as fear of violence, should be identified and addressed. The provider should offer assistance with disclosure when appropriate. Disclosure of a mother's HIV status to her children, who may or may not be infected themselves, is a personal decision and should be honored. The provider should discuss the various considerations in this decision and offer assistance if needed.

G. LIMITED RESOURCE SETTINGS

Currently, in limited resource settings the foundations of HIV care are services to provide basic medical care, treat sexually transmitted infections (STIs), identify HIV infection through voluntary counseling and testing (VCT), and provide primary and secondary HIV prevention services, including prevention of mother-to-child transmission. Prevention and treatment of TB and other opportunistic infections are needed as patients with HIV become more immunosuppressed, but require greater resources in terms of medications, laboratory monitoring, patient and provider education and training, and community engagement. In settings with few resources the ability to use antiretroviral drugs is still limited by issues of cost, accessibility, and health care infrastructure, but this is beginning to change with the growing global consensus that there is a moral imperative to provide these life-sustaining therapies. The Clinical Services Pyramid (Figure 2-1) (JSI/WEI Center for HIV/AIDS, 2001) illustrates the inter-relatedness of the community, laboratory infrastructure, and patient and provider education that is essential at all levels of HIV care. These components of the health care system must exist and be strengthened for both prevention and care and treatment services to succeed and use of anti-retroviral therapy (ARV) to reach those most in need.

Figure 2-1
Clinical Services Pyramid



Source: John Snow, Inc./World Education, Inc. Center for HIV/AIDS. Boston, MA 2001.

H. MEDICAL EVALUATION

INITIAL EVALUATION

The initial evaluation of an HIV-infected woman should include a comprehensive medical assessment, including a detailed HIV history: date of diagnosis, possible routes of exposure, HIV-related symptoms or opportunistic infections, previous antiretroviral or prophylactic therapies, disclosure history, and support systems (see above). Prior antiretroviral treatments should be documented in as much depth as possible, including specific medications, length of treatment, side effects or complications, response, results of resistance testing, if done, and adherence. Current employment, relationship status and child care responsibilities, insurance status, and drug and alcohol abuse must all be considered in decision making about further therapeutic regimens. A comprehensive gynecologic history should be obtained, including menstrual history, sexual practices, contraception and condom use history, previous sexually transmitted and other genital tract infections, prior abnormal Pap smears, and other gynecologic illnesses or symptoms. The initial physical examination should include a baseline pelvic exam with Pap smear and other studies as needed based on history and physical findings. Various studies (Anderson, 1989; Frankel, 1997; Minkoff, 1999) have found that both prevalence and incidence of gynecologic problems are high in HIV-infected women throughout their disease course.

This initial assessment should take place over several closely spaced visits. This will allow the woman and her clinical care team to become familiar with one another and to develop the trust and partnership that will form the foundation of her ongoing care. This is particularly important for the woman with newly diagnosed HIV, who is often struggling with the shock, fear, denial, and despair that accompany the discovery of a life-threatening illness; she should be given the opportunity to assimilate information about HIV and her own clinical status in small bites.

FOLLOW-UP VISITS

Follow-up visits should be scheduled at intervals based on the woman's HIV clinical, immunologic, and virologic status; other medical or comorbid conditions, including substance abuse or mental illness; and other individual needs for counseling or psychosocial support. CD4 cell counts and HIV-RNA levels should be monitored at 3–4-month intervals and more often if results suggest inadequate or failing therapeutic response, or with development of clinical signs or symptoms. At each interval visit the woman should be questioned about new symptoms, side effects, adherence with medications, and psychosocial issues and concerns. Last menstrual period should be documented, as well as current sexual activity and interval use of condoms and contraception. Risk behaviors should be reassessed at regular intervals because sexual and drug-use patterns may vary, and safe practices should be reinforced through positive prevention counseling. (CDC, 2001). Pelvic examination should be repeated at least annually, and more frequently with history of abnormal Pap smears, unsafe sexual practices, exposure to STIs, or development of gynecologic signs or symptoms. STI screening should be performed when the patient reports recent or ongoing high-risk sexual activity. Pelvic examination every 6 months may be considered in women with clinically advanced disease, low CD4 cell counts, and/or high viral loads because their incidence of certain HIV-related gynecologic problems may be increased. The medical and gynecologic evaluation of the HIV-infected woman is described in more detail in Chapter IV on Primary Medical Care and Chapter VI on Gynecologic Problems.

I. FAMILY-CENTERED CARE

HIV is a disease of families. Not only may the woman be infected, but her husband or partner and children may also be living with HIV. Even when other family members are not infected, they are deeply affected by the presence of chronic and life-threatening illness within the family, possible fears of transmission of infection, and often stigma. The HIV-positive woman may neglect her own care while providing care to sick family members or to her children. The provider should encourage all HIV-positive family members to receive appropriate care and should help enlist family support for the infected woman by providing information

and education about HIV and updates on the woman's condition (with her permission) and by assistance in identifying support systems for the entire family.

J. EDUCATION AND COUNSELING

Despite the dramatic advances in therapy, decreases in mortality and hospitalizations, and overall improvement in quality of life, HIV remains a life-threatening and often life-ending disease with no cure on the horizon. For women it is often enveloped by poverty; isolation; person, partner, or community drug use; and the competing priorities of children and family. Mental illness, substance abuse, or domestic violence may complicate the clinical picture. Not dissimilar to diabetes, modern management of HIV disease requires a basic understanding of HIV infection and an intense personal involvement in one's own care — taking multiple medications on fairly strict schedules, food requirements, recognizing and managing side effects, etc. Unlike most other chronic medical conditions, HIV-positive individuals remain infectious for the rest of their lives and must learn about and become empowered to change behaviors that put themselves or others at risk. This learning process is ongoing and lifelong and requires continuous reinforcement. It should aim to correct misconceptions and myths and should recognize that relapses in unsafe sexual or drug-using behaviors and at least episodic problems with adherence are the norm rather than the exception. Peer advocates (HIV-affected women from similar cultural backgrounds) can be effective members of the clinical team to help educate patients, advocate for them, and provide counseling as needed.

K. ACCESS TO CARE

A recent report from the HIV Cost and Services Utilization Study, using a national sample representative of the adult U.S. population infected with HIV and in ongoing care, found significant variations in service utilization and receipt of medication. Women were more likely than men to use the Emergency Department and to be hospitalized and were less likely to have received antiretroviral therapy including a protease inhibitor or nonnucleoside reverse transcriptase inhibitor by early 1998. Other predictors for poor access to care included racial or ethnic minority status and lack of insurance (Shapiro, 1999). If women with HIV are to benefit equally from the advances in understanding and management of this infection, attention must be paid at the individual, community, and societal levels to the factors hindering equal access to care: stigma and isolation, lack of empowerment, competing concerns (e.g., food, housing, care for other family members), child care, transportation, insurance, violence against women, and many more.

III. THE CHRONIC CARE MODEL

The Chronic Care Model (<http://www.improvingchroniccare.org>) was developed and refined by experts in chronic illness management to encourage high quality chronic disease care. It can be applied to a number of chronic illnesses, including HIV/AIDS. The Model identifies the key elements in the system of care that can help patients be healthier, providers more satisfied and that can help reduce costs of care throughout the system. These elements include (Figure 2-2):

A. COMMUNITY-RESOURCES AND POLICIES:

Community programs can support and extend the care for individuals with HIV/AIDS. They can provide resources and support, promote better self-care, and play a broader role in advocacy for patients and for health policies that can better support the lives of individuals with HIV/AIDS.

B. HEALTH SYSTEM-ORGANIZATION OF HEALTH CARE

The health system caring for patients with HIV/AIDS should be organized in such a way that there is flexibility and ability to change, that there are appropriate resources and support for providers and patients, and that there is an emphasis on prevention and maintenance, rather than crisis-oriented care.

C. DECISION SUPPORT

Treatment decisions should be founded on evidence-based guidelines. Clinical providers for individuals with HIV/AIDS need ongoing education and training to remain current, because of the rapid changes in knowledge and practice. Primary care providers for patients also should be kept informed and involved when patients are referred for specialist care.

D. DELIVERY SYSTEM DESIGN

The health care delivery system should be proactive and should focus on keeping patients as healthy as possible. This requires determining what care is needed, clear delineation of roles different members of the team play in care, ensuring that team members have current information about patient status, and facilitating follow-up as a part of standard care.

E. SELF-MANAGEMENT SUPPORT

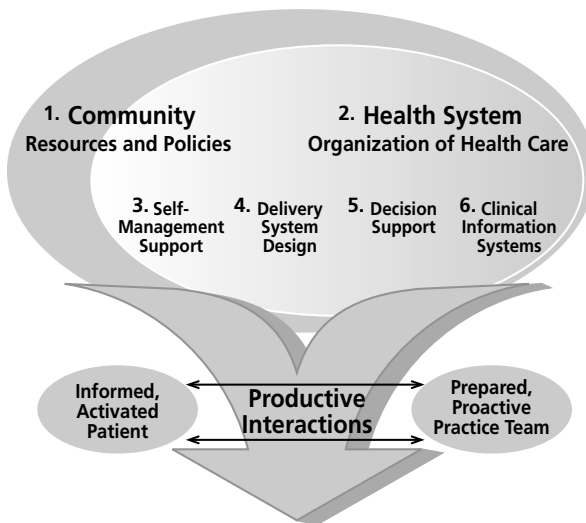
Successful HIV care depends on a well-informed and motivated patient. Although care providers are responsible for appropriate prescribing of antiretroviral drugs and can facilitate adherence, ultimately the woman herself must take the medications properly and return for regular care and follow-up. It is essential that patients be given the tools to better care for themselves, including information about how to take medications, recognition of adverse effects, and tools to minimize or prevent side effects.

Patients should have a central role in making decisions about their care and in problem-solving; this will foster a sense of collaboration, trust, and responsibility. Patient involvement in self-management of other chronic diseases has been shown to reduce emergency and other outpatient visits, decrease health distress, and improve self-efficacy (Bodenheimer, 2002)

F. CLINICAL INFORMATION SYSTEMS

Information systems are essential to track individual patients and populations of patients with HIV/AIDS, and clinical information technology can help prevent serious errors in care, such as medication errors (Bates, et al, 1998). A meta-analysis of published reports of interventions used in management of patients with other chronic illnesses found that education of providers and feedback and reminders to providers significantly increased provider adherence to treatment guidelines and improved disease control (Weingarten, 2002).

Figure 2-2
Overview of the Chronic Care Model



Functional and Clinical Outcomes

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III. PREVENTION OF HIV

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I. INTRODUCTION

Two decades into the human immunodeficiency virus (HIV) epidemic, scientists and clinicians on both the biomedical and behavioral fronts continue to be faced with daunting challenges. While scientists have made progress in vaccine development and in understanding the complexities of the viral-host immune response, highly effective, widely available biomedical preventive measures are still in developmental stages. Thus, there remains a critical need to identify and implement effective behavioral strategies and to more effectively address the complex forces that fuel the heterosexual HIV epidemic, including poverty, migration of populations, social and cultural disruption, gender discrimination, and stigma about sexually transmitted infections (STIs) and HIV.

Many of the measures that women can take to prevent acquisition of STIs and HIV have been known for the past decade: abstaining from intercourse, selecting low-risk partners, negotiating partner monogamy, and male condom use. However, the high rates of incident HIV infections among women in many parts of the world and the rising incidence among women in the United States are a testament to prevention barriers facing women in heterosexual relationships. Women are often unaware of their partners' infection status or level of risk and, in many cases, are unable to insist on abstinence or to negotiate sexual safety with their partners. Importantly, in many parts of the world, prevalence figures suggest that girls are exposed to HIV earlier than boys (UNAIDS/WHO, 2003). Young girls are often emotionally immature, economically disadvantaged, and socially inexperienced, making them vulnerable to sexual relationships that may expose them to HIV and to other sexually transmitted infections that can potentiate HIV transmission. Women in economically disadvantaged nations and in socially marginalized groups in the industrialized world may have less access to medical care for treatment of STIs and contraception, and may also not feel empowered to negotiate for condom use, abstinence, or monogamy within their sexual relationships. Thus, culturally sensitive interventions that target both behavioral and biologic risk factors for HIV are necessary to reduce transmission to women and girls.

This *Guide* is about the care of women who are already HIV-infected, and therefore the focus of this chapter is not on primary prevention strategies such as abstinence aimed at women who are not infected. The vast majority of women with HIV have become HIV-positive through sexual activity, and require assistance in behavioral strategies to negotiate safer sex within existing relationships or, a much more challenging objective in this case, to negotiate abstinence.

This chapter discusses issues regarding HIV testing, including risk assessment and pre- and posttest counseling, and then reviews models of behavioral intervention strategies for HIV prevention, published behavioral intervention trials, and some practical aspects of counseling women on how to reduce sexual risk behavior. Biologic cofactors that may increase risk and thus may be targets for intervention are briefly examined. Finally, new approaches to HIV and STI prevention, including microbicides, vaccines, and postexposure antiviral medication are reviewed. The important issues of substance abuse and strategies for changing drug use behavior are not addressed in this chapter, but are reviewed extensively in Chapter X.

II. RISK ASSESSMENT FOR STI/HIV INFECTIONS

Unprotected sex increases a woman's risk of HIV infection, based in large part on her partner(s)' risk behaviors.

Just as most people would find celibacy an impractical means of reducing sexual risk, many individuals may find changing other specific sex behaviors difficult or unacceptable. Although some sexual behaviors may be less "mainstream" than others, it is important to remember that participation in such behaviors does not necessarily reflect a lack of morals or willpower, but rather different perceptions of enjoyable and common sex behavior. Furthermore, sexually active women may not realize that they are practicing behaviors that put them at risk for HIV infection. Because of the heterogeneous nature of sexual practices, individual risk assessment is crucial in any attempt to reduce risk of HIV by changing sex behavior. In pre- and posttest HIV counseling, individual risk assessment provides a framework in which to conduct further behavioral intervention and identifies patients appropriate for HIV and STI screening. Guidelines for physicians and other care practitioners recommend that HIV and STI risk assessment be conducted for every patient (Phillips, 2003); however, most primary care physicians do not routinely incorporate questions about sexual behavior into routine patient care.

Clinician discomfort and fear of embarrassing or offending the patient when discussing sex are impediments to conducting effective risk assessment.

In such circumstances, the clinician may find it more acceptable to "frame" the discussion by explaining the routine nature of such questions, thus demonstrating that the patient is not singled out because of mannerisms, appearance, or ethnicity. One approach may be to emphasize the importance of this information for patient care: "To be able to provide the best care for you today, we need to understand your risk for certain infections by talking about your sexual practices." Another may be to allude to the universality of many concerns: "Many women find it difficult to get their men to wear condoms; has this been a problem for you?" (Curtis, 1999).

As with any type of medical history taking, open-ended questions probably serve as the most effective means of eliciting information when taking a sexual history.

Language should be clear, easy to understand, nonoffensive, and nonjudgmental. Many clinicians prefer closed-ended questions when they are functioning under time pressures. In such cases, a questionnaire that the patient completes in the waiting room may be a preferred tool. Whenever possible, however, clinician-patient interaction serves as the ideal forum for sexual risk assessment.

Many clinicians are not familiar with risk factors for HIV infection specifically relevant to women.

Risk factors for HIV infection in male homosexuals and intravenous drug users have been well described. In contrast, factors that may increase risk in women, such as a history of unwanted pregnancy, or an incarcerated sex partner, are less specific and less well recognized. Although some risk factors for women can be derived from epidemiologic studies, such as history of “high-risk STIs” (i.e., gonorrhea or syphilis), crack cocaine use, and injection drug use, some women are at risk through monogamous partner relationships with their HIV-infected husbands. A rare case of female-to-female sexual transmission of HIV, possibly through sharing sex toys, was recently reported (Kwakwa, 2003). Therefore, identifying risk behaviors in women requires a careful and skilled clinician. In many cases, a low threshold for recommending HIV testing is necessary. Important risk topic areas to cover are listed in Table 3-1.

Table 3-1: Risk Assessment for STI/HIV for Women
Number of sex partners in the previous year _____, and lifetime: _____
Sex with: <input type="checkbox"/> men, <input type="checkbox"/> women, <input type="checkbox"/> or both
Type of sexual practices: <input type="checkbox"/> vaginal intercourse <input type="checkbox"/> anal intercourse <input type="checkbox"/> oral sex <input type="checkbox"/> use of sex toys <input type="checkbox"/> other (specify) _____
History of abnormal Pap smear: <input type="checkbox"/> yes, or <input type="checkbox"/> no
History of sexually transmitted infection: <input type="checkbox"/> yes, or <input type="checkbox"/> no
History of using: <input type="checkbox"/> intravenous drugs, <input type="checkbox"/> sharing needles, <input type="checkbox"/> use of crystal methamphetamines, or <input type="checkbox"/> crack cocaine
History of a sex partner who was incarcerated: <input type="checkbox"/> yes, or <input type="checkbox"/> no
History of alcohol or drug abuse: <input type="checkbox"/> yes, or <input type="checkbox"/> no
Does she feel that her sex partner(s) puts her at risk? <input type="checkbox"/> yes, or <input type="checkbox"/> no
How does the woman protect herself from HIV/AIDS? _____
How does the woman protect herself from unplanned pregnancy? _____
Is there anything else that she feels she should mention to ensure good medical care? _____

III. HIV COUNSELING AND TESTING

There are clear benefits to HIV testing.

For a woman, knowledge of her serostatus is essential to prevent vertical transmission to her infant and horizontal transmission to her partners, and to seek medical care for herself. With the proven efficacy of several peri-partum antiviral regimens to reduce vertical transmission rates and medical therapy to improve survival among HIV-infected individuals, including in resource-poor settings, there are even stronger reasons to urge sexually active women to seek HIV testing for themselves and their partners. Unfortunately, most women at risk for HIV infection remain unaware of their HIV status (Kitahata, 2002).

Routine provision of HIV testing may be most effective.

Selective screening strategies have targeted intravenous drug users, STI clinic attendees, and economically disadvantaged individuals (Phillips, 2003). The advantage of selective screening is cost-savings, particularly in low-prevalence parts of the world. Many experts favor a universal recommendation for HIV screening, at least for pregnant women. The advantage of universal screening is not only increased detection rates, but perhaps also increased test acceptance. Screening using an opt-out approach, under which testing is done routinely unless actively declined, significantly increases HIV testing rates among pregnant women (Stringer, 2001). Opt-out testing at antenatal clinics in Africa is being promoted as a key strategy to increase uptake of interventions, such as short-course antiretrovirals, for prevention of mother-to-child HIV transmission (Bassett, 2002). In the United States, the Centers for Disease Control and Prevention (CDC) has recently recommended that HIV-1 screening of all pregnant women become part of routine care (CDC, 2003). Universal screening removes the stigma of HIV testing by eliminating any targeted testing based on sexual orientation, socioeconomic status, or race. When HIV testing is stigmatized, women in high-risk groups may be reluctant to identify themselves. Thus, for the general population, current U.S. guidelines recommend routine offering of voluntary testing in all settings where HIV prevalence is >1% or where there is increased risk of acquiring or transmitting HIV, regardless of setting prevalence (CDC, 2003). Offering routine HIV testing is cost-effective under certain circumstances and could lead to earlier identification of infected individuals and linkage to HIV treatment. However, routine offering of HIV testing in high-prevalence areas to hospitalized patients and those presenting to emergency care settings has not been widely adopted. On the other hand, the cost of universal HIV testing is significantly higher than voluntary, selective screening strategies, and there are both practical and ethical issues in implementing universal screening, even in perinatal care.

A. PRE- AND POSTTEST HIV COUNSELING

The counseling that occurs before and after HIV testing has three principal goals (Celum, 1999):

1. to provide counseling about risk reduction for HIV-negative persons,
2. to identify HIV-infected persons for clinical interventions, and
3. to provide counseling to HIV-positive persons about potential transmission.

The components of HIV pretest and posttest counseling are outlined in Table 3-2

Pretest counseling should include discussion about the basic facts of HIV infection, the acquired immunodeficiency syndrome (AIDS), and HIV testing. However, in most situations, emphasis should be placed less on didactic material than on individualized discussion of risk and risk-reduction unless the patient has very limited understanding of HIV/AIDS. Posttest counseling should reinforce these concepts in the context of the test result. Regardless of the test result, resources and referrals for the patient and/or her partner should be provided. For patients at risk for domestic violence, the potential domestic turmoil that a positive test result can elicit should be emphasized. This issue will be further addressed in the section on ethnic and gender considerations.

Make use of an opportunity to provide client-centered counseling

Any time spent with the patient, however short, provides an opportunity for the clinician to conduct individualized counseling about recognizing and reducing high-risk sexual behaviors. Patients who present with concerns or symptoms of STIs are usually also at risk or concerned about risk for STI, including HIV. In the context of a negative HIV test, the posttest counseling session provides a valuable opportunity to develop a risk-reduction plan in a woman who has identified herself as someone who is concerned about risk and may be at high risk. Many clinicians may find it effective to deliver the negative test result in the context of a “second chance,” thus emphasizing that current behaviors are unsafe and can be changed.

Table 3-2: Components of HIV Pre- and Posttest Counseling

<i>Pretest Counseling</i>
<ul style="list-style-type: none"> • Assess understanding of HIV transmission and natural history; psychological stability; social support; impact of a positive result
<ul style="list-style-type: none"> • Discuss likelihood and meaning of positive, negative, and indeterminate test results*
<ul style="list-style-type: none"> • Discuss provisions made at the site for confidentiality. (In the United States, some states have name-based reporting of HIV, and clients should be informed about the availability of anonymous testing)
<ul style="list-style-type: none"> • Ensure that follow-up is available
<ul style="list-style-type: none"> • Emphasize the importance of obtaining test results
<ul style="list-style-type: none"> • Discuss risk-reduction plan and referral to other services
<ul style="list-style-type: none"> • Obtain informed consent for HIV antibody testing
<p>* For patients who identify a high-risk exposure, the clinician should explain that tests are generally positive within 3 mo of exposure. Therefore, repeat testing should be recommended 3 mo after exposure, if the initial test is negative.</p>
<i>Posttest Counseling</i>
<ul style="list-style-type: none"> • Ensure that the client is ready to receive results
<ul style="list-style-type: none"> • Disclose and interpret results: <ul style="list-style-type: none"> <i>For HIV-seronegative persons:</i> <ul style="list-style-type: none"> - Readdress and reinforce risk reduction plan - Discuss the need for repeat testing for those with recent (<3 mo) exposure or ongoing risk behavior <i>For persons with indeterminate HIV-1 Western blots:</i> <ul style="list-style-type: none"> - Discuss prevalence of and risk factors for indeterminate test results - For persons with p24 bands and persons with high-risk behavior: <ul style="list-style-type: none"> • Discuss the possibility of acute HIV infection and need for repeat testing in 1, 3, and 6 mo • Perform HIV polymerase chain reaction, if available, to confirm infection status and determine viral load <i>For HIV-seropositive persons:</i> <ul style="list-style-type: none"> - Differentiate between being HIV-infected and having AIDS - Emphasize the importance of early clinical intervention, if available, and make medical referral - Counsel patient that he/she is HIV-positive and discuss ways to avoid transmitting HIV to others - Assess need for psychological support and provide referral, if appropriate and if available - Assess possibility of domestic violence and provide referral, if necessary and if available - Ensure that the patient has follow-up

B. RAPID TESTS

Rapid tests are a good alternative in many settings.

After all, HIV testing is only of value if patients return for their test results and posttest counseling. Many testing programs in the United States use an initial enzyme-linked immunosorbent assay (ELISA) with confirmation through Western blot. In less developed areas, two ELISAs run in sequence are often used. With both protocols, the patient is required to return to the clinic 1–2 wk after testing for results. In 1995, 25% of persons testing HIV-positive and 33% of persons testing HIV-negative at publicly funded HIV testing sites in the United States failed to return for test results (CDC, 1998a). Similar low return rates have been described in many developing-country settings.

Rapid testing for HIV would result in substantial cost savings and circumvent patient no-show rates (Spielberg, 1996). A number of rapid tests, defined as requiring less than 2 hr, are available. The World Health Organization (WHO) has developed alternative testing strategies using sequential rapid tests, thus obviating the need for expensive and delayed confirmatory testing (UNAIDS, 2002). Some tests require as little as 5 min, use blood obtained from a finger-stick, and can be performed easily by clinical staff using only minimal laboratory facilities. Most tests are 95–100% sensitive and specific. One rapid test (OraQuick Rapid HIV-1 Antibody Test) has been approved by the FDA with a waiver from the Clinical Laboratory Improvements Amendments (CLIA) regulations, allowing it to be used outside of traditional laboratory settings. Thus, HIV rapid testing is expected to become more feasible and widely-adopted in the United States. The CDC is currently conducting demonstration projects to promote the use of rapid testing outside of usual clinical settings, including in correctional facilities, non-medical venues, and during labor and delivery for women who did not receive antenatal testing (CDC, 2003). The CDC has published recommendations that clients receive the results of rapid HIV tests on the day of testing. Patients who test negative can be given a definitive negative result without a return visit. For patients who test positive, it is recommended that they be informed that their screening test was positive, and that they should return to receive a confirmed test result.

In the United States, rapid testing is most appropriate in areas of high prevalence where clinic return rates are low (STI clinics, emergency departments) or an HIV diagnosis will influence immediate management decisions (postexposure prophylaxis, unknown HIV status in a pregnant woman presenting to Labor & Delivery). Rapid and other alternative testing methods (e.g., home testing, oral fluid and urine testing, telephone collection of test results) are being explored as strategies to increase HIV testing among high-risk populations. In many ways, rapid

testing is most appropriate in economically disadvantaged countries where HIV seroprevalence is high, laboratory resources are limited, and patient travel to and from clinic may be very inconvenient. The use of rapid tests has increased substantially over the past few years and has become a key component of HIV prevention and treatment programs in many developing countries (e.g., initiatives for prevention of mother-to-child transmission and general population voluntary counseling and testing).

Rapid tests may result in unwanted test results

Some have expressed concern that rapid HIV testing may not offer patients sufficient time to digest counseling information and to decide whether they truly desire to know their HIV status. In some settings, women in particular may find it difficult to decline unwanted HIV testing, in part due to cultural injunctions against refusing a test offered by a health care worker perceived as an authority figure. Thus, the principal components of HIV testing must remain the same for rapid testing as for traditional screening programs. Regardless of how HIV testing is done, patients must be informed of the nature of the test and the risks and benefits of knowing their HIV status. They should consent voluntarily to the testing procedures, be informed that they can refuse testing, and have their confidentiality strictly preserved. Finally, they should be told that refusal of testing will not lead to denial of usual clinical services.

C. IMPACT OF HIV COUNSELING AND TESTING ON PREVENTION

What is the evidence that HIV testing may change risk behavior? The literature in this area is difficult to synthesize, largely because of evolving counseling practices, varying lengths of follow-up, and lack of randomized trials with well-defined endpoints. Older studies from the United States did not demonstrate a substantial effect. In one observational study from Baltimore from the early 1990s, both HIV-positive and HIV-negative patients had high rates of STIs 6–23 mo after receiving HIV test results and posttest counseling (Zenilman, 1992). A second study found HIV testing was associated with a moderate decrease in gonorrhea incidence among patients in Miami who tested HIV-positive but with a moderate increase among those testing HIV-negative (Otten, 1993). These findings suggest that learning of a positive HIV test result may have a modest effect on sexual risk-taking. The studies also raise important concerns about the effectiveness of HIV testing and counseling in impacting sexual risk-taking, and about potential disinhibition after receiving a negative test result. However, guidelines and training for HIV-1 counseling have improved over the past decade, and thus it is difficult to know the impact that current counseling procedures may have on subsequent sexual behavior.

A more recent large study conducted in Kenya, Tanzania, and Trinidad randomly assigned individuals and couples to either HIV voluntary counseling and testing or basic health information (Voluntary HIV-1

Counseling and Testing Efficacy Study Group, 2000). This trial found that counseling and testing resulted in a significant decline in unprotected intercourse with non-primary partners by both male and female study participants. Newly-identified HIV-infected participants were more likely than HIV-uninfected participants to reduce episodes of unprotected intercourse. Among couples, unprotected intercourse reduced more in those in which one or both members were diagnosed with HIV compared with those in which both members were HIV-uninfected.

Other studies of HIV counseling and testing among couples have demonstrated similarly encouraging results. Among 149 HIV-discordant couples in Zaire, HIV counseling and testing was followed by a dramatic increase in consistent condom use (from <5% to >70%) and a low rate of HIV transmission (3% after 100 person-years of follow-up) (Kamenga, 1991). A recent study of 963 discordant couples from Zambia reported a sustained increase in condom use from <3% to >80% after joint voluntary counseling and testing (Allen, 2003). The authors concluded that couples' counseling and testing should be a top HIV prevention priority. Overall, modeling studies suggest that voluntary counseling and testing is a highly cost-effective HIV prevention strategy (Creese, 2002).

IV. BEHAVIORAL INTERVENTION MODELS

Over the past 20 years, there has been a growing appreciation that behavioral interventions should be based on deterministic models of sexual behavior. These models provide us with guidance on the determinants of high risk sexual behavior, and allow us to develop interventions and measurements for those key determinants. A number of behavioral models are used in HIV/STI prevention research and interventions, including those listed below.

- **The Health Belief Model, the Social Cognitive Theory, the Theory of Reasoned Action, and the Stages of Change Theory** (Bandura, 1996; Fishbein, 1999) have been developed to explain determinants of human behavior change. These models all have in common the theory that perceived risks and benefits of behavioral change predict the likelihood of behavior change and can guide the approach to behavioral interventions. These models are described and contrasted in Table 3-3.
- **The AIDS Risk Reduction Model** integrates the concepts of the above-mentioned theoretical models into a framework providing information, motivation, and behavioral skills specific to AIDS risk reduction (Catania, 1990; Fisher, 1992). With this model, counselors help patients to identify sexual behaviors that put them at risk for acquiring HIV, formulate plans to change these behaviors, and take action to realize these plans.

Table 3-3: Behavioral Theories Relevant to Sexual Risk Reduction Counseling	
<i>Health Belief Model</i>	
Adopting health-protective behavior depends on a person feeling personally threatened by a disease with serious negative consequences, and feeling that the benefits of making the behavior change will outweigh the costs of not changing.	
<i>Social Cognitive Theory</i>	
Adopting health-protective behavior depends on a person believing that he or she has the ability to change (self-efficacy) and that the benefits of making the behavior change will outweigh the costs of not changing.	
<i>Theory of Reasoned Action</i>	
Adopting health-protective behavior depends on a person's strength of intention to perform that behavior. The strength of the intention is based on the person's overall positive or negative attitude toward performing the behavior, based on perceived outcomes, as well as whether the person believes that important family members and friends believe that he or she should alter behavior.	
<i>Stages of Change Theory</i>	
Adoption of new behavior involves five distinct stages:	
1. <i>Precontemplative</i>	<i>Does not see need to do target behavior</i>
2. <i>Contemplative</i>	<i>Sees a need to do target behavior, but is ambivalent</i>
3. <i>Ready for Action</i>	<i>Ready to do target behavior soon, or has already started</i>
4. <i>Action</i>	<i>Doing target behavior consistently 3–6 mo</i>
5. <i>Maintenance</i>	<i>Doing target behavior consistently >6 mo</i>

- **The Stage of Change (SOC) behavioral theory** proposes that the process of behavioral change occurs along a continuum of five fundamental stages (Table 3-3) (Coury-Doniger, 1999). The stages can be used to tailor the counselor's approach to an individual by assessing where an individual is on that continuum for a specific behavior. For example, an individual with multiple partners who sees no need to use condoms consistently would be in the Precontemplative stage. In contrast, a woman in a mutually monogamous relationship who sees the need to know her partner's HIV status, but fears angering her partner by this request, would be in the Action stage. A counselor's approach to these two patients would be different. For the first individual, counseling directed at recognition of risk would be most appropriate, whereas for the second woman, communication and goal-setting skills should be emphasized. Importantly, individuals do not always move forward linearly along this continuum, but may "relapse" and move forward and backward between the stages. At the Rochester STI clinic, clinicians who have formally incorporated the SOC model in their risk assessment and counseling of STI clients report a high degree of satisfaction with the SOC model as a diagnostic tool that guides their specific counseling interventions with a client (Coury-Doniger, 1999).

V. PUBLISHED BEHAVIORAL INTERVENTION TRIALS

Several well-designed randomized controlled trials have been conducted to assess the efficacy of various behavioral intervention strategies, and most conclude that such interventions result in decreased sexual risk-taking (primarily unprotected sex) and, in some studies, STI and HIV incidence. In contrast to didactic education sessions, behavioral interventions focus on recognizing risk and formulating effective risk reduction strategies. Knowledge alone does not motivate change. To translate this concept into an issue many of us have experienced, consider the issue of weight reduction and diet modification. Despite widespread knowledge about the adverse health effects of eating fatty foods, adhering to a diet is notoriously difficult. Similarly, knowledge about STIs and HIV is not enough to implement change in sexual behavior.

Randomized controlled studies using STI incidence as an outcome provide objective evidence of health-related endpoints, thus representing the most valid measurement of an intervention's efficacy. Five such trials, all conducted in the United States, examined the efficacy of behavioral intervention strategies using STI incidence as an outcome measure (Table 3-4). All five studies used similar intervention approaches incorporating education, motivation, and development of a concrete plan for behavioral change. Sessions were structured as individual or group counseling.

Behavioral interventions can lead to lower rates of STI acquisition

As shown in Table 3-4, results of these studies varied. The discrepancy in reported outcomes may be related to several factors. The sample sizes of the National Institute of Mental Health (NIMH) study (NIMH, 1998) and CDC-funded Project RESPECT (Kamb, 1998) study were large, providing excellent ability to detect even a modest effect of the intervention. In the San Francisco study (Boyer, 1997), for example, the sample size provided only 45% power to detect the approximate 20% change in STI incidence detected in the RESPECT study. However, an appreciable effect of the intervention was detected in the San Antonio study (Shain, 1999) despite a sample size of only 617. In this study, ethnic-specific tools and counselors were used, thus perhaps enhancing the effect of the intervention. Indeed, in this study, a 49% decreased STI incidence was detected after 12 mo, compared with a 20% decrease reported in the RESPECT study. Finally, adherence to behavioral session schedule and follow-up with STI exam are crucial elements affecting study validity. The NIMH, RESPECT, and San Antonio studies all reported higher adherence rates and follow-up rates compared to the Houston (Branson, 1998) and San Antonio studies, thus providing increased ability to measure the effectiveness of the intervention.

Table 3-4: Results of Large Randomized Trials of Behavioral Interventions Conducted in the United States						
	National Institute of Mental Health (Multicenter)	Project RESPECT Study Group (Multicenter)	University of Texas (San Antonio)	Centers for Disease Control and Prevention (Houston)	University of California (San Francisco)	
Population	Inner city clinics in multiple cities/men and women screened with questionnaire (74% African American, 25% Hispanic; 58% female)	Inner city clinics in multiple cities/men and women screened with questionnaire (59% African American, 19% Hispanic; 43% female)	Public health clinics/women with norviral STI (69% Mexican American, 30% African American, 100% female)	Medical Center STI clinic (90% African American, 44% female)	STI clinic/men and women (46% African American, 16% Hispanic, 37% female)	
Sample size	3706	5758	617	964	399	
Intervention type	Small group	Individual	Small group	Small group	Individual	
Number of sessions	7 biweekly sessions of 90–120 min each	2 or 4 weekly sessions of 60 min each	3 weekly sessions of 3–4 hr each	4 biweekly sessions and a booster group session at 2 mo	4 weekly sessions of 60 min each	
Control group	1 hr didactic AIDS education	2 didactic 5-min AIDS education sessions	1 standard 15-min session	2 standard 20-min sessions	1 standard 15-min session	
Adherence rates	63% attended ≥ 6 sessions	82% attended all sessions	75% attended all sessions	47% attended ≥ 4 sessions	48% attended all sessions	
Number of STI exams	1 (at 12 mo)	2–4 (at 3, 6, 9, 12 mo, 3 and 9 mo optional)	2 (at 6 and 12 mo)	4 (at 2, 6, 9, and 12 mo)	2 (at 3 and 5 mo)	
Follow-up rates	82%	81% at least 1, 51% all 4	90%	72% at least 1 visit, 47% all 4	72% at least 1 visit, 52% both	
Findings in intervention group compared to control group	<ul style="list-style-type: none"> Improved self-reported prevention efforts Fewer STI symptoms No difference in STI incidence 12 mo after intervention, determined by chart review, STI exam 	<ul style="list-style-type: none"> 30% lower STI incidence after 6 mo 20% lower STI incidence after 12 mo 2 session and 4 session interventions had equivalent results 	<ul style="list-style-type: none"> 34% lower STI incidence after 6 mo 49% lower STI incidence after 12 mo 	<ul style="list-style-type: none"> Self-reported risky sexual behavior and incidence of STIs were similar between intervention and control groups 	<ul style="list-style-type: none"> No change in STI incidence Improved self-reported prevention efforts in men No improvement in self-reported prevention efforts in women 	
Cited behavioral intervention models	<ul style="list-style-type: none"> Risk reduction counseling, model not specified 	<ul style="list-style-type: none"> Theory of Reasoned Action Social Cognitive Theory 	<ul style="list-style-type: none"> AIDS Risk Reduction Model 	<ul style="list-style-type: none"> AIDS Risk Reduction Model 	<ul style="list-style-type: none"> AIDS Risk Reduction Model 	

Even brief (two 20-min) counseling sessions can result in lower STI rates and can be incorporated into clinical settings

The 20-min Project RESPECT counseling sessions may be most applicable to busy practitioners interested in conducting effective behavioral counseling. This study demonstrated that individual “brief” counseling, involving two sessions of 20 min each, was as effective in reducing STI incidence as four “enhanced” 1-hr sessions. Both intervention arms, the two 20-min and four 1-hr counseling sessions, were superior to a didactic message. The first of the two brief 20-min sessions focused on recognizing HIV risk and barriers to risk reduction. After working with the client to agree on an achievable risk reduction plan, the counselors concluded the sessions by identifying a small risk reduction step that could be achieved before the second session. At the second session, counselors reviewed progress and barriers in achieving the behavioral goal, and helped to clients to arrive at a long-term risk reduction plan. Although the four 1-hr “enhanced” sessions also included recognizing risk and formulating risk reduction plans, more energy was focused on key theoretical behavioral elements such as self-efficacy, attitudes, and social norms underlying risk behavior. The fact that the brief two 20-min counseling sessions demonstrated equivalent efficacy to 4 hr of counseling is encouraging to practitioners who would like to integrate effective HIV counseling into busy clinical settings. A follow-up study of the efficacy of a brief counseling intervention in the context of rapid HIV testing is being conducted by the CDC (Respect II) which will be relevant given the increased use of rapid testing both in the U.S. and in resource-poor settings.

Behavioral intervention studies in resource-poor settings

Several early studies among female commercial sex workers in developing country-settings demonstrated that condom promotion activities were accompanied by reduced high-risk sexual activity and a decrease in HIV and STI incidence. More recently, sustained reductions in HIV incidence among sex workers, paralleled by changes in sexual behavior, have been noted in several countries. Encouragingly, a few countries (e.g., Thailand, Uganda) have reported reduced HIV prevalence in the general population as well during the last few years, accompanied by secular changes in sexual behavior. Unfortunately, very few controlled trials of sexual behavior interventions to prevent HIV and STI transmission have been conducted in resource-poor settings. Recently, a large community randomized trial examined the effects of behavioral intervention or behavioral intervention coupled with improved STI services compared with routine government health services on HIV and STI transmission in the Masaka district of rural Uganda (Kamali, 2003). Behavioral interventions focused on knowledge acquisition, skill and attitude development, and motivational support and were accomplished through community-level approaches including public meetings, drama productions, informational leaflets, and individual discussions.

Communities randomized to the behavioral intervention experienced a lower incidence of HSV-2, and those randomized to STI services as well had reduced transmission of gonorrhea and syphilis. In both intervention arms, an increase in condom use was noted. Disappointingly, however, neither intervention arm saw a reduction in HIV incidence compared with the control arm, though HIV incidence in both the intervention and control communities was lower than the investigators expected, likely related to the secular change in HIV transmission that appears to be occurring in Uganda.

Some on-going studies are examining sexual behavior among adolescents, among whom HIV incidence is particularly high in many countries. Additionally, in light of gender differences in sexual decision making in many settings, other intervention trials are targeting behavioral change in men as a way to reduce heterosexual HIV spread. Given the high incidence of HIV in many developing countries, behavioral interventions to prevent heterosexual HIV transmission continue to be desperately needed.

VI. PRACTICAL ASPECTS OF COUNSELING PATIENTS ABOUT SEXUAL RISK REDUCTION

All of this information may seem overwhelming to the health care provider who has no special training in behavioral theory. However, the underlying principle is one that can be applied by any practitioner in any setting: counseling should be individualized to the person receiving the counseling. Any attempt to accomplish individualization of approach would be superior to simply providing a didactic message. Some practical aspects of counseling are listed in Table 3-5 and discussed below.

Table 3-5: Practical Aspects of Counseling
• Focus the counseling session on risk reduction topics
• Listen and react to the patient
• Don't stick to a practiced script
• Avoid overambitious risk reduction plans; focus on realistic goals
• Give the patient a written documentation of the risk reduction plan
• Use culturally sensitive and ethnic-specific language and terminology, when available and appropriate
• Consider issues specifically relevant to women

Focus the counseling session

The cornerstone of the counseling session is to focus the session on the patient's recent sexual activities, their perception of their risk, and motivation to reduce their risk of HIV/STI exposure, redirecting the patient to this topic whenever necessary. Clinicians and counselors may become distracted by providing excessive information about scientific data and principles in response to patient questioning. Such information is probably more effectively dispensed in pamphlet form or by referral to other patient information sources. In addition, women at risk for STIs including HIV frequently come to clinic with multiple complicating issues, including poverty, domestic violence, substance abuse, and child care problems. Often the counselor begins to feel responsible for addressing all of these issues and discouraged by the fact that many of them seem so insurmountable. Furthermore, the patient may be uncomfortable discussing her own risk, and may therefore be emotionally invested in distracting the counselor from that subject. For these reasons, it is important for the counselor to remember that the goal during the limited interaction period with the woman is to directly address, and hopefully impact, risky sexual behavior. Some appropriate topics are listed in Table 3-6. Other longstanding issues may not be easily solvable, and may be more appropriately referred to a social worker, substance abuse counselor, or mental health counselor.

Table 3-6: Appropriate Risk Reduction Topics
<ul style="list-style-type: none"> • Enhance self-perception of risk <ul style="list-style-type: none"> - <i>Identify risk behavior</i> - <i>Assess level of concern</i> - <i>Identify ambivalent feelings about risk</i>
<ul style="list-style-type: none"> • Explore specifics of most recent risk <ul style="list-style-type: none"> - <i>Identify specific risk details</i> - <i>Assess patient acceptable risk level</i> - <i>Address ability to communicate with partner</i> - <i>Identify situations that make the patient vulnerable to risk</i> - <i>Identify triggers of high-risk behavior</i> - <i>Assess patterns of risk behavior</i>
<ul style="list-style-type: none"> • Review previous risk reduction experience <ul style="list-style-type: none"> - <i>Identify successful attempts at risk reduction</i> - <i>Identify obstacles to risk reduction</i> - <i>Synthesize risk patterns</i> - <i>Summarize and reflect patient risk</i> - <i>Address risk in context of patient's life</i> - <i>Convey concerns and urgency regarding risk</i> - <i>Support and encourage the patient to action</i>

Source: Adapted from Kamb ML, 1998.

Listen and react

At the same time, it is important to listen and react to the patient. It is a human quality that we enjoy talking and thinking about ourselves. A counseling technique of summarizing a patient's descriptions and viewpoints about her risk is an extremely effective communication tool. In an effort to be nonjudgmental, counselors may find themselves nodding supportively to just about any statement that the patient may make. Instead, sometimes direct and clear feedback from the counselor about self-destructive behavior may communicate more effectively the importance of reducing risk (Figure 3-1). For example, if a patient is describing an evening during which she had sex with multiple men while using crack cocaine, it may be more appropriate for the counselor to respond with emphasis that such behavior is dangerous. It would also be important to explore the emotional or physical needs leading to such risky sexual behavior and to identify potential alternatives to fulfilling such needs.

Don't stick to a practiced script

In an effort to focus, some counselors may restrict themselves to a practiced script and thus squander opportunities to effectively impact risk behavior. Specific counseling scenarios a provider might encounter are described below:

- references to suicide: "I could have killed myself"
- self-deprecating comments: "I was so stupid"
- overacceptance of risk: "Even if I would have known he was HIV-positive, I wouldn't have used a condom"
- inappropriate behavior: giggling, putting feet up on the table

Such statements are usually pleas from patients for a direct and honest response, and taking such opportunities to acknowledge and problem-solve risky behavior is important in establishing the objectives of the session. Inappropriate patient behavior such as excessive giggling, angry postures, or demonstrations of boredom, should also elicit comment and questions from the counselor. Overlooking such behavior in an effort to be professional, polite, or focused detracts from the ability to communicate.

Avoid overambitious risk reduction plans

The most common error made by counselors is to develop an overambitious risk reduction goal, particularly during sessions in which good rapport has been developed. In many cases, counselors may convince themselves that the woman has acknowledged her risk to such a degree that she is now ready to eliminate any subsequent episodes of unprotected sex. Such goals are likely unrealistic. Behavioral specialists favor extremely concrete goals, such as "On Friday night I am going to ask my partner to wear a condom." Even modest goals, such as stopping at a drug store and purchasing condoms on the way home from the session, may be suggested. Other possible goals are listed in Table 3-7.

Figure 3-1: Listen and React to the Patient

React to what a woman tells you. Use words and body language to express yourself.

Instead of...



Try



<i>Type of Plan</i>	<i>Description</i>
1. Patient will talk about HIV/STI concern/risk to partner/friends	<ul style="list-style-type: none"> - Disclosure or communication with partner - Disclosure or communication with peers - Disclosure or communication with others
2. Patient plans to get herself tested or have partners tested for HIV/STIs before having sex	<ul style="list-style-type: none"> - Patient will test herself again to ensure uninfected - Have partner tested for HIV/STI - Use condoms until partner tested for HIV/STI - Abstain from sex until partner tested for HIV/STI
3. Patient plans to reduce, change, or eliminate at-risk partner(s)	<ul style="list-style-type: none"> - Break up with high-risk partner(s) - Eliminate a particular type of high-risk partner (prostitute, anonymous partner) - Patient will have fewer partners
4. Patient will change the type of partners she has	<ul style="list-style-type: none"> - Patient will get to know partners better before having sex - Patient will remain monogamous with one partner for 3 mo - Patient will abstain from sex for 3 mo
5. Patient plans to change use of alcohol and drugs	<ul style="list-style-type: none"> - Decrease/eliminate alcohol/drug use when having sex - Generally decrease/eliminate a specific drug/alcohol - Change venue where needles/drugs/alcohol used - Do not share needles (exchange or obtain new) - Clean needles or only share with known HIV-negative partner
6. Patient plans to increase condom use or increase situations that she uses condoms	<ul style="list-style-type: none"> - Talk to partner(s) about using condoms - Buy condoms or have them more available - Sex with condoms more often - Use condoms with all partners (vaginal/anal sex) - Use with all non-main partner (vaginal/anal sex) - Use condoms with main partner (vaginal/anal sex)
7. Patient plans to change the kind of sex she will have	<ul style="list-style-type: none"> - Have oral sex instead of vaginal or anal sex - Have mutual masturbation or petting (no penetrative sex)
8. Patient plans to make changes in the situations she is in that are associated with risky behavior	<ul style="list-style-type: none"> - Eliminate going to particularly risky place (bar, park) - Reduce number of times going to particularly risky place - Substitute behavior; go to gym, movies, etc.

Source: Adapted from Kamb ML, 1998, and from Beth Dillon, Project RESPECT training materials.

Put it in writing

Furnishing written documentation of patient goals reinforces verbal instructions and provides additional motivation.

Use time wisely

The question then remains: what amount of time is necessary to effect a behavioral intervention? The Project RESPECT study demonstrated successful intervention with two 20-min sessions within 10 days of each other. An ongoing follow-up study, RESPECT 2, compares a single 1-hr visit with rapid HIV testing to the two 20-min sessions. In busy clinics, where care for genital tract infections and other medical problems may be occurring simultaneously with patient counseling, clinicians may not feel that they have sufficient time to counsel effectively. However, in many cases, patients spend much more time waiting in the reception area or in the exam room than they actually do with the clinician. Optimizing use of patient time by providing educational materials during waiting periods may allow the clinician to limit the amount of didactic information dispensed in the clinic and to spend more time in interactive behavioral modification. A self-assessment of the counseling session will allow clinicians to measure their counseling skills. Goals for the counseling session include exploring behaviors most associated with risk, identifying a reasonable risk reduction plan, and assessing the patient support system. A reasonable checklist for a behavioral intervention session is shown in Table 3-8.

Table 3-8: A Checklist for the Behavioral Intervention Counseling Session
<input type="checkbox"/> Explored behaviors most associated with risk
<input type="checkbox"/> Identified behaviors most amenable to change
<input type="checkbox"/> Identified reasonable change step
<input type="checkbox"/> Developed the change step into a plan for action
<input type="checkbox"/> Problem-solved obstacles to the plan
<input type="checkbox"/> Confirmed with patient that the plan is reasonable
<input type="checkbox"/> Assessed patient's support system
<input type="checkbox"/> Identified referral resource, if necessary and available
<input type="checkbox"/> Reviewed date, time, and goals for next visit
<input type="checkbox"/> Recognized behavior change as a challenge

Source: Adapted from Kamb ML, 1998, and from Beth Dillon, Project RESPECT training materials.

VII. ETHNIC AND GENDER CONSIDERATIONS IN RISK REDUCTION COUNSELING

Language, visual materials, and descriptive terms sensitive to specific cultures and ethnicities may be important in improving communication techniques.

Ethnographic data from the San Antonio study found that African American women in their study population displayed an emphasis on infectious disease prevention, referring to sharing eating utensils as “eating behind” and sharing needles as “fixing behind.” The authors suggested that use of terms such as having sex “behind” someone might be an effective means of communicating the concept of unsafe sexual practices in their study population. In contrast, people of Asian background often conceptualize the human body of being made up of “hot” and “cold” components and may think of disease processes such as STIs as “hot.” Referring to a condom as “cold” may emphasize the effectiveness of such preventative measures. Finally, some studies have shown that the use of visual tools enhances verbal communication in Spanish. It is important to recognize, however, that such colloquialisms or cultural preferences may vary between regions, socioeconomic strata, and religions. If used in the wrong setting, approaches designed for one ethnic group may offend another, and detract from the counselor’s ability to communicate. In the absence of a validated communication tool, the counselor should take their cues from the patient.

Some counseling concerns are particularly relevant to women.

In many economically disadvantaged areas of the world, poverty engenders oppression of women. When education and jobs are scarce, many economies preferentially educate and employ men, thus leaving women financially dependent on their husbands, vulnerable to “sugar daddies,” and bartering sex for food and clothing either in informal relationships or in a structured brothel setting. Many cultures sanction a family structure in which the mother of the husband lives in the home and is responsible for directing household activities and ensuring the well-being of her son. Many cultures also may place more value on men than on women, and may mythologize male prowess and discourage condom use. Finally, many societies do not recognize the legal rights of women in custody battles, thus leaving women tied to their husbands if they wish to remain with their children. In conditions in which women are economically and emotionally dependent on men, women often neglect their basic human rights. Such barriers may be extremely daunting to counselors, and the temptation may be to attempt to debunk societal inequalities or to degenerate into a “male-bashing” session. In such cases, the basic tenets of behavioral counseling should be recalled; focus on risk and tailor the session to the readiness of the woman for behavioral change. Clear, feasible risk reduction plans should be formulated, usually involving self-education about risk and recognition of responsibility to reduce risk.

Domestic violence may need to be addressed.

Domestic violence continues to be a prevalent problem, affecting 20-30% of households in the United States and possibly even higher numbers in other parts of the world. Younger women and those with or at-risk for HIV may be particularly likely to experience domestic violence (Maman, 2002). One study from the early 1990's from Kenya found that only 66 (27%) of 243 HIV infected pregnant women informed their partners of their results, of whom 11 were subsequently chased from their home, 7 were beaten, and 1 committed suicide (Temmerman, 1995). Only one third of women in that research setting returned to receive their HIV results when the testing protocol was later changed to allow women the option of not knowing their HIV status. As voluntary HIV counseling and testing programs become more available in many part of the world, support must be given to women living in abusive relationships so that they can negotiate choices that will have positive effects on their health and that of their children. Anecdotal reports from voluntary counseling and testing centers in several African countries suggest that HIV testing of couples is associated with less partner violence, especially in recent years as HIV testing has become more common.

Fear of domestic violence may also impede a woman's ability to assert her rights in a relationship to reduce her risk of HIV infection. Counselors must realize that such fear may be entirely reasonable, and that counseling patients about domestic violence may be beyond their area of expertise. Whenever possible, appropriate patients should be referred to domestic violence centers. At the same time, counselors can help patients formulate risk reduction plans in the setting of domestic violence. The counselor must approach the issue of HIV testing while mentioning and indeed, when appropriate, emphasizing the possibility of domestic violence and social stigma. Although counselors must encourage disclosure in order to avoid the potential of infecting an uninfected partner, they must remember that the safety of the patient is their first priority. Unfortunately, only increased availability and acceptance of widespread testing and recognition of seroprevalence will succeed in destigmatizing HIV infection. Meanwhile, on the individual level, care must be taken to help the woman identify ways to reduce her risk of physical harm and excessive emotional stress while at the same time initiating the process of recognizing and reducing risk behavior.

VIII SEXUALLY TRANSMITTED INFECTIONS AND THE RISK OF HIV INFECTION

Sexually transmitted infections (STIs) increase susceptibility to HIV infection

The fact that STIs are important cofactors for HIV acquisition has been well established by prospective studies from a variety of populations examining risk factors for seroconversion. In such studies, women with genital ulcer disease, gonococcal or chlamydial cervicitis, or trichomoniasis were at

2–4-fold increased risk for HIV infection. However, study design issues, including small sample sizes and potential confounding by sexual behavior, have limited the ability of these observational studies to fully determine the magnitude of risk that STIs pose for HIV acquisition (Røttingen, 2001). Moreover, even the best-designed prospective studies have been unable to separate STIs acquired at the same time as HIV (perhaps reflecting increased infectiousness of an HIV-infected partner) from those present prior to HIV acquisition that could increase susceptibility. Because of obvious ethical limitations, randomized trials that deny individuals STI treatment cannot be conducted. Thus, as detailed below, community intervention trials of improved STI services or mass STI treatment have been conducted to determine the impact of STIs on population-wide HIV transmission.

Vaginal infections may also increase HIV susceptibility

Several studies, including well-controlled prospective investigations, have demonstrated that disturbances in the normal microbial flora of the vagina may increase HIV risk. One study among women attending an antenatal clinic in Malawi found that those with bacterial vaginosis (defined by vaginal pH >4.5, homogeneous vaginal discharge, presence of clue cells, and positive amine odor) were 2–4 times more likely to acquire HIV during pregnancy and postnatally over an average follow-up of more than 2.5 years (Taha, 1998). A second prospective study from Kenya found that HIV incidence was 2-fold higher among nonpregnant women with abnormal flora on Gram's stain of vaginal fluid or with negative vaginal cultures for *Lactobacillus* species, which are the hydrogen peroxide-producing gram-positive rods that dominate the normal vaginal ecosystem (Martin, 1999). An earlier report from this same cohort of Kenyan women found that *Candida* vaginitis also increased HIV risk ~2-fold (Martin, 1998).

Genital herpes may contribute substantially to HIV spread

A number of recent studies have highlighted the possible role of genital herpes infection (primarily due to HSV-2) in facilitating HIV transmission worldwide. As noted above, genital ulcer disease has long been regarded as a strong risk factor for HIV acquisition. Over the last two decades, HSV-2 has become the major cause of genital ulcer disease in many populations, and HSV-2 seroprevalence has increased substantially as well. A meta-analysis found chronic HSV-2 infection to be associated with a 2-fold increase in the risk of HIV acquisition among the best designed studies (Wald, 2002). Recent studies suggest that primary HSV-2 infection may be associated with even greater HIV risk (del Mar Pujades Rodriguez, 2002). Compellingly, one large survey study from Africa concluded that country-to-country differences in the prevalence of HSV-2 may be one of the principal causes of differential HIV spread across that continent (Avert, 2001). Studies of suppressive antiviral therapy against HSV-2 to prevent HIV transmission are underway and may provide a relatively inexpensive and simple intervention to decrease HIV acquisition, infectiousness, or both.

Community randomized trials of STI treatment offer conflicting results

Observational studies have demonstrated clear and consistent evidence that STIs and other genital tract infections increase HIV susceptibility. This conclusion was supported by the results of a trial conducted in the Mwanza region of Tanzania that randomly allocated communities to improved syndromic management of STIs or to routine government health care services (Grosskurth, 1995). Syndromic STI management resulted in a 40% decrease in new HIV infections in the intervention communities. In contrast, in the Rakai district of Uganda, a community randomized trial of mass antibiotic treatment for STIs, given at 10-month intervals, failed to demonstrate a reduction in HIV seroincidence (Wawer, 1999). One principal reason for the disparate results of these two trials is likely related to the stage of the epidemic in the two locations (Grosskurth, 2000). In Mwanza, the baseline HIV prevalence was 4%, indicating an early phase of the epidemic. In Rakai, the epidemic was at a more mature phase, with a baseline prevalence of 16%. Experts concluded that the core group of high-risk individuals, who are crucial to epidemic transmission and who are most likely to have concurrent STIs, was already HIV-saturated in Rakai, thus minimizing the impact of the intervention. Recently, a third trial, from the Masaka district of Uganda, demonstrated no effect of syndromic STI management on HIV incidence in the context of a mature HIV epidemic (Kamali, 2003). These results confirm that it is not the type of intervention but rather the stage of the epidemic in an area that permits a community-wide impact of better STI services. Subsequent analysis suggested that an important difference between the three studies was the prevalence of curable STIs, which was significantly higher in Mwanza than in Rakai or Masaka, which may explain the larger impact that STI treatment had on HIV transmission in that study (Orroth, 2003). In all the studies, the effect of herpes treatment was not assessed, since medications against genital herpes were not part of the interventions, though a large proportion of STI episodes in all three trials were likely a result of herpes outbreaks. Nevertheless, STIs clearly increase individual-level risk of HIV acquisition, and STI treatment should remain an important part of reducing HIV risk for individuals and populations, even in areas where HIV is already well-established. STI treatment remains one of the most cost-effective HIV prevention strategies for resource-poor settings (Creese, 2002).

How should we counsel women at risk for STIs and HIV?

Important issues in counseling women at risk for STIs and HIV are presented in Table 3-9. Reducing the prevalence and incidence of STIs should reduce the susceptibility to HIV transmission. Measures to reduce STIs include female and male condom use, seeking early diagnosis and treatment of genital tract symptoms, and frequent STI screening and should be a part of HIV prevention in the United States as well as in developing countries (CDC, 1998b). Infections such as yeast vaginitis and bacterial vaginosis are not sexually transmitted,

but arise from disruption of a woman's genital tract flora. For this reason, these infections are often underemphasized in programs to diagnose and treat genital tract infections. However, these are relatively common conditions, and thus they may be responsible for a substantial fraction of HIV infections in some populations. Clinicians should diagnose and have a low threshold to treat both bacterial vaginosis and *Candida* vaginitis in women with high-risk sexual behavior. Vaginal douching, which has no therapeutic benefit, may increase the risk of developing bacterial vaginosis and pelvic inflammatory disease and should be strongly discouraged. Preventable risk factors for *Candida* vaginitis include uncontrolled diabetes mellitus, antibiotics, and high-estrogen oral contraceptives. Other possible risk factors that are less well documented include wearing poorly ventilated clothing, use of low-estrogen oral contraceptives, frequent swimming, feminine hygiene sprays, and use of spermicidal jelly.

Finally, women with a history of genital herpes or with serologic evidence of herpes simplex virus type 2 infection should be taught how to recognize prodromes and recurrences. Suppressing herpes antiviral therapy should be considered in women with frequent recurrences who report high-risk sexual behavior (CDC, 2002).

Table 3-9: Measures to Reduce STIs

• Encourage male and female condom use
• Encourage seeking medical care early for diagnosis and treatment of genital tract symptoms
• Routine screening for genital tract infections, including chlamydia cervicitis, yeast vaginitis, and bacterial vaginosis among sexually active women
• Discourage douching
• Educate women about risk factors for yeast vaginitis
• Teach how to recognize genital herpes recurrences and prodromes and offer antiviral treatment to shorten or suppress recurrences

IX. CONDOMS AND PREVENTION OF HIV INFECTION

Readers of history may know that decorative penile covers have been mentioned in Egyptian writings as far back as 1350 BC. In 1564, the Italian anatomist, Fallopius, described the concept of a penile barrier for the prevention of venereal disease. The famous romancer, Casanova, is said to have protected himself with sheets of sheep intestine. Since that time, technology has allowed the production of latex male condoms and, more recently, polyurethane male condoms and female condoms. Important issues to discuss while counseling women on use of male and female condoms are listed in Table 3-10 and discussed below.

Table 3-10: Important Issues for Patients Being COUNSELED ON CONDOM USE

<ul style="list-style-type: none"> • Store in a cool, dry place, such as a bedroom drawer <ul style="list-style-type: none"> - Avoid excessive humidity, such as in a bathroom - Avoid excessive heat, such as in a wallet carried in a trouser pocket - Avoid exposure to direct sunlight
<ul style="list-style-type: none"> • Use appropriate spermicide or lubricating jelly <ul style="list-style-type: none"> - Mineral-oil-containing compounds, such as petroleum jelly, cooking oils, shortening, or lotions can weaken latex
<ul style="list-style-type: none"> • Use male condom properly <ul style="list-style-type: none"> - Use male condom at the onset of male arousal, even before penetration - Make sure that the male condom is unrolled to extend completely to the penis base - Use enough lubrication to prevent excessive friction that might lead to breakage - Hold the male condom at the base during withdrawal to prevent slippage
<ul style="list-style-type: none"> • Use female condom properly <ul style="list-style-type: none"> - The inner ring must be placed completely onto the cervix or the condom may twist - Additional lubrication may be needed to prevent the condom from twisting - Care must be taken not to insert the penis between the condom and vaginal wall - The outer ring may need to be held in place to keep the condom from slipping into the vagina or anus - During anal intercourse, the insertive partner may have to keep thrusts shallow, because the condom is not as long as the rectum. It also might be advisable to remove the inner ring for anal sex to reduce likelihood of rectal bleeding.

A. MALE CONDOMS

Male condoms prevent transmission of many STIs

The literature on the role of barrier contraception as protection against STIs is vast and the reported degree of protection against specific STIs varies from paper to paper. A distillation of available data produces the conclusion that, of available barrier methods that have been adequately tested, latex male condoms provide substantial protection against infection with HIV and most other STIs, and are currently the most reliable protective measure. In a workshop reviewing the scientific evidence on condom effectiveness, the U.S. National Institutes of Health concluded that consistent condom use reduces a woman's risk of HIV by at least 85% (NIAID, 2001). Moreover, some studies have reported no seroconversions at all among consistent condom users despite repeated coital exposure (Carlin, 1995). A significant increase in condom use, and a lower than anticipated rate of new HIV infections, followed voluntary HIV counseling and testing of HIV discordant couples in one African study (Allen, 1992). In terms of other STIs, male condoms may be less reliably protective against transmission of herpes and human papilloma viruses.

Latex male condoms must be stored and used properly

Male condom failures are more likely caused by postmanufacture defects secondary to latex deterioration than to manufacturing defects. Latex male condoms have proved impermeable to HIV in vitro. In contrast, natural membrane ("skin") condoms have been shown to be permeable to small amounts of HIV and other infectious agents, and are not recommended for disease prevention. Transmission of HIV that occurs with use of latex male condoms is likely due to technical failures or improper usage rather than to manufacturing defects. Since 1987, the Food and Drug Administration in the United States has maintained a high level of quality by limiting the number of defective condoms to four per 1000 count batch. Patients should be counseled that stored male condoms should be replaced often because temperature, light, and animal pests all can contribute to latex deterioration and decreased effectiveness. In clinical studies, breakage rates range from 0.5% to 7% (Stratton, 1993). Studies reporting higher breakage rates tended to include populations from underdeveloped areas or those who participated in anal intercourse.

Male condoms must be used properly to be effective.

Using oil-based lubricating materials such as petroleum jelly, cooking oils, shortening, or lotions during intercourse weakens latex and promotes breakage. Common errors that patients should be cautioned about include delaying condom use until just before full penetration, failure to extend the condom all the way to the penis base, insufficient application of a water-based lubricant, and failure to hold the condom at the base during withdrawal.

Polyurethane male condoms may be a future alternative

Acceptability of male condom use is limited by complaints of decreased male sensitivity and limitation of sexual enjoyment by both men and women. Polyurethane has been hailed as an attractive alternative to latex because of increased tensile strength that should, theoretically, allow for a thinner condom wall translating into increased penile sensation. A male polyurethane condom, Avanti, has been popular since its introduction in late 1994, but after increasing numbers of complaints of condom breakage, the manufacturers have changed specifications to produce a thicker condom labeled "Intended for Latex Sensitive Condom Users Only." Breakage rates, patient acceptability, and the ability of this product to protect against STI and HIV infection are yet to be demonstrated.

B. FEMALE CONDOMS

Also made of polyurethane, the female condom has been available for use in the United States since 1993 (Bounds, 1997) and offers women more control over use than with the male condom. The female condom is a sheath, closed at one end, with flexible rings at both ends (Figure 3-2). The device is inserted into the vagina by compressing the closed-end ring and pushing against the cervix, while the outer ring covers

the labia (Figure 3-3). Only one female condom is currently available, marketed under the name “Reality” in the United States and Canada and “Femidom” in other parts of the world. Limited data are available on the efficacy of the female condom in preventing HIV and STIs, although most experts have extrapolated from the data on male latex and polyurethane condoms to conclude that, if used properly, female condoms would be impermeable to most viruses and other microorganisms. In a study sponsored by the United Nations Programme on HIV/AIDS (UNAIDS), female commercial sex workers in Thailand were randomized into a group instructed to consistently use male condoms, and a group given the option to use female condoms if the male refused to wear a condom (Fontanet, 1998). Both groups reported universal male or female condom use rates of approximately 97%, although 9% of the women in the “option group” used the female condom. Before introduction of the female condom, women in the study population were experiencing an average of two STIs per year (trichomoniasis, chlamydial infection, gonococcal infection, genital ulcer disease). This rate was surprisingly high, particularly given the high rate of reported condom use, and may be due to overreporting of condom use or STIs acquired from their husbands or nonpaying partners. Nevertheless, the group randomized to the option to use either type of condom demonstrated a 24% decrease in the incidence of STI compared with the male condom-only group. Importantly, female condoms were reportedly well accepted by both the women and their clients. Condom tears occurred less frequently with the female condom than the male condom. A recent study found that the female condom acts as an effective barrier for the vast majority of uses, and exposures to semen become less frequent with greater user experience (Macaluso, 2003).

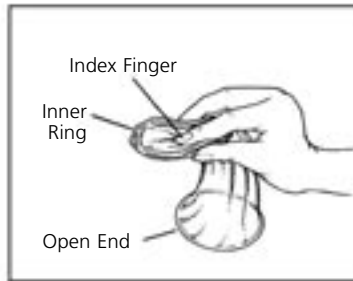
Figure 3-2 : The Female Condom



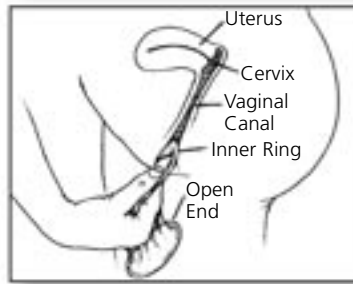
Source: The Female Health Company, Chicago, IL.

Figure 3-3: Female Condom Insertion and Positioning

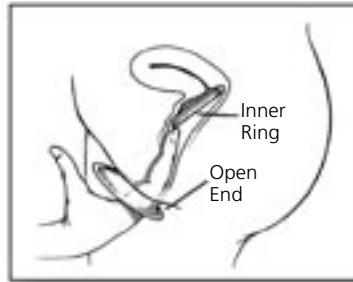
STEP 1
Inner ring is squeezed for
insertion.



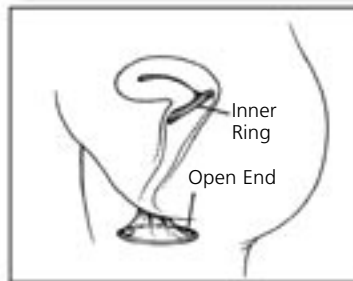
STEP 2
Sheath is inserted,
similarly to a tampon.



STEP 3
Inner ring is pushed up
as far as it can go with
index finger.



STEP 4
Female condom is in
place



Source: Adapted from Reality brand female condom literature.

C. ACCEPTABILITY OF MALE AND FEMALE CONDOMS

Factors influencing condom use are presented in Table 3-11. These factors are complex, and often differ between men and women. Surveys have shown that both men and women are influenced by perceived social norms and attitudes about condom use, and by the recognition that condoms may prevent STIs. Ability to obtain condoms without excessive cost or embarrassment, ease of using the condom, and preservation of pleasurable sexual sensation are clearly concerns for both men and women. Acceptability of the male condom for both men and women is increased by normal appearance and feel, lack of odor, lack of slippage, the presence of a reservoir tip, and spermicidal lubrication. Men may be more likely to use the male condom if they feel that the woman may perceive them as being more sensitive and caring if they do so. Women, on the other hand, have complained that the interruption of foreplay negatively affects the acceptability of the male condom. For the female condom, both men and women have complained about the aesthetic appearance of the external ring, and the noise during intercourse. The fact that the female condom is made of polyurethane and not latex may increase its acceptability, particularly among latex-allergic users. Women have reported that inserting the female condom interrupts foreplay. Interestingly, in several surveys, more women have said that they would be likely to use the female condom again than have said that they liked using it, suggesting that women may be willing to sacrifice comfort and pleasure during sex for protection against STIs and pregnancy. Many women have also strongly expressed a preference for a female-controlled device to prevent STIs. Finally, in surveys, pregnancy prevention is more important to women than to men, and most women feel that both the male and female condom may be inferior to other contraceptive methods (Grady, 1999).

D. SPECIAL CONSIDERATIONS FOR WOMEN WHO HAVE SEX WITH WOMEN

Discussion of recommendation of protective sexual practices should not be limited to exclusively heterosexual women. Sexual transmission of HIV between women has been described. The use of barriers such as dental dams should be recommended for oral-genital contact, particularly in HIV discordant relationships. Sexual activity should be avoided during menstruation or when there are symptoms of genital tract infection. The sharing of sex toys contaminated with blood was implicated in a recently described case of female-to-female sexual transmission of HIV (Kwakwa, 2003).

Table 3-11: Factors Associated with Condom Use and Non Use		
<i>Condoms in General</i>	<i>Important to Men</i>	<i>Important to Women</i>
Negative image of condom use associated with disease, promiscuity, and distrust of sex partner	■	■
Actual and perceived social norms governing condom use	■	■
Perceived ability to protect against sexually transmitted infections	■	■
Ease of obtaining or purchase	■	■
Ease of putting on or in	■	■
Slippage during intercourse	■	■
Adequate lubrication	■	■
Sensation during intercourse	■	■
<i>Male Condoms</i>	<i>Important to Men</i>	<i>Important to Women</i>
Normal appearance and feel	■	■
Lack of odor	■	■
Reservoir tip	■	■
Spermicide coating	■	■
Interruption of foreplay		■
Inferior contraceptive method		■
Perception that partner may believe user is sensitive and caring	■	
<i>Female Condoms</i>	<i>Important to Men</i>	<i>Important to Women</i>
Aesthetic appearance of external ring	■	■
Noise during intercourse	■	■
Polyurethane material	■	■
Interruption of foreplay		■
Female controlled device		■
Inferior contraceptive method		■

Source: Adapted from Grady. 1999.

X. OTHER FORMS OF CONTRACEPTION AND THE RISK OF HIV INFECTION

The role of hormonal contraceptives in HIV transmission is controversial

The association between hormonal contraception and HIV infection has been the subject of controversy. Because of the unique considerations that contribute to contraceptive choice, a clinical trial randomizing a woman to contraception or placebo is probably not feasible. Thus, although many studies presenting data on the association have been published, all are population surveys or observational studies. The reported effects of oral contraceptives on HIV susceptibility are widely divergent, ranging from protective, to no effect, to an increased risk. A meta-analysis on the subject reported that the use of oral contraceptives may be associated with a small increased risk of HIV infection (Wang, 1999). When the results of all 28 published studies were combined, a pooled odds ratio of 1.2 (95% confidence interval 0.99–1.42) was found. This pooled risk estimate increased with increasing study quality, suggesting that a true association, albeit small, does exist. In addition, two prospective studies found that use of the injectable contraceptive depo-medroxyprogesterone acetate (Depo-Provera) was associated with increased risk of HIV infection. One, conducted among 779 commercial sex workers in Mombasa, Kenya, found women using Depo-Provera were at a 2-fold increased risk of acquiring HIV compared with women using no contraceptive method, after controlling for differences in sexual behavior, condom use, and STIs (Martin, 1998). Insufficient data exist on other hormonal contraceptive methods to reach a conclusion about the effect on a woman's susceptibility to HIV. A large observational study currently being conducted among family planning clinic attenders in Zimbabwe, Uganda, and Thailand is examining the relationship between hormonal contraceptive use and HIV acquisition in a lower-risk population of women, with preliminary results expected in 2004.

Other contraceptive methods and HIV acquisition

Cervical barrier contraceptive devices, such as the diaphragm or cervical cap, have been postulated as potentially protective against HIV (Moench, 2001). Evidence supporting this hypothesis comes from laboratory investigations suggesting the cervical epithelium is particularly susceptible to HIV infection and observational studies that found lower rates of cervical STIs, like gonorrhea, among women who used the diaphragm. However, cervical barrier devices do not cover much of the vagina and thus still would result in significant mucosal exposure to HIV. A large randomized trial of the diaphragm to decrease HIV acquisition will be conducted in Africa. If successful, cervical barriers would be a discreet, easy, female-controlled method to prevent HIV infection.

The use of **spermicides** as a sole method for HIV prevention should be discouraged. The most well-studied vaginal spermicidal product is nonoxynol-9 (N-9). A large meta-analysis of several controlled trials concluded that N-9 provides no protection from HIV (summary relative risk 1.12, 95% confidence interval 0.88-1.42) or other STIs and slightly increases the risk of genital ulceration (Wilkinson, 2002). This last finding may be of particular concern to women at high risk of HIV. In the largest randomized trial of N-9, conducted among commercial sex workers in several developing countries, a nearly 2-fold increased HIV risk was seen among the subset of women who used the product several times per day (Van Damme, 2002). Overall, N-9 is not recommended for HIV prevention, especially among high-risk women.

Data on the relationship between the use of **intrauterine devices (IUDs)** and HIV acquisition is sparse. In general, IUDs are not recommended for women at high risk for STIs because of possible increased risk of pelvic inflammatory disease, though IUDs are a safe, long-lasting, and effective contraceptive method for lower-risk women. Like many other contraceptive methods, IUDs provide no barrier protection and thus would be unlikely to decrease HIV risk. A theoretical increase in HIV risk has been hypothesized due to the foreign body reaction and accompanying intrauterine inflammation associated with IUD use. In addition, use of non-progestin releasing IUDs are associated with longer and heavier menses, which may increase risk of transmission bidirectionally.

Female **sterilization** by tubal ligation has no effect on male-to-female HIV transmission. Additionally, HIV has been acquired vaginally by women who have had hysterectomies. Early penile withdrawal, while theoretically reducing the inoculum size, has not been studied and should not be recommended. Although the exact effect of vasectomy on the ability to transmit HIV from male to female is unknown, HIV has been cultured from the ejaculate of HIV-infected vasectomized men (Anderson, 1991).

Contraception and prevention of infection are separate issues

The issue of contraception for sexually active woman of reproductive age is obviously complex. The importance of preventing unwanted pregnancies is clear. Any counselor working with women is familiar with the issue of controlling and planning family size while taking into account economic factors, maternal health, and social pressures. Hormonal contraception is one of the most effective means to prevent pregnancy. The message conveyed to women must be that contraception and protection against STIs, including HIV, are separate considerations. Regardless of which method women choose for pregnancy prevention, counselors must emphasize that male and female condoms are the only methods proven to prevent STI transmission.

The effectiveness of various contraceptive methods in reducing risk of HIV infection is summarized in Table 3-12.

Table 3-12: Contraception and prevention of HIV-1 infection

<i>Method</i>	<i>May Increase Risk*</i>	<i>No Effect or Insufficient Data*</i>	<i>Protective – Strong Evidence</i>
Male condom			■
Female condom			■
Intrauterine device		■	
Diaphragm		■	
Cervical cap		■	
Tubal ligation		■	
Vasectomy		■	
Early penile withdrawal		■	
Oral contraceptives	■		
Depo-Provera	■		

* Counsel that condoms should be used to prevent HIV-1 infection.

XI. NEW APPROACHES TO HIV AND STI PREVENTION: MICROBICIDES, VACCINES, AND POSTEXPOSURE PROPHYLAXIS

Given the difficulties that many women encounter in negotiating condom use, other prevention strategies under the control of women have been sought, such as topical microbicides. Although microbicides have generated considerable enthusiasm, progress in this area has been relatively slow. Most of the research in microbicides over the past 10 years has focused on safety and efficacy of nonoxynol-9 (N-9). Unfortunately, as reviewed in section X, N-9 is unlikely to provide significant protection from HIV or STIs and may increase the likelihood of HIV transmission to high-risk women (Van Damme, 2002; Wilkinson, 2002). Policy organizations such as the CDC and WHO have recently circulated advisories to discourage use of N-9 for STI and HIV prevention.

Although the concept of topical microbicides is promising, the process of developing and testing new microbicial products for safety and ultimately efficacy in preventing HIV in clinical trials will take a number of years

A number of new topical microbicial products are in early clinical trials, and many more are in preclinical development (McCormack, 2001). These include agents with broad-spectrum activity (acidic buffers such as BufferGel, surfactants such as C31G, and natural *Lactobacillus* suppositories), inhibitors of viral entry (such as PRO2000, carrageenan, and dextrin sulfate), and inhibitors of viral replication (such as gel formulations of antiretroviral medications, including tenofovir). Efficacy

trials of topical microbicides face many challenges, including issues of compliance, product safety and acceptability, and the potential for sexual behavior to change as a result of product use. Moreover, microbicide studies have faced difficulty in the development of biologically inert but physically identical placebos for use in efficacy trials, as even inactive gel placebos may provide some degree of HIV protection simply as a result of their physical or barrier properties.

Vaccines hold the most promise for preventing the largest number of HIV infections transmitted sexually, perinatally, or through drug use

Only one HIV prophylactic vaccine has completed efficacy testing. This vaccine, which used a recombinant HIV subtype B gp120 protein developed by the VaxGen corporation, provided essentially no reduction in HIV acquisition in a large trial conducted in North America and Europe (McCarthy, 2003). A similar trial of a bivalent HIV subtype B/E construct among Thai injection drug users also failed to prevent HIV acquisition. Overall, the necessary components of an immunogen that could induce protection against infection are not yet completely understood. Clues have emerged from dissecting the properties of immunity that offer protection against other pathogens, and also those that arise in individuals infected with HIV. Primate studies, using the related simian immunodeficiency virus (SIV) or SIV/HIV chimeric virus constructs, have provided important information about how the virus establishes itself during early infection as well as about the immunologic potential of candidate vaccines. In addition, studies of persons demonstrating unusual control of HIV infection (e.g., who remain uninfected despite repeated HIV exposure or who demonstrate long-term nonprogression although infected with HIV) suggest there are unique host defense characteristics, particularly cellular immunity, that might be able to be replicated by a vaccine.

Our understanding of the mechanism of action of other effective viral vaccines and of HIV pathogenesis is guiding HIV vaccine development. Most licensed vaccines prime host immunity to control initial infection more efficiently, rather than provide sterilizing immunity. Protection is commonly mediated by induction of antibodies that block infection, which allows time for antigen-specific T cells to mature and overtake any cells that do become infected. However, HIV preferentially targets T helper cells and often establishes latent infection within them. Thus, a vaccine must induce sufficient immunity to block such HIV "seeding" or prevent viral reemergence from latently infected cells. Unfortunately, HIV is not easily neutralized by antibody, so vaccine strategies that use recombinant proteins, like in the effective hepatitis B vaccine, are unlikely to be successful for HIV (as demonstrated by the unsuccessful HIV recombinant gp120 subunit vaccine). Most experts believe that regimens priming both the cellular and humoral immune arms are the best candidates for protection. Considerable research into cellular immunity against HIV has been conducted over the past few years,

and vaccine constructs that induce cell-mediated responses, at least in a moderate proportion of individuals, have been developed. These generally consist of poorly replicating viral or bacterial vectors (e.g., vaccinia, canarypox, adenovirus, salmonella) expressing a selection of HIV gene products, such as *gag*, *pol*, *env*, *nef*, or a variety of isolated T-cell epitopes. Alternative strategies include naked DNA vaccines, which can induce some degree of cellular and antibody-mediated immunity and have the advantage of being considerably more stable in tropical climates.

The development of an effective HIV vaccine faces several additional challenges. The remarkable ability of HIV to undergo genetic change suggests that vaccines based on individual viral strains, especially laboratory adapted strains, may not induce immunity with sufficient flexibility to prevent a new infection. The predominance of distinct HIV subtypes in different regions of the world may complicate development of a single universal HIV vaccine, although cross-clade cellular immune responses have been demonstrated in human immunogenicity trials. Moreover, since HIV transmission occurs predominantly by sexual contact, protection will likely require mucosal as well as systemic immunity. Finally, a number of logistic and ethical considerations relevant to the conduct of HIV vaccine research have been raised, including the need for unbiased counseling towards risk reduction for vaccine participants, the obligation to provide HIV care to individuals infected during a trial, and the commitment to rapidly provide vaccine to at-risk communities should an effective candidate be found.

Numerous clinical studies of various HIV vaccine constructs have been conducted, are in progress, or are planned. On-line updated lists of trials of HIV vaccines are maintained by the International AIDS Vaccine Initiative (www.iavi.org) and the HIV Vaccine Trials Network (www.hvtn.org).

Postexposure prophylaxis (PEP) may reduce the likelihood of HIV infection after a high-risk exposure

Theoretically, PEP can prevent HIV transmission either by blocking initial viral infection of cells or by inhibiting viral dissemination, thus allowing for immune clearance of a small number of already infected cells. The data for efficacy of antiretrovirals as PEP comes primarily from a single case-control study of health care workers who experienced occupational HIV exposures, mostly though needlestick injuries. Those who received zidovudine had an 80% lower likelihood of becoming infected, though this study was limited by a small sample size, retrospective design, and other potential sources of bias. The rationale for PEP after sexual exposure is largely that the probability of infection after a single unprotected sexual exposure is similar to that after a needlestick exposure (i.e., ~0.1%, though slightly higher for receptive anal intercourse) (Katz, 1998; USPHS, 1998). Animal models suggest that PEP may be effective for mucosal and needle exposures, particularly when used within 24–48 hr. Ethical and pragmatic considerations make it unlikely that a randomized trial of PEP will be conducted. The effectiveness of PEP is likely to be influenced by

time to initiation of treatment, duration of treatment, size of inoculum, and drug resistance profile of the virus in the source individual. While the risks and benefits of PEP for sexual exposure remain to be fully defined, studies suggest that provision of PEP for nonoccupational exposures is feasible (Kahn, 2001). Recently, some have suggested that routine antiretroviral chemoprophylaxis, with relatively safe agents such as nevirapine or tenofovir, be tested as an HIV prevention strategy for individuals at particularly high risk (e.g., commercial sex workers in high HIV prevalence settings) (Youle, 2003).

Individual providers who are approached by anxious patients who have recently had a high-risk sexual exposure must weigh the likelihood of HIV infection in the contact, antiretroviral treatment history if the contact is known to be HIV-infected, specific nature and timing of the exposure (since initiation of PEP within 48 hr may be important), and possible risks of drug toxicity or side effects in choosing whether to use PEP and which drugs to prescribe. CDC guidelines recommend 2–3 antiretroviral medications, depending on the intensity of the exposure, for 4 weeks for occupational exposures having at least moderate HIV risk (CDC, 2001). A similar approach has been adopted by many providers when selecting a regimen for “sexual PEP.” The source partner’s likelihood of resistant virus, based on treatment history, stage of disease, and viral load, can be factored into the choice of a PEP regimen. Other considerations should include evaluation for other STIs, emergency contraception when appropriate, and possible indication for hepatitis B vaccination. Informed consent is recommended when administering PEP.

PEP should not be administered routinely, with exposures at low risk of transmission, or when care is sought after 72 hr from the time of exposure. Situations in which PEP should be especially considered include condom breakage with serodiscordant couples and sexual assault. PEP is not a substitute for risk reduction and should not be considered a form of primary HIV prevention. Individuals presenting for possible PEP should have reinforcement of the importance of initiating, resuming, or improving risk reduction activities. Providers are requested to report nonoccupational PEP use to a national registry maintained by the CDC at (877) 448-1737 or <http://www.hivpepregistry.org>.

XII. PREVENTION MESSAGES FOR HIV-INFECTED WOMEN

While this chapter has largely focused on factors that may increase a woman’s risk of acquiring HIV, prevention messages are equally important for women who are already HIV-infected. Studies have shown that women with HIV are concerned about factors that may increase their infectiousness to their sexual partners and children. In general, the central messages for preventing sexual HIV transmission apply to HIV-infected women as well as to those who are uninfected and at risk through their or their partners’ behaviors. These include the importance of knowing one’s HIV status and that of one’s sexual partners, the ability

for behavioral change to prevent transmission, and the potential for consistent condom use to significantly reduce HIV risk. Issues relevant to the prevention of mother-to-child transmission of HIV are covered in chapter VII.

Perhaps not surprisingly, many factors that increase the risk of HIV acquisition also appear to increase HIV infectiousness (reviewed in Baeten, 2003). Because of logistical limitations, relatively few studies have been conducted to assess the risk that HIV-infected women pose to susceptible sexual partners. However, numerous studies have now demonstrated that HIV shedding in genital secretions is likely a reliable marker of infectiousness, based on good biologic plausibility that factors that increase genital HIV shedding increase HIV transmission and on strong agreement between correlates of HIV transmission in epidemiologic studies and correlates of genital shedding of HIV. Thus, most studies of factors that influence the infectiousness of women with HIV have examined HIV shedding in the genital tract.

Plasma viral load is the strongest predictor of HIV infectiousness

In a large study of HIV-discordant couples from Uganda, HIV plasma viral load was the principal predictor of heterosexual transmission and demonstrated a clear dose-response effect (Quinn, 2000). The rate of transmission from female index cases to their uninfected male partners was similar to that from male index cases to uninfected female partners, suggesting that HIV-infected women are no less likely to transmit the virus than are infected men. The results of this study were not necessarily surprising—higher viral load is a strong risk factor for mother-to-child HIV transmission and HIV shedding in genital tract secretions. Epidemiologic studies suggest that individuals with primary HIV infection and advanced HIV disease, which are both characterized by high systemic and genital viral burdens, are more likely to transmit the virus to sexual partners. The only study to assess the effect of antiretroviral therapy on sexual HIV transmission found that men taking zidovudine monotherapy were at 50% decreased risk of transmitting HIV to female partners (Musicco, 1994). Given the dramatic reductions in plasma viral load and in the risk of mother-to-child HIV transmission that result from combination antiretroviral therapy, it is likely that effective regimens would significantly decrease a woman's risk of transmitting HIV to sexual partners. However, studies have shown that genital HIV shedding may not be fully suppressed among individuals on therapy, even those with undetectable plasma viral loads, suggesting that antiretroviral therapy may not completely eliminate transmission risk.

STIs and other genital tract infections increase the risk of HIV transmission

Numerous studies have demonstrated that genital ulcer disease, cervical infections, and vaginal infections increase HIV shedding in the female genital tract, and that successful treatment reduces shedding (Baeten, 2003). In areas where antiretroviral therapy is not available, control

of STIs should be a primary intervention to decrease sexual HIV transmission. Moreover, in all settings, STI screening and treatment may reduce HIV infectiousness among persons who do not qualify for antiretroviral therapy (e.g., those with CD4 counts >200–350) or even among those who are on therapy, since these infections may stimulate genital viral replication even in the context of good systemic HIV suppression. Recent studies have found that genital herpes shedding is associated with increased HIV shedding, suggesting that suppressive therapy for HSV may reduce HIV infectiousness. Studies to determine the efficacy of HSV therapy to decrease HIV shedding and transmission are planned.

Contraception, menstruation, and HIV infectivity

Oral and injectable hormonal contraception were associated with increased genital HIV shedding in two cross-sectional studies from Kenya (Mostad, 1997). No published prospective studies have yet assessed the effect of initiation of hormonal contraception or duration of hormonal contraceptive use on genital HIV shedding over time. Very little information is available from epidemiologic studies on the relationship between hormonal contraceptive use and HIV transmission risk. Thus, there is no recommendation against use of hormonal contraception by HIV-infected women. Given the importance of preventing unintended pregnancies, effective methods of contraception should be strongly encouraged, and condom use should be promoted as well as an adjunct method to decrease HIV infectiousness.

The effect of the diaphragm or cervical cap on HIV shedding and transmission is unknown. Cervical secretions tend to have significantly higher viral concentrations than vaginal secretions, potentially suggesting that cervical barrier devices may decrease transmission risk. However, women who have had hysterectomies can shed significant amounts of virus in the vagina, so even complete removal of cervical secretions does not eliminate HIV risk. One study from Kenya demonstrated that IUDs are a safe method of contraception for some HIV-infected women (Sinei, 1998), and a secondary analysis found no increase in HIV shedding in cervical secretions after IUD insertion.

Several studies have now demonstrated that the quantity of HIV shed in the genital tract varies over the course of the menstrual cycle (Coombs, 2003). Shedding appears to be lowest during the peri-ovulatory period and highest near the time of menstruation, which is in agreement with epidemiologic studies that found increased transmission risk for male partners of infected women who had unprotected intercourse during menses. However, these results are difficult to translate into a prevention message since HIV is shed to some degree throughout the menstrual cycle, and some women may shed high quantities of virus at all times. Overall, recommendations to women with HIV should stress the importance of consistent condom use to decrease HIV transmission risk.

New interventions to decrease HIV transmission risk

There remains a great need for simple, inexpensive interventions to prevent and treat HIV among individuals living in resource-poor settings. Several observational studies suggested that micronutrient deficiencies increased HIV infectivity and accelerated disease progression. However, subsequent randomized trials of micronutrients, conducted among HIV-infected African women among whom the prevalence of nutritional deficiencies was high, failed to demonstrate any substantial benefit of supplementation with vitamin A or other vitamin and mineral preparations (Baeten, 2002; Baeten, 2003). Vaginal microbicides offer a potentially promising strategy to decrease HIV transmission risk, since these products may decrease the infectiousness of virus shed into the genital tract. An effective therapeutic vaccine against HIV (i.e., one that could reduce systemic and genital viral burden among infected individuals) could significantly slow the global spread of the epidemic. No therapeutic vaccine has yet demonstrated clinical efficacy, though research in this area is continuing.

XIII. CONCLUSIONS

Prevention of HIV remains a critical priority, particularly amidst increasing complacency related to enthusiasm about more effective treatments for HIV. The most effective available strategies for prevention are HIV counseling and testing, behavioral interventions to become abstinent or to reduce risk-taking, and condoms. STI treatment decreases individual-level risk of acquiring and transmitting HIV and has been shown to be an effective population-wide intervention in some settings. Topical microbicides may provide a prevention strategy directly under the control of women, although N-9 has not been shown to have significant efficacy against HIV transmission in commercially available spermicidal concentrations. New microbicide products are early in preclinical and clinical trial testing. Development of an effective HIV vaccine will likely be essential to controlling the global epidemic, and a number of candidate vaccines are undergoing clinical testing at this time. Lastly, postexposure prophylaxis is occasionally being prescribed for high-risk exposures, although there are very few data on safety and efficacy. While these new strategies are being tested, providers must continue risk assessments to identify women at risk for acquiring or transmitting HIV and assist them in reducing their risk through setting achievable risk reduction plans.

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IV. PRIMARY MEDICAL CARE

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I. INTRODUCTION

No field in medicine today is moving as swiftly as that of HIV/AIDS. The speed at which new developments occur and the rapidity with which they are superseded by newer data are nothing short of breathtaking. As a consequence, most studies are typically out of date at the time of publication. Because of the rapid turnover of key information, this chapter focuses on the essential principles of care for the HIV-infected woman. "Cutting-edge" treatment strategies currently being studied will be mentioned but not described in detail. To be truly useful, we indicate the general directions in which this field is moving and how to access updated information.

Several studies have demonstrated that positive clinical outcomes are a function of the clinician's experience in caring for HIV-infected individuals (Kitahata, 1996). Nonspecialists are urged to seek expert advice and consultation whenever there is any question about the best way to manage a specific patient. This is especially important in the setting of antiretroviral treatment failure and in advanced HIV disease when patients are vulnerable to multiple simultaneous opportunistic processes.

There is as yet no compelling evidence that the clinical course of HIV infection in women differs significantly from that in men, with the obvious exception of the associated gynecologic conditions and obstetric issues (described elsewhere, see Chapters VI and VII). Although recent data have indicated that women may have lower HIV viral loads than men with an equivalent degree of immunosuppression, this does not appear to confer benefit in terms of overall survival or complication-free survival (see Chapter I: Epidemiology and Natural History of HIV Infection in Women). At present, the approach to management of HIV-infected women and men is the same. With prolonged survival now possible, general preventive strategies and health maintenance, such as smoking cessation, control of hypertension, minimizing cardiovascular risk factors, and routine screening for malignancy (cervical, breast, colon), are all part of routine care for HIV-seropositive adults.

II. INITIAL EVALUATION

A. HISTORY

A comprehensive database is valuable to the primary caregiver in assessing the patient's current status and in formulating a management plan. It is critical to remember that most patients are anxious and frightened at their initial encounter for HIV care; the ability to empathize, to share knowledge without being patronizing, to provide reassurance, and to remain nonjudgmental are essential to gaining the patient's trust and to obtaining accurate information (see Chapter II: Approach to the Patient). In addition to all the usual aspects of history-taking, the following areas are of particular importance in HIV disease and deserve special attention.

- **HIV diagnosis:** When did you first test positive for HIV? Why were you tested? This neutral, open-ended start permits the patient to ask questions about HIV risk behaviors and possible route(s) of transmission, including sexual partners and practices and alcohol/drug use behaviors. If the patient can identify the source of new infection, it is valuable to know if the source patient has been treated for HIV, as the acquisition of drug-resistant infection has increasingly been reported. Was the patient ever tested for HIV before? If prior test(s) were negative, it is valuable to assess whether HIV has been relatively recently acquired by looking for evidence of the acute seroconversion syndrome within the past 6–9 mo. These symptoms are classically those of seronegative mononucleosis — fever, aches, pharyngitis, lymphadenopathy, and frequently rash, although the range of possible clinical manifestations of acute HIV infection is very broad.
- **HIV treatment history:** If the patient has already been treated for HIV disease, then it is extremely valuable to know the patient's pretherapy CD4 cell count, HIV viral load, and specific treatment history. What was her prior antiretroviral therapy, including duration? Were there any difficulties with adherence, response to therapy, adverse effects, or history of treatment-limiting intolerance to any agent? Was resistance testing done and, if so, are results available? It is important to determine what, if any, obstacles she has experienced in taking antiretroviral therapy as prescribed (see Chapter V on Adherence). Has she had any HIV-associated diagnoses and was she treated for these conditions? Has she taken any opportunistic infection prophylaxis? Has she ever been hospitalized? If so, was it for an HIV-related problem?
- **History of sexually transmitted infections and other infectious diseases:** Including syphilis, gonorrhea, herpes simplex, pelvic inflammatory disease, anogenital warts; tuberculosis (PPD status, exposure to active case, prior prophylaxis or treatment for active disease); hepatitis A, B, or C; prior vaccinations, including those for childhood illnesses, hepatitis A and/or B, pneumococcal infection

and influenza; history of chicken pox or shingles; complete gynecologic history (see Chapter VI on Gynecologic Problems), including most recent evaluation, Pap smear, and results.

- **History of other medical diagnoses:** With particular attention to hypertension, type 2 diabetes, cardiovascular disease, premalignant or malignant conditions.
- **Sexual practices:** Including use of condoms (male and/or female versions) and/or other forms of birth control, consistency of use; number of current partners and their HIV status (if known); sexual activity with men, women, or both; history of trading sex (oral or intercourse) for drugs or money; history of anal sex.
- **Presence of HIV-associated signs and symptoms:** Fatigue, lymphadenopathy, weight loss, skin problems, bacterial pneumonia, thrush (oral, vaginal), as well as signs/symptoms more typical of advanced HIV disease, including fevers, night sweats, persistent diarrhea, severe headache, respiratory symptoms (especially progressive dyspnea on exertion and cough, whether productive or nonproductive), mental status changes, difficulty swallowing, midline substernal discomfort with swallowing, and visual changes, particularly the presence of floaters or visual field deficits.
- **Mental health history:** Past and current problems, evidence of depression (trouble sleeping, early awakening, change in appetite, loss of interest in usual activities, anhedonia).
- **Family history:** Age and health of children, including HIV test results if performed; HIV in other family members; other medical diagnoses, especially hypertension, type 2 diabetes, cardiovascular disease, malignancy in family members.
- **Medications taken regularly:** Including prescription and over-the-counter remedies; history of and attitude toward regular medication use; use of alternative (nontraditional) medications for HIV or other conditions; drug allergies.
- **Social history:** Place of birth, where patient was raised, where and with whom patient lives and relationship to others in the household; childcare responsibilities; history of domestic violence; pets, especially reptiles (risk of salmonellosis) and kittens (risk of toxoplasmosis); extent of formal education; occupational history and potential toxic exposures; travel history; cigarette, alcohol, and illicit drug use in the past or continuing; misuse of prescription medications.
- **Sources of support:** To whom has the patient disclosed her diagnosis and what were their reactions? Are there friends or family to whom disclosure seems possible either now or perhaps in the future? Are other family members HIV-positive? Are family or friends able to care for the patient's children in the event of illness? Does she have a job and, if so, does it provide health insurance?

Just as important as the information that the clinician obtains in the history-taking process is the information about HIV disease that is shared with the patient. Counseling and education are important elements of the therapeutic bond with the caregiver, but because this entails an enormous amount of information, it is best broached initially and then reintroduced and reinforced at appropriate intervals.

Many patients are in a state of shock following diagnosis, or may be suffering from situational depression or fear of their partner's response. Be kind. Be patient. Schedule enough time (1 hr) for the initial visit. Make sure the patient knows your purpose is to support her and care for her. Another key bond is the one between the patient and the office/clinic nurse, which should be encouraged. Ensure that she has a path to reach you or the nurse for any questions, complaints, or symptomatic therapy, especially when starting antiretroviral therapy.

It is important to convey information in lay language at a level of complexity appropriate to the patient's level of comprehension (remembering that formal educational levels may not necessarily correlate with the patient's ability to understand complicated medical concepts). These include the following areas.

- **HIV pathogenesis:** What are CD4 lymphocytes and why are they important? How does HIV infection affect CD4 cells?
- **Natural history of HIV disease:** How is "AIDS" different from "HIV infection" (or "HIV disease")? What is the typical time course between acquisition of HIV and the development of HIV-associated problems? AIDS?
- **Monitoring the activity of HIV disease:** What do CD4 cell counts and HIV viral load tests measure? How are they used, and how often will they be repeated?
- **Goals of HIV disease management:** To maintain or improve the patient's immune system, control HIV replication; avoiding or minimizing side effects of medications; preventive care (vaccinations, opportunistic infection prophylaxis, periodic Pap smears, other appropriate screening tests).
- **Principles of HIV treatment:** Describe the available viral targets and classes of drugs used, and the value of combination therapy in preserving health and prolonging life. Underscore the importance of adherence.
- **Preventing spread of HIV infection:** Notifying sexual partners and drug use contacts, safer sexual practices, safer needle use including needle exchange programs, ready availability of bleach in the household for cleaning up blood, appropriate wound care for accidental injuries, reassurance about the difficulty of transmitting HIV to casual contacts and to family members even in the close context of everyday family life.

Last, because a diagnosis of HIV infection means a chronic, life-threatening disease and still carries a social stigma, the clinician plays a key role in exploring mental health and psychosocial needs, helping the patient identify potential sources of support, and referring the patient for additional medical, psychiatric, and/or social services.

B. PHYSICAL EXAMINATION

The examination may yield clues to specific HIV-associated conditions. Vital signs should be tracked carefully, particularly temperature and weight. The discovery of hypertension, largely ignored in the past, should trigger appropriate attempts at control, including weight loss, reduction of salt intake, and medication if necessary. Special attention should be paid to the following areas.

- **General:** Evidence of wasting, often prominent at the temples; fat redistribution syndromes including the development of a buffalo hump, enlarged breasts, and truncal obesity, which may coexist with or be separate from marked subcutaneous fat loss in the extremities, face, and buttocks.
- **Eyes:** The conjunctival surfaces should be examined for the purplish spots of Kaposi's sarcoma (KS) and for petechiae. Fundoscopy may reveal "cotton wool" spots (microinfarcts of the retinal nerve fiber layer due to occlusion of retinal capillaries). These must be differentiated from the typical 'eggs and ketchup' appearance of the infiltrates and hemorrhages caused by cytomegalovirus (CMV) retinitis in patients with very advanced HIV disease; visual field deficits are common in CMV retinitis and may be uncovered with simple field testing by confrontation.
- **Oropharynx:** Oral examination often yields the earliest physical evidence of HIV infection with thrush (white plaques on buccal mucosa or posterior pharynx that are readily scraped with a tongue blade) and oral hairy leukoplakia (furry white plaques most often found on the lateral margins of the tongue that cannot be scraped off); purplish spots or plaques on mucosal surfaces, including the area under the tongue, typically indicate Kaposi's sarcoma but may also be consistent with bacillary angiomatosis. No examination of an HIV-infected person, regardless of disease stage, should be considered complete without a careful assessment of the oropharynx.
- **Lymph nodes:** Nontender or minimally tender generalized adenopathy may wax and wane and most often is related to HIV infection itself, but may also indicate lymphoma. Regional adenopathy is more frequently associated with local pathology, such as intrathoracic adenopathy in tuberculosis or abdominal adenopathy in disseminated *Mycobacterium avium* complex (MAC) infection. Extremely tender lymph nodes should trigger an evaluation for the etiology.

- **Lungs:** Fine, dry “cellophane” rales are classic for *Pneumocystis carinii* pneumonia (PCP), but are a late finding and may be absent.
- **Hepatosplenomegaly:** Organomegaly typically reflects disseminated infection with MAC, tuberculosis, or histoplasmosis, or may be a sign of lymphoma.
- **Pelvic examination:**
 - **External genitalia/perineum:** Sores or ulcers are usually indicative of sexually transmitted infections, especially herpes simplex virus (HSV) or syphilis. In very immunosuppressed patients, ulcers may be caused by other opportunistic pathogens, such as CMV, or may represent aphthous ulcers. Condyloma acuminata may appear as small, fleshy papules or may be exuberant, florid growths reaching several centimeters in diameter; other human papillomavirus-associated lesions may be recognized only with magnification and/or application of acetic acid. Raised and pigmented lesions may represent premalignant changes (vulvar intraepithelial neoplasia).
 - **Speculum and bimanual pelvic examination:** Abnormal vaginal discharge can be caused by various forms of vaginitis (yeast, bacterial vaginosis, or trichomoniasis) or cervicitis. Pap smears should be obtained to rule out cervical dysplasia. Cervical motion, and uterine and adnexal tenderness suggest possible pelvic inflammatory disease. (Gynecologic exam is discussed in detail in Chapter VI.)
- **Neurologic:** Motor deficits may reflect space-occupying lesions of the central nervous system (CNS) such as toxoplasmosis, CNS lymphoma, and progressive multifocal leukoencephalopathy, or may be due to neurosyphilis. Symmetrical, distal sensory deficits (especially decrease or loss of vibratory or proprioceptive sensation), typically affecting the feet more than the hands, indicate peripheral neuropathy, which may be due to HIV itself or to drug toxicity from the dideoxy nucleoside analogues. Poor short-term memory, diminished concentration, and sensorimotor retardation are the hallmarks of AIDS dementia complex (HIV encephalopathy). Dysphoric mood or flat affect may reveal depression.
- **Skin:** Like the oropharynx, careful examination of the skin often yields early clues about HIV infection, and should be performed regularly. Early manifestations include pruritic papular eruptions that may be bacterial folliculitis, eosinophilic folliculitis, or scabies. Pearly papules, often with central umbilication, are typical of molluscum contagiosum. A painful vesicular rash may be HSV but in a dermatomal distribution is usually shingles (varicella-zoster virus). Seborrheic dermatitis may be severe and appears as scaly, erythematous areas on the face, especially the nasolabial fold and eyebrows, or may be confined to the scalp and hairline. Psoriasis is another common scaling lesion. Purplish macules or plaques may be either KS or bacillary angiomatosis, similar to their appearance on mucosal surfaces; however, in dark-skinned individuals, KS may appear more brown than purple.

III. LABORATORY TESTING

A. INITIAL DIAGNOSIS

Because of the advances made in HIV treatment, with associated decreases in HIV-related morbidity and mortality; concerns about possible increases in HIV incidence; and the new availability of a simple rapid HIV test (Oraquick), the CDC recommends that voluntary HIV testing be made a routine part of medical care for all patients in high HIV-prevalence clinical settings and for those with risks for HIV in low HIV-prevalence clinical settings. (CDC, 2003).

HIV infection is usually diagnosed by serologic tests that detect antibody to the virus. Infection may also be detected by nucleic acid-based assays that either measure the number of copies of the virus in plasma (RNA polymerase chain reaction [PCR]) or detect the virus in cells (DNA). Informed consent, with pre- and posttest counseling, is legally mandatory for performing HIV serologic tests in most locations, and should be procured at all times when the test is offered.

- **Serology:** The most common method of HIV detection is with an enzyme-linked immunosorbent assay (ELISA) test for screening, followed by confirmation with a Western blot. For a positive Western blot, the Centers for Disease Control and Prevention (CDC) and Association of State and Territorial Public Health Laboratory Directors require a band pattern indicating antibodies to two of the following proteins: p24, gp41, and gp120/160. A serologic test may be reported as positive if the ELISA is positive and Western blot criteria are met. The test may also be reported as indeterminate if the ELISA is positive, but only a single band is detected by Western blot. Serologic tests generally become positive 3–12 wk after infection occurs. The interpretation of an indeterminate test during this window period may be clarified by a quantitative virology assay with a PCR-based technique (see below). An indeterminate test may reflect the process of seroconversion, but may also be a constant finding in an uninfected individual. Causes of indeterminate results include:
 - seroconversion;
 - advanced HIV infection with decreased titers of p24 antibodies (rare)(seroreversion);
 - autoantibodies due to autoimmune or collagen vascular diseases or malignancy;
 - cross-reactive alloantibodies from pregnancy, blood transfusions, or organ transplantation; and
 - previous receipt of an experimental HIV vaccine.

When indeterminate results are obtained, risk assessment is important, since women in low-risk categories with indeterminate tests are unlikely to be infected and can be reassured. Nevertheless, after indeterminate test results, repeat testing should be performed at 1, 2, and 6 months, and precautions should be

taken to prevent HIV transmission to others until seroconversion is ruled out. In general, patients with indeterminate tests who are in the process of seroconversion usually have positive Western blots within 1 month. In high-risk patients or in other situations where seroconversion is suspected HIV nucleic acid amplification (HIV-DNA PCR, HIV-RNA PCR) may be considered and has high sensitivity during acute infection, often before antibodies to the virus have developed.

The window period before seroconversion and agammaglobulinemia are possible causes of false-negative results.

Although infection with HIV-2 (more common in West Africa) and HIV-1 subtype O have been associated with indeterminate and false negative results on earlier generation serologic tests, most currently used assays will detect these infections.

Accuracy of HIV serologic testing is quite high (>99% sensitivity and specificity), but the predictive value of a positive or negative test depends on the seroprevalence of HIV in the patient population. In a low prevalence population, the rate of false-positive results of combined ELISA and Western blot testing is < .001%. The frequency of indeterminate results in a low prevalence population is .02%.

- **Viral detection**

- Nucleic acid amplification. May be used to clarify the diagnosis of HIV infection in acute infection, during the window period (after exposure, before seroconversion), when serologic tests are indeterminant, or with neonatal infection.

- > **Plasma HIV RNA.** Routinely used to monitor the course and treatment of HIV infection (see below). The three most common techniques are reverse transcriptase polymerase chain reaction (RT-PCR), a branched DNA (bDNA) technique, and nucleic acid sequence-based amplification (NASBA). These tests report the number of copies of virus per milliliter of plasma. The assays are considered equally reliable, but vary somewhat in lower levels of detection and dynamic range. Lower limits of detection for standard tests are 100–400 copies/mL, but ultrasensitive assays are available that can detect as few as 20–50 copies/mL. Sensitivity is 90–95% overall, but is increased to 98–100% with CD4 counts < 200/mm³. False-positive rates are 2–3%, usually with low HIV RNA titers (Rich, 1999).

- > **DNA PCR.** A qualitative test used to detect intracellular virus, and primarily used for viral detection with neonatal infection and with indeterminant serology. Sensitivity is >99% at all stages of infection and specificity is approximately 98%.

- **Viral isolation.** Qualitative or quantitative cultures are used primarily for diagnosis in neonatal HIV infection, and for more in-depth viral analysis. The procedure is expensive and labor intensive. Sensitivity is 95–100%.

- **Alternative tests**

- **Home testing:** Home Access Express Test is the only available home test for HIV as of May 2003. Filter paper with a blood sample obtained with a lancet is mailed in to a laboratory in a coded, anonymous process. Dried blood samples are tested by the same ELISA and Western blot tests used on venous blood. Sensitivity and specificity approach 100%. Results are provided by phone (a recorded message for those with negative results, counseling for those with positive results).
- **Rapid tests:** The OraQuick Rapid HIV Test provides results in 10–20 minutes. Sensitivity approaches 100%; specificity is also >99%, but positive results should be confirmed with standard serology. Rapid tests may prove useful in STI clinics or emergency rooms (where patients often do not return for tests results) or on labor and delivery wards for high-risk pregnant women who have not previously been tested.
- **Saliva test:** The OraSure test uses ELISA and Western blot testing to detect antibodies to HIV in saliva. Sensitivity and specificity are similar to that with standard serology. This test is useful for people with poor venous access or those who want HIV testing, but refuse blood tests.
- **Urine test:** The only currently available urine test (Calypte HIV-1 Urine EIA) is licensed for screening only and must be administered by a physician; a positive result requires confirmation by another method.

B. BASELINE LABORATORY EVALUATION

After the diagnosis of HIV has been confirmed, a baseline laboratory evaluation is needed to establish the stage of disease, and exposure to other infectious diseases (Table 4-1). In addition, routine tests of hematology, chemistry, and lipid profiles are needed at baseline, because HIV and other concomitant illness may affect these values, and detected abnormalities may also have an impact on the choice of therapy for the individual patient.

- **CD4 lymphocyte count:** The hallmark of HIV infection is the progressive decline in CD4+ (helper) T lymphocytes. Normal laboratory ranges for CD4 lymphocyte counts are usually 500–1400/mm³. CD4 counts may drop precipitously at the time of primary HIV infection, and then usually rebound to near-baseline levels. The natural history of HIV then involves a progressive loss of CD4 cells, averaging 30–60 cells/yr (Figure 4-1). The risk of opportunistic infections increases with declining counts. (See Chapter I on Epidemiology and Natural History.)

Knowledge of the baseline CD4 count is of vital importance in assessing the patient: staging of HIV infection (Table 1-3 in Chapter I), recommendations for antiretroviral treatment (see Section IV. C), and prophylaxis against specific opportunistic infections (see Section V. A) are based on the degree of immunosuppression as quantified by the CD4 count.

Many factors may cause variability in the CD4 count. These include:

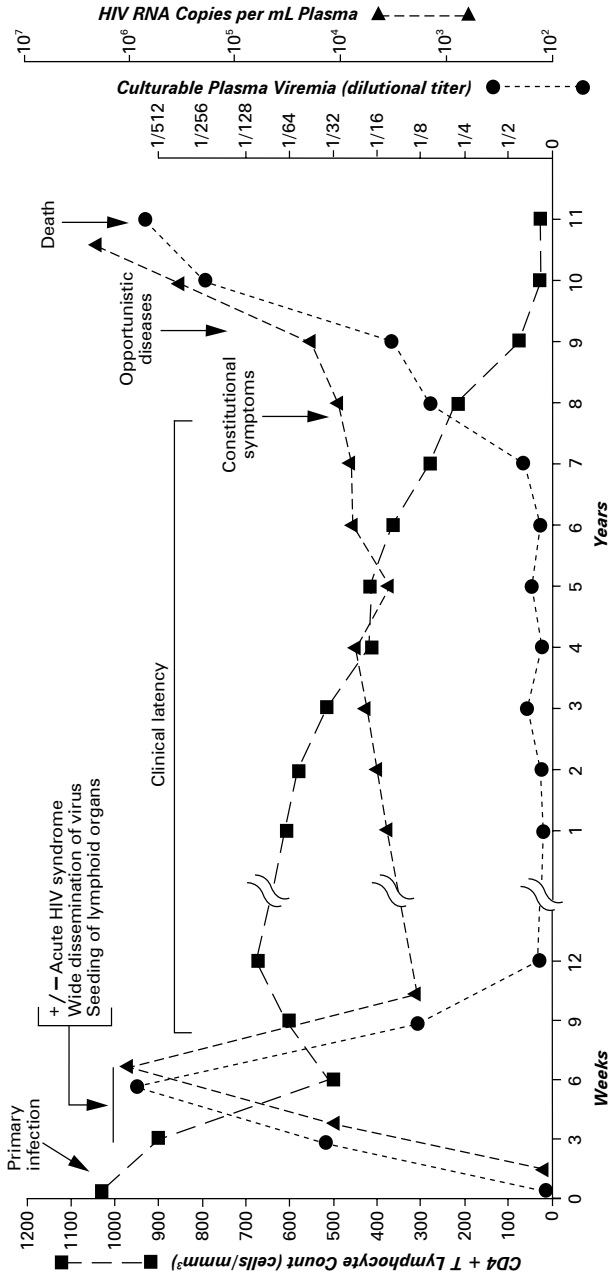
- interlaboratory variations;
- seasonal and diurnal variation (lowest levels at noon, highest in the evening)
- the use of corticosteroids (decreases values)
- intercurrent illness (decreases values)
- HTLV-1 coinfection (increases values).

In addition, because the CD4 count is a value derived by determining the percentage of white blood cells that are lymphocytes, and then the percentage of lymphocytes that are CD4 receptor-positive, there may be variation in other white blood cell compartments (as may occur in pregnancy) that leads to variations in the CD4 count. Because the CD4 percentage is the directly measured value and the absolute CD4 count is the calculated one, it is more useful and accurate to focus on the CD4 percentage to assess trends in this important parameter.

Table 4-1: Baseline Laboratory Evaluation

<input type="checkbox"/> Confirm HIV diagnosis (usually with ELISA and Western blot)
<input type="checkbox"/> CD4 count
<input type="checkbox"/> Viral load
<input type="checkbox"/> Chemistry panel: including liver and renal function
<input type="checkbox"/> Hematology panel: including white blood cell count differential
<input type="checkbox"/> Lipid profile: total cholesterol, HDL, LDL, triglycerides
<input type="checkbox"/> Serologies: syphilis, toxoplasmosis, CMV, varicella-zoster virus (if no history of chickenpox or shingles), hepatitis A, hepatitis B, hepatitis C
<input type="checkbox"/> PPD
<input type="checkbox"/> G6PD (in selected patients)
<input type="checkbox"/> Pap smear/STI screening

Figure 4-1: Natural History of HIV Infection without the Use of Antiretroviral Therapy



Source: Fauci, 1996. Copyright American College of Physicians. Reprinted with permission.

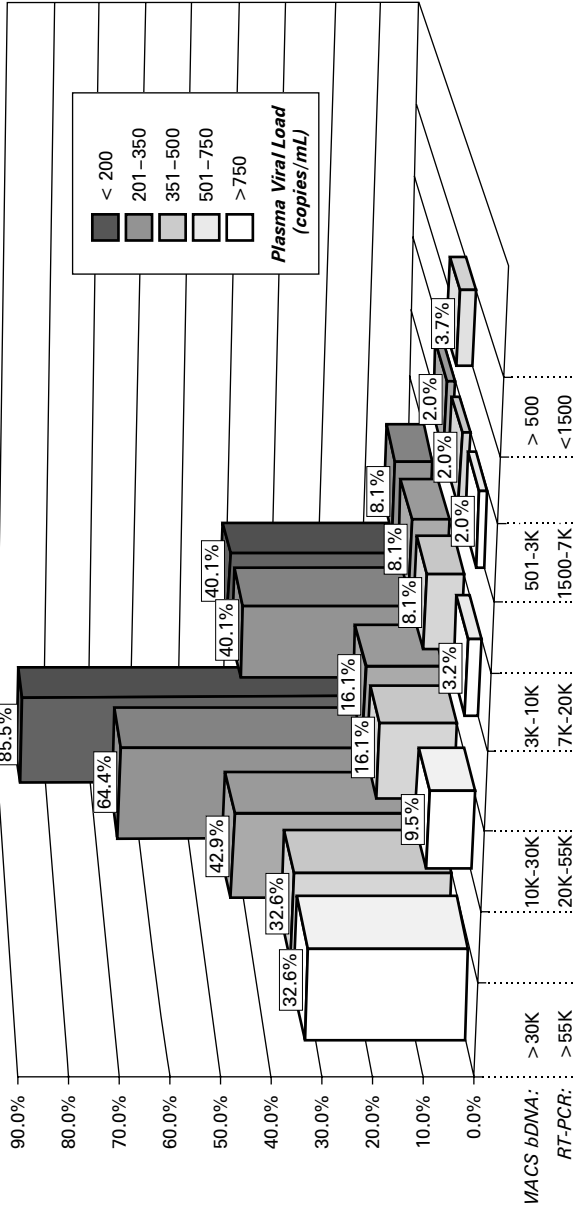
- **Quantitative virology/viral load assays:** The HIV RNA level or “viral load” is also of pivotal importance in assessing the HIV-infected patient. Whereas the CD4 count indicates the current degree of immunosuppression, the viral load indicates the rapidity with which the disease is likely to progress: higher viral loads have repeatedly been shown to be associated with a more rapid rate of disease progression (Figure 4-2). Recent studies have shown that women have lower viral loads than men at comparable CD4 cell counts, although these viral load differences tend to disappear several years after seroconversion and they have not been associated with slower disease progression or longer survival (see Chapter I: Epidemiology and Natural History of HIV Infection in Women).

The most commonly used methods to quantify HIV RNA are RT-PCR, bDNA, and NASBA techniques (see Viral Detection, above). Standard tests have lower limits of detection of 100–400 copies/mL, but current ultrasensitive assays can detect as few as 20 copies/mL. Although results of different viral load assays correlate, absolute values differ and there is no standard multiplication factor to translate between results in the different assays. Therefore, the same assay should be used to follow an individual patient longitudinally. Intraperson variability on viral load assays is $< .5$ log, but this degree of variability is important to consider when determining clinical significance of a reported change in viral load values for an individual patient.

Indications for plasma HIV RNA testing are shown in Table 4-2. It is also critical to repeat any HIV RNA result that is being used as the basis for a change in patient management.

- **Hematology and chemistry panels:** The effects of HIV and related infections may involve hematologic, renal, or hepatic abnormalities. A complete blood count is necessary at baseline to evaluate for leukopenia, anemia, and thrombocytopenia. In addition, the total white blood cell count and lymphocyte count are needed to calculate an absolute CD4 count. A chemistry panel that includes an evaluation of renal and hepatic function is also necessary: HIV-associated nephropathy may be indicated by elevations in blood urea nitrogen/creatinine, and the effects of viral hepatitis, alcohol, or medications may cause abnormalities of liver function tests. Any of these findings provide important information in their own right, but will also have an impact on the patient's options for antiretroviral therapy.
- **Other serologies:**
 - **Syphilis:** High rates of coinfection with other STIs necessitate routine syphilis serology in all HIV-infected patients. A reactive nontreponemal assay (RPR or VDRL) must be confirmed with the treponemal-specific FTA or MTPA. Cerebrospinal fluid evaluation is indicated in HIV-infected persons with latent syphilis, treatment failure (when a nontreponemal test does not decline 4-fold within 6–12 mo after treatment), and those patients with neurologic signs or symptoms.

Figure 4-2: Likelihood of Developing AIDS within 3 Years



Source: Adapted from Mellors, 1997. Copyright American College of Physicians. Reprinted with permission.

Table 4-2: Indications for Plasma HIV RNA Testing*

<i>Clinical Indication</i>	<i>Information</i>	<i>Use</i>
Syndrome consistent with acute HIV infection	Establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis [†]
Initial evaluation of newly diagnosed HIV infection	Baseline viral load "set point"	Decision to start or defer therapy
Every 3–6 mo in patients not on therapy	Changes in viral load	Decision to start therapy
2–8 wk after initiation of antiretroviral therapy	Initial assessment of drug efficacy	Decision to continue or change therapy
3–6 mo after start of therapy	Maximal effect of therapy	Decision to continue or change therapy
Every 3–6 mo in patients on therapy	Durability of antiretroviral effect	Decision to continue or change therapy
Clinical event or significant decline in CD4+ T cells	Association with changing or stable viral load	Decision to continue, initiate, or change therapy

* Acute illness (e.g., bacterial pneumonia, tuberculosis, HSV, PCP, etc.) and immunizations can cause increase in plasma HIV RNA for 2–4 wk; viral load testing should not be performed during this time. Plasma HIV RNA results should usually be verified with a repeat determination before starting or making changes in therapy.

† Diagnosis of HIV infection made by HIV RNA testing should be confirmed by standard methods such as Western blot serology performed 2–4 mo after the initial indeterminate or negative test.

Source: DHHS, 2005.

- **Toxoplasmosis:** Serologic evidence of latent toxoplasmosis infection, as detected by *Toxoplasma gondii* IgG, may be relevant for decisions on prophylaxis, evaluation of neurologic symptoms in patients with advanced immunosuppression, and avoidance of exposure in those who have not been previously infected. There is great worldwide variation in the prevalence of latent toxoplasma infection: in the United States the rate is approximately 30%.
- **CMV:** Latent CMV infection is present in most HIV-infected adults. Knowledge of CMV antibody status can guide the medical provider to the use of CMV-negative blood products if transfusions are required.
- **Varicella:** In patients who do not have a known history of chickenpox or shingles, varicella serology should be obtained. The knowledge that a patient is varicella IgG-negative is important in the event of a subsequent exposure: postexposure prophylaxis with varicella immune globulin could then be given.

- **Hepatitis:** Hepatitis A serology will identify those who are not immune, and are therefore vaccine candidates. Hepatitis A vaccine should be given to patients with hepatitis C co-infection, other chronic liver disease, and perhaps to all HIV-infected patients. Hepatitis B serologies should be performed routinely: hepatitis B surface antigen (HBsAg) and hepatitis B core or surface antibodies (anti-HBc and anti-HBs) allow determination of active hepatitis (HBsAg-positive) and of those who are not immune to hepatitis B (anti-HBc-negative, anti-HBs-negative). Hepatitis B vaccination is then recommended in those who are not immune; and antiviral therapy, such as lamivudine (which has anti-hepatitis B activity), can be considered in those who are HBsAg-positive. Hepatitis C virus (HCV) serology (anti-HCV IgG) is also routinely recommended. Recombinant immunoblot assays (RIBA) for HCV are used to confirm the diagnosis if a screening ELISA is positive. HCV RNA, as detected by RT-PCR or bDNA assay, can also be used to confirm the diagnosis and allows determination of active HCV infection. Knowledge of hepatitis C antibody status is needed to guide therapeutic decision for possible HCV treatment and may also be relevant for decisions regarding antiretroviral therapy and other potentially hepatotoxic agents, and frequency of assessment of liver function tests during such therapy (see Table 4-3).

<i>Hepatitis Virus</i>	<i>Laboratory Test</i>	<i>Interpretation</i>
A	Anti-HAV IgM	Recent HAV infection
	Anti-HAV IgG	Immunity to HAV
B	HBsAg	Current (acute or chronic) HBV infection
	HBeAg	Current HBV infection with high risk of infectivity
	Anti-HBc	Past or present HBV infection
	Anti-HBs	Immunity to HBV (past infection or after vaccination)
C	Anti-HCV IgG (ELISA)	Past or present HCV infection
	Anti-HCV IgG (RIBA)	Confirms HCV ELISA
	HCV RNA	Current HCV infection

- **Tuberculosis:** A baseline PPD should be obtained in all patients who do not have a history of a positive PPD in the past. A positive PPD is considered >5mm induration in the setting of HIV infection.
- **Glucose-6-phosphate dehydrogenase:** A relative deficiency of glucose-6-phosphate dehydrogenase (G6PD) may be found in up to 2% of African American women and an absolute deficiency is occasionally found in women of Mediterranean descent. Absolute

G6PD deficiency predisposes to hemolytic anemia upon exposure to certain medications, including several that are commonly used in HIV treatment: dapsone, sulfonamides, primaquine. A relative deficiency is not usually clinically significant. Baseline testing in selected patients is helpful so that these agents may be safely administered at a later date without needing to determine G6PD levels at that point.

- **Lipid profile:** Many antiretroviral agents have been associated with the development of hypertriglyceridemia and hypercholesterolemia. A baseline fasting lipid profile should be performed to determine total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels before beginning any antiretroviral therapy.
- **Pap smear/STI screening:** A Pap smear should be obtained, and testing done for gonorrhea and *Chlamydia* (see Chapter VI Gynecologic Problems).

C. INTERVAL MONITORING

In an asymptomatic patient not taking antiretroviral therapy with a high ($> 500/\text{mm}^3$) CD4 count, follow-up every 6 mo may be appropriate. For those patients who are symptomatic and/or receiving antiretroviral therapy, visits should occur at least every 3 mo. For those who have just initiated or changed antiretroviral therapy, follow-up in 4–6 wk may be appropriate. Laboratory evaluation at each of these visits should routinely include the following: complete blood count with differential, CD4 lymphocyte count, and viral load. Chemistry panels may be done less frequently (every 6 mo) in a patient with prior normal values who remains clinically stable.

Hematology and chemistry values are needed to monitor possible medication toxicities, complications of HIV, and other possible illnesses. The CD4 count and viral load allow assessment of disease progression and effects of antiretroviral therapy. In following the CD4 count over time, it is important to recognize the causes of variability discussed above. Use of the CD4 percentage, rather than absolute CD4 count, may help eliminate some of this variability to clarify CD4 response to medications. In interpreting viral load changes over time, the variability of tests results must be noted: .3–.5 log. In a patient who previously had a viral load below the limit of detection of the assay being used (“undetectable”), who now has quantifiable virus, a repeat test should be performed as soon as possible, rather than waiting until routinely scheduled follow-up.

The frequency with which lipid profiles are checked will vary by individual patient characteristics. In patients not taking antiretroviral therapy, a baseline lipid profile should be done with the initial evaluation or before beginning antiretroviral therapy. The profile should include total cholesterol, HDL,

LDL, and triglycerides. If the baseline is normal and the patient is not on antiretroviral therapy, there is no need for interval monitoring beyond that which would be done in an HIV-uninfected adult. In patients taking combination antiretroviral therapy, general guidelines are:

1. Get a baseline lipid profile (fasting) before starting therapy.
2. Follow total cholesterol with routine chemistry panels.
3. Obtain a complete fasting lipid profile annually or if the total cholesterol begins to increase on routine testing.
4. Follow complete lipid profiles every 3–6 mo for patients in whom a lipid abnormality has been detected, both before starting any antihyperlipidemic therapy and once such therapy has been started.

Recommendations for management of hyperlipidemia may be found at <http://www.americanheart.org>.

Annual monitoring of syphilis serology for reactivation or new infection is generally recommended. PPDs should also be checked annually if the patient belongs to a population with high epidemiologic risk of tuberculosis.

Baseline data and interval monitoring may be followed by the use of a flow sheet such as the one developed at the Johns Hopkins Outpatient HIV Clinic (Figure 4-3).

Figure 4-3: Patient Intake Flow Sheet

Attach Label		Race	Risk	
		Provider		
		Site: () Moore Clinic () GSS () Country		
		Hopkins Function () 1° Care () Specialty () Consultation		
		Other PCP		
DATES				
1° Infection		HIV+	Confirmation	1st JHH visit
AIDS		AIDS Reported	Psychosocial	Nutrition
BASELINE DATA				
HBsAg		HBsAb	anti-HCV	total HAV
Toxo		CMV	VZC	G6PD
Baseline lipids:	T Chol.	HDL Chol	LDL Chol	TG
IMMUNIZATIONS				
Pneumovax (q 5 yr)		dT (q 10 yr)		
HBV	#1 (mo. 0)	#2 (mo. 1)	#3 (mo. 6)	
HAV	#1 (mo. 0)	#2 (mo. 6)		
ONGOING HEALTH CARE MAINTENANCE				
Years				
Full Physical Exam				
PPD (annual if at risk)				
RPR (annual)				
Ophtho exam (CD4 < 50)				
Occ. Bld (age 50+, annual)				
Flex. Sig./Colonoscopy				
GC/Chlamydia				
Flu vaccine (annual)				
Other				
Women:				
Pap Smear (annual)				
Mammogram				
Birth control review (annual)				
Men:				
PSA (consider 50+, annual)				
MISCELLANEOUS				
Advance Directives (dates discussed, location of documents)				
Family/Contacts (names, contact info)				
Case Manager				
Home Care				

IV. ANTIRETROVIRAL THERAPY

A. GENERAL PRINCIPLES

Three characteristics of HIV infection have significant implications for antiretroviral therapy (see Chapter VII HIV and Reproduction for discussion of antiretroviral therapy in pregnancy).

1. Between the time of initial infection and the development of clinical disease there is progressive immunosuppression as evidenced by a decline in CD4 lymphocyte counts.
2. Viral replication is extremely rapid: the half-life of HIV in plasma is less than 48 hr and there is turnover of up to 1 billion virions per day (Ho, 1995).
3. HIV has a high degree of inherent genetic mutability: mutations that may confer resistance to antiretroviral therapy arise rapidly.

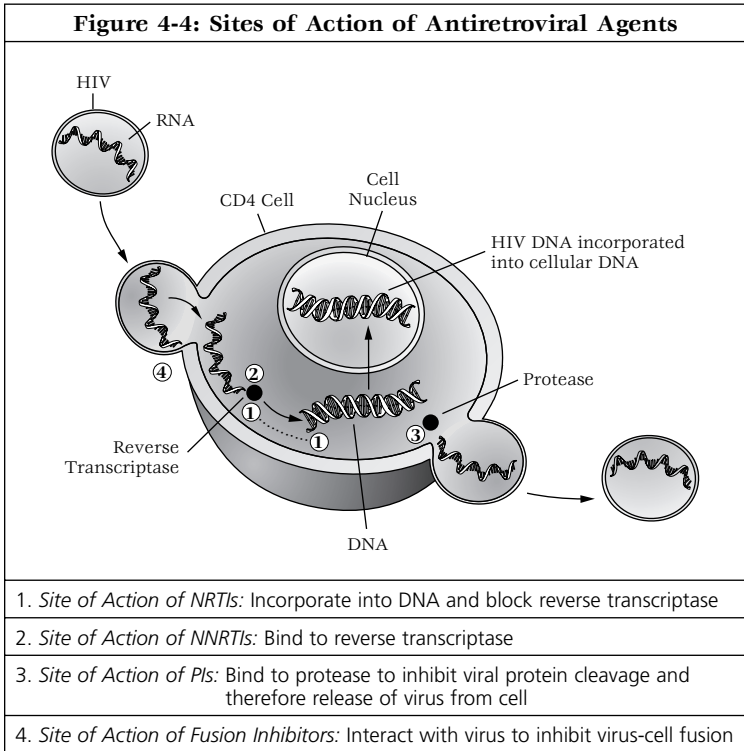
Thus, there is a rationale for initiating antiretroviral therapy before the onset of symptoms (i.e., to prevent immunosuppression), and therapy must be maintained to prevent viral replication. Strategies of antiretroviral therapy have therefore evolved to prevent the development of viral resistance. Although monotherapy with any of the antiretroviral agents will increase CD4 count, the clinical benefit of such therapy is very limited, largely because of the development of viral resistance. Combination antiretroviral therapy has been shown to have superior effectiveness in controlling viral replication and in limiting the emergence of resistant virus. These effects translate into greater clinical benefit: combination therapy reduces the risk of HIV progression and death. In addition, patients with levels of circulating virus that are below 400–500 copies/mL (the limit of detection in the past few years), but greater than 20–50 copies/mL (the limit of detection in the newest generation of tests) will experience virologic failure sooner than those with viral loads below 20–50 copies/mL (Raboud, 1998). Therefore, achievement of the lowest possible viral load should be a guiding principle in the selection of a treatment regimen.

The specific combination of antiretroviral therapy selected for a patient must take into account many factors. These include the specific side effects, dosing schedules, drug-drug interactions of different medications, and history of antiretroviral therapy. See Chapter XIV on Pharmacologic Considerations in HIV-infected Pregnant Patients for information on highly active antiretroviral therapy in pregnancy and Chapter XV on Resources for sources of complete updated information on antiretroviral therapy.

B. ANTIRETROVIRAL AGENTS

NUCLEOSIDE ANALOGUES

Nucleoside analogue reverse transcriptase inhibitors (NRTIs) were the first class of agents shown to be effective in the treatment of HIV infection. The target enzyme for this group of drugs is HIV reverse transcriptase, an RNA-dependent DNA polymerase (see Figure 4-4).



Seven NRTIs are currently licensed in the United States: zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), abacavir, (ABC) and emtricitabine (FTC). There are also 3 combination NRTIs (Combivir, Trizivir, Epzicom), a nucleotide reverse transcriptase inhibitor (tenofovir) and a nucleoside-nucleotide reverse transcriptase inhibitor combination (Truvada) (Table 4-4).

Table 4-4: Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitors			
<i>Generic Name</i>	<i>Trade Name</i>	<i>Standard Dosing</i>	<i>Common Side Effects</i>
Zidovudine (AZT)	Retrovir	200 mg tid or 300 mg bid (2–6 pills/day)	Anemia, nausea, headache
Didanosine (ddI)	Videx/Videx - EC	200 mg bid or 400 mg qd (125 mg bid if <60 kg) (1–4 pills/day)	GI symptoms (diarrhea), peripheral neuropathy, pancreatitis
Zalcitabine (ddC)	Hivid	0.75 mg tid (3 pills/day)	Peripheral neuropathy, pancreatitis
Stavudine (d4T)	Zerit	40 mg bid (30 mg bid if <60 kg) (2 pills/day)	Peripheral neuropathy, pancreatitis
Lamivudine (3TC)	Epivir	150 mg bid or 300 mg qd (1–2 pills/day)	Headache
Lamivudine/zidovudine	Combivir	1 pill bid	As for 3TC and AZT
Abacavir	Ziagen	300 mg bid (2 pills/day)	Hypersensitivity,* rash, GI symptoms
Abacavir/lamivudine/zidovudine	Trizivir	1 pill bid	As per abacavir (including hypersensitivity), 3TC, and AZT
Tenofovir disoproxil fumarate	Viread	300 mg qd (1 pill/day)	GI symptoms
Emtricitabine	Emtriva	200 mg qd (1 pill/day)	Headache, nausea, diarrhea, rash
Abacavir/lamivudine	Epzicom	1 tablet qd	As for 3TC and abacavir
Emtricitabine/tenofovir DF	Truvada	1 tablet qd	As for FTC and TDF

* 3-4% of patients will develop a hypersensitivity reaction to abacavir with symptoms that include fever, rash, myalgias. Rechallenge with abacavir after hypersensitivity reaction may be life-threatening and should never be done.

In addition to the side effects listed for each medication, lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) noncompetitively inhibit HIV reverse transcriptase by binding to a site distant from the enzyme's active site. Three NNRTIs are currently available in the United States: nevirapine, delavirdine, and efavirenz (Table 4-5).

<i>Generic Name</i>	<i>Trade Name</i>	<i>Standard Dosing</i>	<i>Common Side Effects</i>
Nevirapine	Viramune	200 mg qd x 14 days, then 200 mg bid (2 pills/day)	Rash, hepatitis
Delavirdine	Rescriptor	400 mg tid (12 pills/day)	Rash
Efavirenz	Sustiva	600 mg qd (qhs administration may limit CNS side effects) (1 or 3 pills/day)	Headache, dizziness, cognitive effects, rash

PROTEASE INHIBITORS

Protease inhibitors (PIs) prevent maturation of virus protein by competitively inhibiting HIV protease, an enzyme essential for viral protein cleavage. When this enzyme is blocked, immature, noninfectious virus particles are produced. The other important properties that protease inhibitors share include their limited central nervous system penetration and their metabolism by the cytochrome P450 enzyme system and resultant multiple drug-drug interactions (Table 4-6).

<i>Generic Name</i>	<i>Trade Name</i>	<i>Standard Dosing</i>	<i>Common Side Effects</i>
Saquinavir (hard gel capsules)	Invirase	600 mg tid (9 pills/day)	Diarrhea, nausea, abdominal discomfort
Saquinavir (soft gel capsules)	Fortovase	1200 mg tid (18 pills/day)	Diarrhea, nausea, abdominal discomfort
Ritonavir	Norvir	600 mg bid (12 pills/day)	Nausea, abdominal discomfort, circumoral paresthesias
Indinavir	Crixivan	800 mg q8h (6 pills/day)	Nephrolithiasis, GI symptoms
Nelfinavir	Viracept	750 mg tid (or 1250 mg bid) (4–10 pills/day)	Diarrhea
Amprenavir	Agenerase	1200 mg bid (16 pills/day)	GI symptoms, rash

Lopinavir/ ritonavir	Kaletra	Lopinavir 400 mg/ ritonavir 100mg (3 capsules or 5mL) bid (6 capsules/day)	Diarrhea, nausea, abdominal discomfort
Atazanavir	Reyataz	400 mg qd (2, 200 mg capsules/day) 300 mg qd (2, 150 mg capsules/day) if combined with ritonavir 100 mg qd (1 capsule/day)	Nausea, diarrhea, unconjugated hyperbilirubinemia
Fosamprenavir	Lexiva	1400 mg bid (2, 700 mg tablets twice daily) 1400 mg qd (2, 700 mg tablets/day) if combined with ritonavir 200 mg qd (2 capsules/day) 700 mg bid (1, 700 mg tablet twice daily) if combined with ritonavir 100 mg bid (1 capsule twice daily) Adjustment of ritonavir dose needed when fosamprenavir plus ritonavir are administered with efavirenz	GI symptoms, headache, rash

In addition to the medication-specific side effects listed here, a number of abnormalities are associated with protease inhibitors as a class. Patients taking protease inhibitors may develop serum lipid abnormalities (hyperlipidemia, hypertriglyceridemia), redistribution of body fat (lipodystrophy), and/or glucose intolerance.

FUSION INHIBITORS

Fusion inhibitors interact with HIV directly, rather than with the host cell. This interaction prevents fusion of HIV to the cell. The first fusion inhibitor, enfuvirtide (T-20, Fuzeon) was licensed in the U.S. in March 2003. Enfuvirtide must be given by subcutaneous injection (twice daily). The most common side effect is local injection site reactions.

C. ADVERSE CLINICAL EVENTS ASSOCIATED WITH ANTIRETROVIRAL THERAPY

There are several significant adverse clinical events that have been associated with use of antiretroviral therapy. In some cases these are drug specific, while in others an increased risk of a specific adverse event appears to involve an entire class of antiretroviral drugs. The complications discussed below are of particular clinical significance or concern. In general, decisions about management, including future antiretroviral management, should be made in consultation with an HIV expert.

1. **Lactic Acidosis/Hepatic Steatosis:** This is a rare but life-threatening complication associated with use, often prolonged, of NRTIs and appears to more commonly be seen in women. The initial clinical signs and symptoms are nonspecific and may include nausea and vomiting, diarrhea, anorexia, abdominal pain, generalized weakness, myalgias, ascending neuromuscular weakness, and hepatomegaly. In addition to elevated lactate levels, laboratory evaluation may reveal elevated liver function tests, creatine phosphokinase, lipase, and amylase or increased anion gap. There are technical difficulties associated with serum lactate testing and routine testing is not recommended. However, providers should have a low threshold for measuring serum lactate in the presence of suggestive signs or symptoms or other associated laboratory abnormalities. When interpreting serum lactate levels, levels of 2-5 mmol/dL are considered elevated and need to be correlated with symptoms; levels >5mmol/dL are abnormal; and levels > 10 mmol/dL indicated serious and possibly life-threatening situations. Antiretroviral treatment should be stopped if clinical and laboratory manifestations of lactic acidosis occur.
2. **Hepatotoxicity:** Hepatotoxicity, defined as a 3–5 fold increase in serum transaminases, may occur with or without clinical hepatitis. It has been reported with all NNRTIs and PIs and may be present with lactic acidosis associated with NRTI use. Most patients with hepatotoxicity are asymptomatic. Nevirapine has the greatest potential for causing hepatotoxicity (up to 12%) and this complication appears to be more common in women (Martinez, 2001; Bartlett, 2003). Nevirapine-associated hepatitis might also be part of a hypersensitivity syndrome, associated with other symptoms such as skin rash, fever, and eosinophilia. In a recent retrospective analysis of controlled and uncontrolled clinical trials, women with CD4 cell counts > 250 cells/mm³, including pregnant women, receiving chronic treatment for HIV infection, were at significantly higher risk (12-fold) of hepatotoxicity. In some cases hepatic injury progressed despite discontinuation of treatment and fatalities have occurred. (Boehringer-Ingelheim, 2004). Approximately two-thirds of nevirapine-associated clinical hepatitis occurs within the first 12 weeks of treatment and the greatest risk for severe hepatotoxicity in the recent analysis occurred in the first six weeks of treatment and was often associated with rash. However, risk continues after this time and patients should be closely monitored for the first 18 weeks of treatment. Initial presentation may include nonspecific gastrointestinal and flu-like symptoms, and liver enzyme abnormalities may or may not be present. However, this syndrome can progress rapidly to fulminant hepatic failure. A two-week lead-in dosing with 200 mg once daily before dose escalation to 200 mg twice daily is recommended to reduce the incidence of hepatotoxicity. Many clinicians advise close monitoring of clinical symptoms and liver enzymes after starting nevirapine (e.g., every 2 weeks for the first month, then monthly for the first 12 weeks,

and every 1–3 months thereafter). Nevirapine should not be used in future regimens in women who experience severe liver toxicity while taking nevirapine. PI-associated hepatotoxicity can occur any time during the treatment course. Risk factors for liver toxicity include hepatitis B or C infection, alcohol abuse, baseline elevated liver enzymes, stavudine (d4T) use, and concomitant use of other hepatotoxic agents (DHHS, 2003; <http://AIDSinfo.nih.gov>).

3. **Hyperglycemia:** Hyperglycemia has been reported in 3–17% of patients on PI-containing antiretroviral regimens (DHHS, 2003. <http://AIDSinfo.nih.gov>). Preexisting diabetes may be exacerbated. Although routine use of glucose tolerance testing is not recommended, patients should be advised about symptoms of hyperglycemia (i.e., polydipsia, polyphagia, polyuria) and fasting blood glucose measurements should be considered at 3–4 month intervals during the first year of PI treatment for patients with no prior history of diabetes. Patients with preexisting diabetes should be monitored closely.
4. **Lipodystrophy (Fat Maldistribution Syndromes):** Recognition of fat maldistribution syndromes has increased in the era of combination antiretroviral therapy; they are characterized by fat wasting (lipoatrophy) or fat accumulation. The absence of standard case definitions makes it difficult to estimate prevalence. Lipodystrophy might be associated with serum dyslipidemias, glucose intolerance, or lactic acidosis (Joffe, 2001; Carr, 1998). Fat accumulation is most commonly seen in the abdomen, the dorsocervical fat pad, and the breasts. This complication has been most associated with use of PI-containing regimens and prevalence increases with duration of therapy (Miller, 1998). Lipoatrophy most commonly affects the face and extremities and risk has been reported to increase with long-term NRTI exposure (Mallal, 1999). Women seem particularly prone to developing truncal obesity (increased abdominal girth, increased breast size). The etiology of these syndromes is unknown and at the present time, there is no clearly effective therapy. Women who perceive significant changes in body habitus related to their antiretroviral regimen may be at increased risk for nonadherence. It may be useful to obtain some standard measurements, such as minimum waist, maximum hip, and neck circumference at an early visit, before antiretroviral therapy is started. It is important to question the patient at regular intervals about any perceived changes in body shape or changes in clothing and brassiere size, and anthropomorphic measurements may be repeated to document any changes.

Detailed descriptions of medications, drug-drug interactions, and medication use in pregnancy may be found in Chapter XIV on Pharmacologic Considerations in HIV-infected Pregnant Patients.

5. **Hyperlipidemia:** Combination antiretroviral therapy, primarily regimens containing protease inhibitors, has been associated with elevation in total serum cholesterol and low-density lipoprotein (LDL) and in increases in fasting triglycerides (Thiebaut 2000; Romeu 1999). Therapeutic intervention may be needed and, although data remain inconclusive, lipid elevations seen with antiretroviral therapy may be associated with increased risk of cardiovascular complications. Indications for monitoring and treatment of antiretroviral-associated dyslipidemias are the same as among uninfected persons (Adult Treatment Panel III, 2001), although patients with additional risks for atherosclerotic disease should be especially closely monitored (Dube 2000). Low-fat diet, regular exercise, control of hypertension, and smoking cessation should be routinely recommended for all patients, including those treated with antiretroviral agents. When treatment is indicated, statins are generally considered first-line therapy, although potential drug-drug interactions between statins and PIs must be kept in mind and agents that are less affected by the inhibitory effect of PIs via the cytochrome P450 system are preferred (e.g., pravastatin). If lipid elevations are severe or do not respond to other therapy, a change in antiretroviral regimen may be indicated, such as replacement of the PI component with an NNRTI.
6. **Bone Disorders:** There is evidence that avascular necrosis involving the hips and decreased bone density (osteopenia, osteoporosis) may be linked to combination antiretroviral therapy regimens in adults and children (Tebas 2000; Scribner 2000). Diagnosis of osteonecrosis is generally made with CT or MRI ordered in response to complaints of pain. Diagnosis of osteopenia or osteoporosis is made with bone densitometry (dual energy X-ray absorptiometry or DEXA; quantitative ultrasound). Losses in bone mineralization appear to be more common in PI-containing regimens (Tebas 2000). Women are at increased risk for decreased bone density and adequate intake of calcium and vitamin D and appropriate weight-bearing exercise should be recommended. There are no recommendations for routine monitoring of bone density among asymptomatic HIV-infected persons, but additional risk factors, including estrogen deficiency (e.g., menopausal women), alcohol or tobacco abuse, sedentary lifestyle or immobilization, Caucasian or Asian race, wasting, and thin body habitus, should prompt consideration of screening. When significant decreases in bone density are recognized, treatment with bisphosphonates, raloxifene, or calcitonin may be indicated.
7. **Rash:** Skin rash most commonly occurs with NNRTI-containing regimens, and is most frequent and most severe with nevirapine. Most cases are mild to moderate and occur within the first weeks of therapy. Women appear to be at increased risk for more serious skin rashes (Bersoff-Matcha, 2001). More serious cutaneous manifestations (e.g., Stevens-Johnson Syndrome and toxic epidermal necrosis) should result in prompt and permanent discontinuation of NNRTI or other offending agents. A severe

and potentially life-threatening syndrome consisting of drug rash, eosinophilia, and systemic symptoms (DRESS) has been described (Bourezane, 1998). Outside of the NNRTI drug class, skin rash occurs most frequently with abacavir and amprenavir. If rash is determined to be from an abacavir-associated systemic hypersensitivity reaction, then abacavir should be discontinued and not restarted. Amprenavir is a sulfonamide and should be used with caution in patients with history of sulfa allergy.

D. TREATMENT GUIDELINES

The Department of Health and Human Services (DHHS) Panel on Clinical Practices for Treatment of HIV Infection continuously updates treatment guidelines. Updated recommendations are available at <http://www.aidsinfo.nih.gov>. The guidelines detail indications for therapy in chronically infected patients, recommendations for initial therapy, considerations for changes in therapy, and possible regimens for such changes (Table 4-7).

<i>Clinical Category</i>	<i>CD4+ Cell</i>	<i>Plasma HIV RNA</i>	<i>Recommendation</i>
Symptomatic (AIDS or severe symptoms)	Any value	Any value	Treat
Asymptomatic, AIDS	CD4+ cells <200/mm ³	Any value	Treat
Asymptomatic	CD4+ cells >200/mm ³ but ≤ 350/mm ³	Any value	Treatment should be offered, although controversial.*
Asymptomatic	CD4+ T cells >350/mm ³	>100,000 (by RT-PCR or bDNA)	Some experienced clinicians recommend initiating therapy, recognizing that the 3-year risk for untreated patients to develop AIDS is >30%; in the absence of increased levels of plasma HIV RNA, other clinicians recommend deferring therapy and monitoring the CD4+ T cell count and level of plasma HIV RNA more frequently; clinical outcome data after initiating therapy are lacking.
Asymptomatic	CD4+ T cells >350/mm ³	<100,000 (by RT-PCR or bDNA)	Most experienced clinicians recommend deferring therapy and monitoring the CD4+ T cell count, recognizing that the 3-year risk for untreated patients to experience AIDS is <15%.

Source: Adapted from DHHS, 2004.

* Clinical benefit has been demonstrated in controlled trials only for patients with CD4+ T cells <200/mm³, however, the majority of clinicians would offer therapy at a CD4+ T cell threshold <350/mm³.

The strength of the recommendation for starting therapy in an asymptomatic patient must take into account prognosis for disease-free survival, potential benefits and risks of therapy, and the willingness of the patient to take, and adhere to, therapy (see Chapter V on Adherence to HIV Therapies). Prognosis for disease-free survival may be assessed by utilizing the data in Table 4-8. However, given the sex-based differences in viral load and CD4 count (See Chapter 1 Epidemiology and Natural History of HIV Infection in Women), these data, generated from a prospective cohort of men who have sex with men (MSM), should be extrapolated with caution to women.

Among the benefits of therapy are:

- prevention of progressive immunosuppression by control of viral load,
- delayed progression of clinical disease/progression to AIDS,
- prolongation of life, and
- possible decreased risk of transmission (Quinn, 2000).

The risks of starting therapy include:

- a decrease in quality of life associated with adverse drug effects and inconvenience of dosing,
- limitations of future options for therapy if resistance develops to current agents,
- potential long-term toxicity of therapy,
- unknown duration of effectiveness of therapy, and
- possible transmission of drug-resistant virus.

Table 4-8: Risk for Progression to AIDS-Defining Illness Among a Cohort of Men Who Have Sex with Men, Predicted by Baseline CD4+ T Cell Count and Viral Load*

CD4 ≤ 200 cells/mm³ Plasma Viral Load (copies/mL)†		Percentage of AIDS-defining illness			
bDNA	RT-PCR	n	3 years	6 years	9 years
≤ 500	≤ 1,500	0 [§]	–	–	–
501 – 3,000	1,501 – 7,000	3	–	–	–
3,001 – 10,000	7,001 – 20,000	7	14.3	28.6	64.3
10,001 – 30,000	20,001 – 55,000	20	50.0	75.0	90.0
> 30,000	> 55,000	70	85.5	97.9	100.0
CD4 201 – 350[¶] cells/mm³ Plasma Viral Load (copies/mL)†		Percentage of AIDS-defining illness			
bDNA	RT-PCR	n	3 years	6 years	9 years
≤ 500	≤ 1,500	3	–	–	–
501 – 3,000	1,501 – 7,000	27	0	20.0	32.2
3,001 – 10,000	7,001 – 20,000	44	6.9	44.4	66.2
10,001 – 30,000	20,001 – 55,000	53	36.4	72.2	84.5
> 30,000	> 55,000	104	64.4	89.3	92.9
CD4 > 350 cells/mm³ Plasma Viral Load (copies/mL)†		Percentage of AIDS-defining illness			
bDNA	RT-PCR	n	3 years	6 years	9 years
≤ 500	≤ 1,500	119	1.7	5.5	12.7
501 – 3,000	1,501 – 7,000	227	2.2	16.4	30.0
3,001 – 10,000	7,001 – 20,000	342	6.8	30.1	53.5
10,001 – 30,000	20,001 – 55,000	323	14.8	51.2	73.5
> 30,000	> 55,000	262	39.6	71.8	85.0

* Adapted from data from the Multicenter AIDS Cohort Study (MACS). (Source: Mellors, JW, Rinaldo CR Jr, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 1996; 272:1167-70. Erratum: *Science* 1997; 275:14; adapted by Alvaro Muñoz, PhD, Johns Hopkins University, Baltimore, MD, 2001.)

† MACS numbers reflect plasma HIV RNA values obtained by version 2.0 bDNA testing. RT-PCR values are consistently 2–2.5-fold higher than first-generation bDNA values, as indicated. The version 3.0 bDNA assay provides similar HIV-1 RNA values as RT-PCR, except at the lower end of the linear range (<1,500 copies/mL).

§ Too few subjects were in the category to provide a reliable estimate of AIDS risk.

¶ A recent evaluation of data from the MACS cohort of 231 persons with CD4+ T cell counts >200 and <350 cells/mm³ demonstrated that of 40 (17%) persons with plasma HIV RNA <10,000 copies/mL, none progressed to AIDS by 3 years (Phair, 2002). Of 28 individuals (12%) with plasma viremia of 10,000 – 20,000 copies/mL, 4% and 11% progressed to AIDS at 2 and 3 years, respectively. Plasma HIV RNA was calculated as RT-PCR values from measured bDNA values.

Source: DHHS, 2004.

RECOMMENDATIONS FOR INITIAL TREATMENT REGIMENS

Recommendations for antiretroviral treatment continue to evolve with the development of new medications and additional data from clinical trials. The most recent guidelines from the DHHS are shown in Table 4-9.

Although these guidelines illustrate generally recommended regimens, nonspecialists should consider expert consultation regarding initiation of a specific regimen whenever there is any question about patient management.

Although there are multiple possible effective regimens, individualized decisions about therapy should take into account considerations such as pill burden, dosing frequency, toxicities and side effects, drug-drug interactions, and specific patient variables (e.g., pregnancy, co-morbid conditions, plasma HIV-RNA level, lifestyle, etc).

Table 4-9a: Antiretroviral Regimens Recommended for Treatment of HIV-1 Infection in Antiretroviral-Naive Patients		
<i>This table is a guide to treatment regimens for patients who have no previous experience with HIV therapy. Preferred regimens are in bold type; these regimens have been selected by experts based on the totality of virologic, immunologic, and toxicity data. Clinicians initiating antiretroviral regimens in the HIV-1 infected pregnant patient should refer to Chapter VII HIV and Reproduction and to "Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States" (http://www.aidsinfo.nih.gov/guidelines/).</i>		
NNRTI-Based Regimens		# of pills per day
Preferred Regimens	efavirenz + (lamivudine or emtricitabine) + (zidovudine or tenofovir DF) – except for pregnant women or women with pregnancy potential	2–3 pills/day
Alternative Regimens	efavirenz + (lamivudine or emtricitabine) + abacavir or (didanosine or stavudine*) – except for pregnant women or women with pregnancy potential**	2–4 pills/day
	nevirapine + (lamivudine or emtricitabine) + (zidovudine or stavudine or didanosine or abacavir or tenofovir)	3–6 pills/day
PI-Based Regimens		
	lopinavir/ritonavir (co-formulated as Kaletra®) + (lamivudine or emtricitabine) + (zidovudine)	8–9 pills/day
	atazanavir + (lamivudine or emtricitabine) + (zidovudine or stavudine* or abacavir or didanosine) or (tenofovir + ritonavir 100mg/d)	3–6 pills/day
	indinavir/ritonavir [†] + (lamivudine or emtricitabine) + (zidovudine or stavudine* or abacavir or tenofovir or didanosine)	7–12 pills/day
	lopinavir/ritonavir (co-formulated as Kaletra®) + (lamivudine or emtricitabine) + (stavudine* or abacavir or tenofovir or didanosine)	7–10 pills/day
	nelfinavir [§] + (lamivudine or emtricitabine) + (zidovudine or stavudine* or abacavir or tenofovir or didanosine)	5–8 pills/day
	saquinavir (sgc or hcg) [¶] /ritonavir [†] + (lamivudine or emtricitabine) + (zidovudine or stavudine* or abacavir or tenofovir or didanosine)	13–16 pills/day
	fosamprenavir + (lamivudine or emtricitabine) + (zidovudine or stavudine* or abacavir or tenofovir or didanosine)	5–8 pills/day
	fosamprenavir/ritonavir + (lamivudine or emtricitabine) + (zidovudine or stavudine* or abacavir or tenofovir or didanosine)	5–8 pills/day

Triple NRTI Regimen - Only when an NNRTI- or a PI-based regimen cannot or should not be used as first line therapy		# of pills per day
	abacavir + lamivudine + zidovudine	2 pills /day

* Higher incidence of lipodatrophy, hyperlipidemia, and mitochondrial toxicities reported with stavudine than with other NRTIs

** Women with child bearing potential implies women who want to conceive or those who are not using effective contraception

† Low-dose (100–400 mg) ritonavir

§ Nelfinavir available in 250 mg or 625 mg tablet

ø sgc = soft gel capsule; hgc = hard gel capsule

Source: Adapted from DHHS, 2004.

ARV Class	Antiretroviral Agent(s)	Advantages	Disadvantages
NNRTIs		NNRTI Class Advantages: <ul style="list-style-type: none"> • Less fat maldistribution and dyslipidemia than PI-based regimens • Save PI options for future use 	NNRTI Class Disadvantages: <ul style="list-style-type: none"> • Low genetic barrier to resistance • Cross-resistance among NNRTIs • Skin rash • Potential for CYP450 drug interaction
	Efavirenz	<ul style="list-style-type: none"> • Potent antiretroviral activity • Low pill burden and frequency (1-tablet per day) 	<ul style="list-style-type: none"> • Neuropsychiatric side effects • Teratogenic in nonhuman primates, contraindicated in pregnancy and avoid use in women with pregnant potential
	Nevirapine	<ul style="list-style-type: none"> • No food effect • No evidence of increased adverse hepatic events with single-dose NVP for prevention of mother-to-child transmission 	<ul style="list-style-type: none"> • Higher incidence of rash than with other NNRTIs, including rare serious hypersensitivity reaction • Higher incidence of hepatotoxicity than with other NNRTIs; including serious cases of hepatic necrosis • Women with CD4 > 250 cells/mm³ are at higher risk of symptomatic hepatic events

Table 4-9b: Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (continued)

		PI Class Advantages:	PI Class Disadvantages:
		<ul style="list-style-type: none"> • NNRTI options saved for future use • Longest prospective study data including data on survival benefit 	<ul style="list-style-type: none"> • Metabolic complications – fat maldistribution, dyslipidemia, insulin resistance • CYP3A4 inhibitors & substrates – potential for drug interactions (esp. with ritonavir-based regimens)
	Lopinavir/ritonavir	<ul style="list-style-type: none"> • Potent antiretroviral activity • Co-formulated as Kaletra® 	<ul style="list-style-type: none"> • Gastrointestinal intolerance • Hyperlipidemia • Little experience in pregnant women • Food requirement
	Atazanavir	<ul style="list-style-type: none"> • Less adverse effect on lipids than other PIs • Once-daily dosing • Low pill burden 	<ul style="list-style-type: none"> • Hyperbilirubinemia (indirect) • PR interval prolongation – generally inconsequential unless combined with another drug with similar side effect • Interaction with tenofovir and efavirenz – avoid concomitant use unless combined with RTV (ATV 300 mg qd + RTV 100 mg qd) • Food requirement
PIs	Fosamprenavir	<ul style="list-style-type: none"> • Lower pill burden than amprenavir (4 vs 16 capsules/day) • No food effect 	
		<ul style="list-style-type: none"> • Lower pill burden than amprenavir/ritonavir • Once daily regimen in patients with no history of PI failure • No food effect 	
		<ul style="list-style-type: none"> • Low-dose ritonavir/indinavir T_{1/2} & C_{min} allows for twice-daily instead of 3-times-daily dosing • Eliminates food restriction of indinavir 	<ul style="list-style-type: none"> • Possibly higher incidence of nephrolithiasis than with IDV alone • High fluid intake required (1.5–2 liters of fluid per day)
	Nelfinavir	<ul style="list-style-type: none"> • More favorable safety and pharmacokinetic profile in pregnant women than with other PIs 	<ul style="list-style-type: none"> • Diarrhea • Higher rate of virologic failure than with other PIs in comparative trials • Food requirement
	Saquinavir (hgc or sgc) + ritonavir	<ul style="list-style-type: none"> • Low-dose ritonavir reduces saquinavir daily dose and frequency - ↑ C_{max}, C_{min}, & T_{1/2} 	<ul style="list-style-type: none"> • Gastrointestinal intolerance (sgc worse than hgc)
NRTIs		<ul style="list-style-type: none"> • Established backbone of combination antiretroviral therapy 	<ul style="list-style-type: none"> • Rare but serious cases of lactic acidosis with hepatic steatosis reported with most NRTIs
Triple NRTI regimen	Abacavir + zidovudine + lamivudine only	<ul style="list-style-type: none"> • Abacavir + zidovudine + lamivudine - Co-formulated as Trizivir® • Minimal drug-drug interactions • Low pill burden • Saves PI & NNRTI for future option 	<ul style="list-style-type: none"> • Inferior virologic response when compared to efavirenz-based and indinavir-based regimens • Potential for abacavir hypersensitivity reaction

Dual NRTIs backbone of three or more drug combination therapy	Zidovudine + lamivudine	<ul style="list-style-type: none"> • Most extensive and favorable virological experience • Co-formulated as Combivir® – ease of dosing • No food effect • Lamivudine – minimal side effects 	<ul style="list-style-type: none"> • Bone marrow suppression with zidovudine • Gastrointestinal intolerance
	Stavudine + lamivudine	<ul style="list-style-type: none"> • No food effect • Once-daily dosing (when extended release stavudine formulation becomes available) 	Adverse effects associated with stavudine: <ul style="list-style-type: none"> • Peripheral neuropathy, lipoatrophy, hyperlactatemia and lactic acidosis, reports of progressive ascending motor weakness, potential for hyperlipidemia • Higher incidence of mitochondrial toxicity with stavudine than with other NRTIs
	Abacavir + lamivudine	<ul style="list-style-type: none"> • No food effect • Once-daily dosing • Co-formulation (Epzicom) 	<ul style="list-style-type: none"> • Potential for abacavir hypersensitivity reaction • Higher incidence of severe hypersensitivity reactions with once daily dosing reported in 1 study
	Tenofovir + lamivudine	<ul style="list-style-type: none"> • Good virologic response when used with efavirenz • Well tolerated • Once-daily dosing 	<ul style="list-style-type: none"> • Data lacking for tenofovir use in patients with renal insufficiency • Tenofovir – some reports of renal impairment • Drug interactions with atazanavir and didanosine requiring dose adjustment
	Didanosine + lamivudine	<ul style="list-style-type: none"> • Once-daily dosing 	<ul style="list-style-type: none"> • Peripheral neuropathy, pancreatitis – associated with didanosine • Food effect – needs to be taken on an empty stomach • Requires dosing separation from most PIs • Potential increase in toxicities when used with ribavirin, tenofovir, hydroxyurea
	NRTI + emtricitabine	<ul style="list-style-type: none"> • Long half-life of emtricitabine allows for once daily dosing (of emtricitabine) • Co-formulation with tenofovir (Truvada) 	

Source: Adapted from DHHS, 2004.

RECOMMENDATIONS FOR ANTIRETROVIRAL THERAPY IN THE TREATMENT-EXPERIENCED PATIENT

The need for a change in antiretroviral therapy most commonly arises in two situations: medication toxicity and treatment failure.

- **Medication toxicity:** When the need to change therapy arises because of medication toxicity, it may be possible to simply change one component of a regimen. If the toxicity occurs in a regimen that has provided effective virologic control, the goal is to continue effective therapy by changing the component that causes toxicity. For example, in a patient taking an effective regimen of AZT/3TC/PI, the development of anemia could be attributed to AZT. A different NRTI that does not commonly cause bone marrow suppression (e.g., d4T) could be substituted. The similar toxicities of certain agents must be remembered when making such changes: for example, in a patient taking ddi, the development of peripheral neuropathy would not be expected to be alleviated by substituting d4T.

There are other situations in which the toxicity is not as easily attributed to a single component of a regimen (e.g., rash, GI symptoms). In these instances,

a “drug holiday” (temporary discontinuation) of the entire regimen may be necessary to allow symptoms to resolve, and a new regimen initiated with some change in components. In most cases reinitiation of antiretroviral therapy would not be expected to be associated with any increase in side effects. However, in the case of certain serious or life-threatening toxicities (see C. on page 115), such as abacavir-associated hypersensitivity or severe liver toxicity with nevirapine, the offending agent should never be resumed.

- **Treatment failure:** Changes in regimen for lack of efficacy may be triggered by evidence of clinical progression, progressive decline in CD4 count, and, most commonly, for incomplete virologic suppression or virologic rebound. Clinical failure is defined by the occurrence of HIV-related events after at least 3 months on an antiretroviral regimen, excluding immune reconstitution syndromes. Immunologic failure is the failure to increase 25–50 cells/mm³ above the baseline CD4 count in the first year of therapy or a decrease in the CD4 count below baseline while on therapy. Virologic failure is the failure to achieve HIV RNA < 400 copies/mL by 24 weeks or < 50 copies/mL by 48 weeks on therapy or repeated detection of viremia after complete virologic suppression. When changes in therapy are contemplated, an increase in viral load or a downward trend in CD4 count should be confirmed with repeat determinations before changes are made. In general virologic failure occurs first, followed by immunologic failure, and then by clinical failure, although these events may be separated by months to years.

There are a number of possible reasons for treatment failure: patient factors (e.g., age (in some cohorts), pretreatment HIV-RNA level and CD4 count, active substance use, depression, baseline drug resistance or resistance related to prior treatment regimens); suboptimal adherence (including running out of medications); medication side effects or toxicity; pharmacokinetics (e.g., absorption, metabolism, penetration into body reservoirs, food or fasting requirements, drug-drug interactions); potency of the current regimen; and other unknown reasons. Sex, race, pregnancy and history of substance abuse have not been associated with treatment failure. It is important to try to distinguish among these different causes of treatment failure, since approaches to management will differ.

Failure increases the risk of disease progression and should be addressed aggressively. Assessing and managing a patient with extensive prior antiretroviral experience and treatment regimen failure is complex and expert advice is critical.

Table 4-10 summarizes guidelines for patient assessment and management with suspected treatment failure. In general a distinction is made between patients with limited prior treatment and those with extensive prior treatment, since those with more limited antiretroviral experience have a greater likelihood of achieving maximal viral suppression with an appropriate change in regimen. In these patients changing therapy sooner rather than later is recommended to minimize continued selection of resistance mutations.

Table 4-10: Guidelines for Changing an Antiretroviral Regimen for Suspected Treatment Regimen Failure

Patient Assessment

- Review antiretroviral treatment history (drugs, doses, duration, adherence, tolerability, prior resistance testing).
- Perform physical exam to assess for signs of clinical progression.
- Assess adherence, tolerability, and pharmacokinetic issues.
- Distinguish between first or second, and multiple treatment regimen failures.
- Perform resistance testing while patient is taking therapy.
- Identify susceptible drugs and drug classes.

Patient Management: Specific Clinical Scenarios

- Limited prior treatment with low (but not suppressed) HIV RNA level (e.g., up to 5000 copies/mL: The goal of treatment is to re-suppress viral replication. Consider intensifying with one drug (e.g., tenofovir) or pharmacokinetic enhancement (use of ritonavir boosting of a protease inhibitor) or most aggressively, change to a completely new regimen. If continuing the same treatment regimen, need to follow HIV RNA levels more closely, because ongoing viremia will lead to the accumulation of resistance mutations.
- Limited or intermediate prior treatment with single drug resistance: Consider changing one drug pharmacokinetic enhancement (few data available) or, most aggressively, change to a completely new regimen.
- Limited or intermediate prior treatment with more than 1 drug resistance: The goal of treatment is to suppress viremia to prevent further selection of resistance mutations. Consider optimizing regimen by changing classes (e.g., PI-based to NNRTI-based and vice versa) and/or adding new active drugs.
- Prior treatment with no resistance identified: Consider the timing of obtaining the drug resistance test (e.g., was the patient off antiretroviral medications?) and/or nonadherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., 2–4 weeks) to see if a resistant strain has been selected.
- Extensive prior treatment and drug resistance: It is reasonable to continue the same antiretroviral regimen if there are few or no treatment options. In general, avoid adding a single active drug because of the risk of the development of resistance to that drug. In advanced disease with a high likelihood of clinical progression, adding a single drug may reduce the risk of immediate clinical progression. In this complicated scenario, expert advice should be sought.

Source: Adapted from DHHS, 2004

Viral suppression may be difficult to achieve in patients with extensive prior drug exposure and the primary goals are to preserve immune function and prevent clinical progression. In a patient with extensive prior treatment and lower CD4 count (e.g., < 200/mm³) a change in therapy is indicated to prevent clinical progression; with higher CD4 counts, risk of progression is less and a well-tolerated regimen may be continued, if it is impossible to construct a new regimen that is effective. Discontinuing therapy, even in the presence of ongoing viremia, leads to a rapid increase in viral load, a decrease in CD4 count, and increases the risk of clinical progression (Deeks, 2001; Lawrence, 2003) and is therefore not recommended (DHHS, 2004).

When a regimen is changed for lack of efficacy, the goal is to use medications that will minimize the likelihood of further viral resistance. Prior to the general availability of resistance testing, regimen changes to improve efficacy were made empirically. Some of the general principles from that empiric practice are still worth emphasizing, e.g. often an entire regimen (not just one medication) must be changed, and there is often significant cross-resistance among agents within a class. Now, however, when antiretroviral therapy is changed for lack of efficacy, information from resistance testing can be of pivotal importance in choosing a new regimen (see “Resistance Testing” below). Recommendations for regimen changes may also be found at <http://www.aidsinfo.nih.gov>.

“Intensification” refers to the theory that some patients with a suboptimal decrease in viral load from an early regimen, may benefit from the early addition of a single new agent. This may also refer to the situation in which rebound occurs after complete viral suppression with limited prior treatment. In these patients, low levels of detectable virus (usually < 1000 c/mL) are present, generally too low to obtain accurate resistance testing. This may be a unique situation in which it may be reasonable to add only a single medication, or to change only a portion of the combination, adding an agent to which the patient will likely be sensitive.

RESISTANCE TESTING

There are two main techniques to assess the development of viral resistance to antiretroviral therapy. Phenotypic assays directly determine the amount of a medication required to inhibit HIV. Genotypic assays determine changes in the nucleotide sequences of the genes that code for the protease and reverse transcriptase enzymes. Interpretations of genotypic results require knowledge of which specific changes are associated with resistance. Results are reported as a string of three pieces of information for each mutation detected:

1. wild-type amino acid,
2. codon involved, and
3. amino acid coded for by mutated codon.

Table 4-11 shows the mutations known to be associated with resistance to specific agents (Bartlett, 2003). Updated listings of mutations and associated resistance can be found at: <http://hiv-web.lanl.gov> or <http://hivdb.stanford.edu>.

Table 4-11 Resistance Mutations Adapted from IAS-USA		
<i>Drug</i>	<i>Codon Mutations*</i>	<i>Comment</i>
Nucleosides and Nucleotides		
AZT	41, 67, 70, 210, 215, 219	Mutations are "TAMs"*** reduces susceptibility to AZT, d4T, ABC, ddl, ddC, TDF, 3TC.
3TC	184 (44, 118)	184 – high level 3TC resistance, increases activity of d4T, AZT, and TDF, reduces susceptibility to ddl, ddC, ABC.
ddC	65, 69, 74, 184	
ddl	65, 74	Presence of 74 or 65 alone or combined with TAMs is associated with resistance to ddl. Multiple TAMs also decrease ddl susceptibility
d4T	41, 67, 70, 75, 210, 215, 219	The d4T-specific mutation at 75 is seen mostly in vitro. In vitro resistance depends on number of TAMs, which reduce susceptibility to all NRTIs.
ABC	41, 65, 67, 70, 74, 115, 184, 210, 215, 219	Resistance depends on number of TAMs ± M184V; 184 alone does not confer resistance. Presence of M184V plus ≥3-4 TAMs associated with ABC resistance. ABC selects for mutations that may confer cross-resistance to 3TC, ddl, and TDF.
TDF	65, 69 insertion, ≥ 3 TAMs including 41L or 210W	Reduced activity with K65R and resistance with 69 insertion.
Multinucleoside resistance – A Q151M complex	151, 62, 75, 77, 116	Occurs with or without TAMs. Confers resistance to all NRTIs except tenofovir.
Multinucleoside resistance – B T69 insertion	69 (insertion), 41, 62, 67, 70, 210, 215, 219	Requires TAMs. Confers resistance to all NRTIs and TDF but not to DAPD.
Multinucleoside resistance – Multiple TAMs	41, 67, 70, 210, 215, 219	Confers resistance to all NRTI including TDF.
NNRTIs		
NVP	100, 103, 106, 108, 181, 188C/L/H, 190	Y181C is favored mutation with NVP, unless combined with AZT, in which case K103N is favored.
DLV	103, 181, 236, 318	
EFV	100, 103, 108, 181, 188L, 190, 225	181C is not selected, but its presence contributes low-level cross resistance. Resistance with 188L but not 188C or 188H.
Multi-NNRTI resistance	103, 188L	Either mutation substantially reduces activity of all NNRTIs
Multi-NNRTI resistance accumulation	100, 106, 181, 190, 230	≥2 of the mutations substantially reduces activity of all NNRTIs

Table 4-11 Resistance Mutations Adapted from IAS-USA (continued)			
<i>Drug</i>	<i>Major[†]</i>	<i>Minor[‡]</i>	<i>Comment</i>
Protease Inhibitors (PIs)			
IDV	46, 82, 84	10, 20, 24, 32, 36, 54, 71, 73, 77, 90	At least 3 mutations required for resistance (4x decreases in susceptibility).
NFV	30, 90	10, 36, 46, 71, 77, 82, 84, 88	D30N most common mutation: No PI cross-resistance. L90M occurs in some, leading to greater PI cross-resistance.
RTV	82, 84	10, 20, 32, 33, 36, 46, 54, 71, 77, 90	Cross resistance with IDV common.
SQV	48, 90	10, 54, 71, 73, 77, 82, 84	90 develops 1st, then 48; Codon 48 mutation unique, but L90M contributes to PI cross-resistance.
APV	50V, 84	10, 32, 46, 47, 54, 73, 90	I50V is associated with cross-resistance to LPV.
LPV/r	73	10, 20, 24, 32, 33, 46, 47, 50V, 53, 54, 63, 71, 73, 82, 84, 90	≥6 mutations cause reduced response; the number may be as low as 4. I50V (selected by APV) decreases LPV susceptibility.
Atazanvir	50L	32, 46, 54, 71, 82, 84, 88, 90	Selects for 50L and 71 when initial PO; in PI experienced patients selects for 54 and 84.
Multi-PI resistance	46, 82, 84, 90	10, 54	≥4 or 5 usually cause multiple PI resistance.
Fusion Inhibitors			
Enfuvirtide (T20)			Resistance in the gp41 envelope gene at positions 36-45.

Source: Adapted from D'Acquilla, 2002. Updated October, 2003 by the Drug Resistance Mutations Group, International AIDS Society–USA. Available at <http://www.iasusa.org>. (Accessed 3/04.)

* The distinction between primary and secondary mutations has been eliminated for NRTIs and NNRTIs by the International AIDS Society Expert Committee; this distinction has been retained for PIs, but with the terms "Major" or "Minor".

** Thymidine-associated mutations

† **Major Mutations** develop first or are associated with decreased drug binding or reduced viral activity; these effect phenotype resistance.

‡ **Minor Mutations** appear later and, by themselves, do not significantly change phenotype resistance.

Both phenotypic and genotypic assays are difficult to perform if the viral copy number is less than 1000 c/mL. Their utility is also limited by an inability to detect resistant virus that makes up less than 20% of the total viral burden in a sample. It is also critical to recognize that these assays will only reliably detect mutations conferring resistance to medications the patient is taking at the time the assay is performed; samples from patients who are off therapy at the time of resistance testing are likely to show reversion to wild-type (sensitive) virus as the predominant circulating

viral strain. Thus, resistance testing is insensitive to mutations secondary to selective pressure that is no longer present after a change in regimen. Virions with these mutations likely still exist as a small percentage of circulating virus and may lead to clinical resistance if inactive drugs that test “sensitive” but are vulnerable to these resistance mutations are used; current assays will not detect their presence. A comparison of genotypic and phenotypic assays is shown in Table 4-12.

Table 4-12: Comparison of Genotypic and Phenotypic Assays	
Genotypic Assays	
Advantages	Disadvantages
<ul style="list-style-type: none"> • Less expensive (\$300 to \$480/test) • Short turn-around of 1 to 2 weeks • May detect presence of resistance mutations before they have resulted in phenotypic resistance 	<ul style="list-style-type: none"> • Detect resistance only in dominant species (>20%) • Interpretation requires knowledge of mutational changes, i.e., expertise • Technician experience influences results • May show discrepancy with phenotype • Require viral load > 1000 c/mL
Phenotypic Assays	
Advantages	Disadvantages
<ul style="list-style-type: none"> • Interpretation more analogous to resistance testing of bacteria • Assesses total effect, including mutations, mutational interactions • Reproducibility is good • Advantage over genotype when there are multiple mutations 	<ul style="list-style-type: none"> • More expensive (usually \$800 to \$1000) • Report takes 2 to 3 weeks • Thresholds to define susceptibility are arbitrary and do not account for boosted PI levels • Detects resistance only to single drug, not combinations • Detect resistance only in dominant species (>20%) • Require viral load >500-1000 c/mL

Source: Bartlett, 2003.

Many studies have shown that patients for whom resistance analysis is done before a change in antiretroviral therapy have a better virologic response to the new regimen than do patients in whom a change in therapy is based solely on antiretroviral history (Baxter, 1999; Durant, 1999, Zolopa 1999). Resistance testing may be useful in the following ways.

1. To determine the role of resistance in patients with virologic failure and maximize the number of active medications in a new regimen.
2. To determine the role of resistance in patients with suboptimal virologic control on a HAART regimen (and again maximize the number of active medications in a new regimen).
3. To determine whether there is drug resistance in a patient with acute HIV who is considering antiretroviral therapy (see “Treatment of Acute HIV Infection,” below).

Patients with pan-sensitive virus in the face of virologic failure should be questioned carefully, but nonjudgmentally, about their medication-taking behaviors. Therapeutic drug monitoring (TDM) can also be considered, although data are not yet available demonstrating that TDM improves clinical outcome. Current USPHS recommendations for the use of drug resistance assays are outline in Table 4-13.

Table 4-13: Recommendations for Using Drug-Resistance Assays	
<i>Clinical Setting/recommendations</i>	<i>Rationale</i>
Drug-Resistance assay recommended	
Virologic failure during combination antiretroviral therapy (AI)*	Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen
Suboptimal suppression of viral load after antiretroviral therapy initiation (BIII)	Determine the role of resistance and maximize the number of active drugs in the new regimen, if indicated
Acute human immunodeficiency virus (HIV) infection, if decision is made to initiate therapy (AIII)	Determine if drug-resistant virus was transmitted and change regimen accordingly
Drug-resistance assay should be considered	
Chronic HIV infection before therapy initiation (CIII)	Available assays might not detect minor drug-resistant species. However, should consider if significant probability that patient was infected with drug-resistant virus (i.e., if the patient is thought to have been infected by a person receiving antiretroviral drugs).
Drug-resistance assay not usually recommended	
After discontinuation of drugs (DIII)	Drug-resistance mutations might become minor species in the absence of selective drug pressure, and available assays might not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value, but its absence does not rule out the presence of minor drug-resistant species
Plasma viral load <1,000 HIV RNA copies/mL (DIII)	Resistance assays cannot be consistently performed because of low copy number of HIV RNA; patients/providers may incur charges and not receive results

Source: DHHS, 2004.

* See Notes for Table 4-16 for explanation of evidence grading.

TREATMENT INTERRUPTIONS (DRUG HOLIDAY)

Interruption of antiretroviral therapy has been considered in a variety of different scenarios. Intermittent therapy was previously hypothesized by some to improve HIV-specific immunity. A clinical trial failed to show evidence for this. There do remain two situations where treatment interruptions are being assessed: 1) as a way to reduce total exposure to medication (which could provide a cost or toxicity benefit), and 2) prior to attempts at salvage therapy in patients with virologic failure and multiple resistance mutations. At the current time, however, treatment interruption should be considered experimental in both of these situations.

D. TREATMENT OF ACUTE HIV INFECTION

To consider treatment of acute HIV infection, the clinician must first recognize its presence. In more than half of all patients who acquire HIV infection, there are clinical symptoms 1–6 wk after exposure. The symptoms vary in severity, but commonly include fever, lymphadenopathy, fatigue, rash, myalgias, and pharyngitis — a symptom complex that mimics mononucleosis. HIV antibodies will not yet be present at this point, but techniques that detect viral nucleic acids (see “Initial Diagnosis,” above) will confirm the diagnosis: a negative or indeterminate antibody test in conjunction with a positive HIV RNA or HIV DNA test is diagnostic of acute HIV infection. It is important to note, however, that a low level of HIV RNA (e.g., < 5000 c/mL) may be a false-positive result and should be repeated (Rich, 1999). In addition, an HIV DNA assay could be performed to clarify the diagnosis; this should almost always be positive in an infected person, regardless of RNA level. Relatively recent infection may also be diagnosed in a patient with negative HIV serologies in the previous 6–9 mo and a first positive result, even in the absence of a seroconversion syndrome.

The benefits of treating acute HIV infection are not completely defined. The rationale for early treatment is that there will be early suppression of viremia, which may preserve CD4 cell number and function including HIV-specific CD4 cells. There are also risks associated with early treatment that include the toxicities of the medications used and the possibility of early development of resistance. These unanswered questions about risks and benefits of early therapy should be addressed with the patient; enrollment in clinical trials and observational studies of acute HIV should be considered. In treating acute HIV, it is always important to use a three- or four-drug regimen that would be expected to provide complete viral suppression. In addition, after considering the source of exposure and local epidemiologic information, genotypic resistance testing may prove useful in this setting. In acute HIV infection, the patient's predominant virus will be the strain that was transmitted, without reversion to the wild-type (pan-sensitive) virus seen in chronically infected patients who have stopped treatment. The potential risks and benefits of treating acute HIV are summarized in Table 4-14.

POSTEXPOSURE PROPHYLAXIS

See Chapter XIII on Occupational Exposure.

TREATMENT IN PREGNANCY

Antiretroviral treatment is indicated in pregnancy to reduce the risk of perinatal transmission whether or not therapy is yet needed to treat maternal disease. Specific guidelines for optimal therapy are addressed in Chapter VII (HIV and Reproduction). Information is also provided at <http://www.aidsinfo.nih.gov>.

Table 4-14: Risks and Benefits of Early Initiation of Antiretroviral Therapy in Acute HIV Infection

Potential Benefits	<ul style="list-style-type: none"> • Control of viral replication and rate of mutation • Prevention of progressive immunodeficiency; potential maintenance of a normal immune system • Delayed progression to AIDS and prolongation of life • Possible decreased risk of viral transmission • Decreased severity of acute infection symptoms • Possibly decreased viral setpoint (which may have a subsequent effect on rate of disease progression)
Potential Risks	<ul style="list-style-type: none"> • Reduction in quality of life from adverse drug effects and inconvenience of current maximally suppressive regimens • Earlier development of drug resistance, if therapy fails to effectively suppress viral replication <ul style="list-style-type: none"> - Transmission of drug resistant virus - Limitation in future choices of antiretroviral agents due to development of resistance • Drug-related short- or long-term serious toxicity • Unknown duration of effectiveness of current antiretroviral therapies

Source: Adapted from DHHS, 2004.

IMMUNE-BASED THERAPY

Therapy to augment the immune response to HIV may be possible through the use of HIV vaccines or cytokines, such as interleukin-2. Such strategies to enhance the control of HIV already provided by antiretroviral medications are being assessed in clinical trials, but are not part of current standard care.

ALTERNATIVE OR COMPLEMENTARY THERAPY

Some patients may present with knowledge or questions about alternative or complementary therapy or may indicate that they are already taking such therapy. All patients should be specifically asked about their use of such therapies, as they may not consider these to be medications and may not volunteer the information to their provider. Specific complementary therapies change rapidly, and their use varies widely with geography and patient demographics. For patients who do choose such therapies it is important to make sure that agents that have overlapping toxicities with a patient's prescribed therapy are avoided and that discussions of alternative therapy are held in a way that does not alienate the patient from her involvement in medical care.

V. COMPLICATIONS: OPPORTUNISTIC DISEASES

The risk for various opportunistic processes — so called because they take advantage of patients with a weakened immune system — is defined by the total CD4 lymphocyte count. They include opportunistic infections (OIs) and certain malignancies, and are similar to the diseases seen in other immunocompromised hosts such as recipients of solid organ transplants. In fact, AIDS was first recognized as a new entity by the characteristic pattern of opportunistic diseases — especially *Pneumocystis* pneumonia and Kaposi's sarcoma — that were being diagnosed in young, previously healthy gay men. The pattern and sequence of OIs that are seen as the total CD4 cell count decreases is so reliable that in most cases the total CD4 cell count limits the differential diagnosis (see Table 4-15).

Table 4-15: Correlation of Complications With CD4 Cell Counts

<i>CD4 Cell Count*</i>	<i>Infectious Complications</i>	<i>Noninfectious† Complications</i>
>500/mm ³	<ul style="list-style-type: none"> • Acute retroviral syndrome • Candidal vaginitis 	<ul style="list-style-type: none"> • Persistent generalized lymphadenopathy (PGL) • Guillain-Barré syndrome • Myopathy • Aseptic meningitis
200-500/mm ³	<ul style="list-style-type: none"> • Pneumococcal and other bacterial pneumonia • Pulmonary tuberculosis • Herpes zoster • Oropharyngeal candidiasis (thrush) • Cryptosporidiosis, self-limited • Kaposi's sarcoma • Oral hairy leukoplakia 	<ul style="list-style-type: none"> • Cervical intraepithelial neoplasia • Cervical cancer • B-cell lymphoma • Anemia • Mononeuritis multiplex • Idiopathic thrombocytopenic purpura • Hodgkin's lymphoma • Lymphocytic interstitial pneumonitis
<200/mm ³	<ul style="list-style-type: none"> • <i>Pneumocystis carinii</i> pneumonia • Disseminated histoplasmosis and coccidioidomycosis • Miliary/extrapulmonary TB • Progressive multifocal leukoencephalopathy (PML) 	<ul style="list-style-type: none"> • Wasting • Peripheral neuropathy • HIV-associated dementia • Cardiomyopathy • Vacuolar myelopathy • Progressive polyradiculopathy • Non-Hodgkin's lymphoma
<100/mm ³	<ul style="list-style-type: none"> • Disseminated herpes simplex • Toxoplasmosis • Cryptococcosis • Cryptosporidiosis, chronic • Microsporidiosis • Candidal esophagitis 	
<50/mm ³	<ul style="list-style-type: none"> • Disseminated cytomegalovirus (CMV) • Disseminated <i>Mycobacterium avium</i> complex 	Central nervous system (CNS) lymphoma
<p>* Most complications occur with increasing frequency at lower CD4 cell counts.</p> <p>† Some conditions listed as "non-infectious" are probably associated with transmissible microbes. Examples include lymphoma (Epstein-Barr virus [EBV]) and cervical cancer (human papillomavirus [HPV]).</p> <p>Source: Bartlett, 2003. Reprinted with permission.</p>		

At total CD4 cell counts above 500, illnesses are rarely specifically associated with the patient's HIV serostatus. Non-Hodgkin's lymphoma and mucocutaneous KS are occasional exceptions; they can occur at varying CD4 cell counts, but are more frequently diagnosed at lower values. Infections that are virulent among HIV-seronegative individuals, such as tuberculosis and bacterial pneumonia, may, of course, occur at any CD4 cell count but are increasingly more common and more severe as the CD4 count declines. Between 200 and 500 cells, less serious HIV-associated problems begin to manifest themselves, such as oral hairy leukoplakia, various skin problems, shingles, and oral or vaginal candidiasis (thrush). *Candida vaginitis*, which is also common among women who do not have HIV, may be the first indication of HIV infection (Imam, 1990).

According to the 1993 version of the CDC case definition, AIDS may be defined by a number of serious opportunistic illnesses or by a decline in the total CD4 cell count below 200 (see Table 1-3 in Chapter I). This CD4 cell count criterion acknowledges an important threshold for OI risk. *Pneumocystis carinii* pneumonia (PCP), the most common AIDS-defining OI and leading cause of death, is usually diagnosed as patients approach and drift below this critical number of total CD4 cells. Other OIs, such as toxoplasmosis, cryptococcal meningitis, and disseminated histoplasmosis, tend to occur as the CD4 cell count declines from less than 200 to below 100 cells. Typically, end-stage illnesses such as CNS lymphoma, CMV end-organ disease, and disseminated MAC, tend to occur at very low CD4 cell counts, often less than 25 cells.

Antimicrobial therapy works in concert with the individual's immune system to clear infection. Before the advent of potent combination antiretroviral therapy, HIV-associated opportunistic diseases could not be controlled without ongoing suppressive therapy, because the patients' immune function was too weak to effect that control. Once an OI was diagnosed and treated acutely ("induction" therapy, borrowing from the language of oncology), treatment would be continued at lower "maintenance" levels or the OI would inevitably recur. "Cure" of OIs was not part of the vocabulary of HIV disease management. With potent combination antiretroviral therapy resulting in dramatic improvement in CD4 cell counts and immune function, both prophylactic and chronic suppressive therapies are being withdrawn successfully in responders. This has opened an entirely new era in the care of people with advanced HIV (see below).

A. OPPORTUNISTIC INFECTION PROPHYLAXIS

One of the early significant advances in the management of HIV/AIDS was the demonstration that chemoprophylaxis could prevent PCP and thereby improve survival. Before the development of potent combination antiretroviral therapy an important focus of the clinical research effort was to identify effective prophylactic agents for the other common OIs. The success of this research was in part responsible for the slowing of the death rate from AIDS that was first apparent near the end of 1995, just before the era of potent combination antiretroviral therapy began.

Recommendations for prophylaxis for specific OIs depend on a number of factors: the CD4 threshold that defines the greatest risk, the overall effectiveness of a given approach, the risk of resistance development, the presence of pregnancy, toxicity, and cost. The USPHS/IDSA guidelines for OI prophylaxis are updated periodically to reflect the most current understanding of disease risk and prevention. Current recommendations for initiating primary OI prophylaxis can be found at <http://www.aidsinfo.nih.gov>, or in *2003 Medical Management of HIV Infection* by John Bartlett, listed in the Resources appendix. (USPHS/IDSA, 2002) Table 4-16 summarizes recommendations for primary prophylaxis of the most common OIs.

Table 4-16: Prophylaxis to Prevent First Episode of Opportunistic Disease in Adults and Adolescents Infected with HIV			
Pathogen	Preventive Regimens		
	Indication	First Choice	Alternatives
I. Strongly Recommended as Standard of Care			
<i>Pneumocystis carinii</i> ¹	CD4+ count <200/ μ L or oropharyngeal candidiasis	Trimethoprim-sulfamethoxazole (TMP-SMX), 1 DS po q.d. (A) TMP-SMX, 1 SS po q.d. (A)	Dapsone, 50 mg po b.i.d. or 100 mg po q.d. (B); dapsone, 50 mg po q.d. <i>plus</i> pyrimethamine, 50 mg po q.w. <i>plus</i> leucovorin 25 mg po q.w. (B); dapsone 200 mg po <i>plus</i> pyrimethamine, 75 mg po <i>plus</i> leucovorin, 25 mg po q.w. (B); aerosolized pentamidine, 300 mg q.month via Respigard II(TM) nebulizer (B); atovaquone, 1500 mg po q.d. (B); TMP-SMX, 1 DS po t.i.w. (B)
<i>Mycobacterium tuberculosis</i> Isoniazid-sensitive ²	TST reaction \geq 5 mm or prior positive TST result without treatment or contact with case of active tuberculosis regardless of TST result (BII)	Isoniazid, 300 mg po <i>plus</i> pyridoxine, 50 mg po q.d. x 9 mo (AII) or isoniazid, 900 mg po <i>plus</i> pyridoxine, 100 mg po b.i.w. x 9 mo (BII)	Rifampin, 600 mg po q.d. (BIII) x 4 mo or rifabutin 300 mg po q.d. (CIII) x 4 mo Pyrazinamide, 15-20 mg/kg po q.d. x 2 mo <i>plus</i> either rifampin, 600 mg po q.d. (B) x 2 mo or rifabutin, 300 mg po q.d. (CIII) x 2 mo
Isoniazid-resistant	Same as above; high probability of exposure to isoniazid-resistant tuberculosis	Rifampin 600 mg po (AIII) or rifabutin, 300 mg po (BIII) q.d. x 4 mo	Pyrazinamide 15-20 mg/kg po q.d. <i>plus</i> either rifampin, 600 mg po (B) or rifabutin, 300 mg po (CIII) q.d. x 2 mo
Multidrug-(isoniazid and rifampin) resistant	Same as above; high probability of exposure to multidrug-resistant tuberculosis	Choice of drugs requires consultation with public health authorities. Depends on susceptibility of isolate from source patient	-----

Table 4-16: Prophylaxis to Prevent First Episode of Opportunistic Disease in Adults and Adolescents Infected with HIV (continued)

Pathogen	Preventive Regimens		
	Indication	First Choice	Alternatives
<i>Toxoplasma gondii</i> ³	IgG antibody to <i>Toxoplasma</i> and CD4+ count <100/ μ L	TMP-SMX, 1 DS po q.d. (All)	TMP-SMX, 1 SS po q.d. (BIII); dapsone, 50 mg po q.d. <i>plus</i> pyrimethamine, 50 mg po q.w. <i>plus</i> leucovorin, 25 mg po q.w. (B); dapsone, 200 mg po <i>plus</i> pyrimethamine, 75 mg po <i>plus</i> leucovorin, 25 mg po q w (B); atovaquone, 1500 mg po q.d. with or without pyrimethamine, 25 mg po q.d. <i>plus</i> leucovorin, 10 mg po q.d. (CIII)
<i>Mycobacterium avium</i> complex ⁴	CD4+ count <50/ μ L	Azithromycin, 1,200 mg po q.w., (AI) q.d. or clarithromycin, 4 500 mg po b.i.d. (AI)	Rifabutin, 300 mg po (B); azithromycin, 1,200 mg po q.w. <i>plus</i> rifabutin, 300 mg po q.d. (CI)
Varicella zoster virus	Significant exposure to chickenpox or shingles for patients who have no history of either condition or, if available, negative antibody to VZV	Varicella zoster (VZV) immune globulin (VZIG), 5 vials (1.25 mL each) im, administered \leq 96 h after exposure, ideally within 48 h (AIII)	
II. Generally Recommended			
<i>Streptococcus pneumoniae</i> ⁵	CD4+ count > 200/ μ L	23 valent polysaccharide vaccine, 0.5 mL im [BII]	None
Hepatitis B virus ^{6,7}	All susceptible (anti-HBc-negative) patients	Hepatitis B vaccine: 3 doses (BII)	None
Influenza virus ^{6,8}	All patients (annually, before influenza season)	Inactivated trivalent influenza virus vaccine: one annual dose (0.5 mL) im (BIII)	Oseltamivir, 75 mg po q.d. (influenza A or B) (CIII); rimantadine, 100 mg po b.i.d. (CIII), or amantadine, 100 mg po b.i.d. (CIII) (influenza A only)

Table 4-16: Prophylaxis to Prevent First Episode of Opportunistic Disease in Adults and Adolescents Infected with HIV (continued)

Pathogen	Preventive Regimens		
	Indication	First Choice	Alternatives
Hepatitis A virus ^{6,7}	All susceptible (anti-HAV-negative) patients at increased risk for HAV infection (e.g., illicit drug users, men who have sex with men, hemophiliacs) or with chronic liver disease, including chronic hepatitis B or hepatitis C	Hepatitis A vaccine: two doses (BIII)	None
III. Evidence for Efficacy but Not Routinely Indicated			
Bacteria	Neutropenia	Granulocyte-colony-stimulating factor (G-CSF), 5-10 µg/kg sc q.d. x 2-4 w or granulocyte-macrophage colony-stimulating factor (GM-CSF), 250 µg/m ² sc iv x 2-4 w (CII)	None
<i>Cryptococcus neoformans</i>	CD4+ count <50/µL	Fluconazole, 100-200 mg po q.d (CI)	Itraconazole capsule, 200 mg po q.d. (CIII)
<i>Histoplasma capsulatum</i> ⁹	CD4+ count <100/µL, endemic geographic area	Itraconazole capsule, 200 mg po q.d.(CI)	None
Cytomegalovirus (CMV) ¹⁰	CD4+ count <50/µL (and CMV antibody positivity)	Oral ganciclovir, 1g po t.i.d. (CI)	None

NOTES: Information included in these guidelines might not represent Food and Drug Administration (FDA) approval or approved labeling for the particular products or indications in question. Specifically, the terms "safe" and "effective" might not be synonymous with the FDA-defined legal standards for product approval. The Respirgard II nebulizer is manufactured by Marquest, Englewood, Colorado.

Letters and roman numerals in parentheses after regimens indicate the strength of the recommendation and the quality of evidence supporting it. Categories reflecting the quality of evidence forming the basis for recommendations regarding the use of a product or measure for the prevention of opportunistic infection in HIV-infected persons: I — Evidence from at least one properly randomized, controlled trial; II — Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies or dramatic results from uncontrolled experiments; III — Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

ABBREVIATIONS: Anti-HBc = antibody to hepatitis B core antigen; b.i.w. = twice a week; DS = double-strength tablet; HAART = highly active antiretroviral therapy; HAV = hepatitis A virus; HIV = human immunodeficiency virus; im = intramuscular; iv = intravenous; po = by mouth; q.d. = daily; q.m. = monthly; q.w. = weekly; SS = single-strength tablet; t.i.w. = three times a week; TMP-SMX = trimethoprim-sulfamethoxazole; sc = subcutaneous; and TST = tuberculin skin test.

¹Prophylaxis should also be considered for persons with a CD4+ percentage of <14%, for persons with a history of an AIDS-defining illness, and possibly for those with CD4+ counts >200 but <250 cells/μL. TMP-SMX also reduces the frequency of toxoplasmosis and some bacterial infections. Patients receiving dapsone should be tested for glucose-6 phosphate dehydrogenase deficiency. A dosage of 50 mg q.d. is probably less effective than 100 mg q.d. The efficacy of parenteral pentamidine (e.g., 4 mg/kg/month) is uncertain. Fansidar (sulfadoxine-pyrimethamine) is rarely used because of severe hypersensitivity reactions. Patients who are being administered therapy for toxoplasmosis with sulfadiazine-pyrimethamine are protected against *Pneumocystis carinii* pneumonia and do not need additional prophylaxis against PCP.

²Directly observed therapy is recommended for isoniazid, e.g., 900 mg b.i.w.; isoniazid regimens should include pyridoxine to prevent peripheral neuropathy. If rifampin or rifabutin are administered concurrently with protease inhibitors or non-nucleoside reverse transcriptase inhibitors, careful consideration should be given to potential pharmacokinetic interactions (54). See discussion of rifamycin interactions in paragraph 11 in section on Tuberculosis. There have been reports of fatal and severe liver injury associated with the treatment of latent TB infection in HIV-uninfected persons treated with the 2 month regimen of daily rifampin and pyrazinamide; therefore it may be prudent to use regimens that do not contain pyrazinamide in HIV-infected persons whose completion of treatment can be assured (CDC. Update: Fatal and Severe Liver Injuries Associated with Rifampin and Pyrazinamide for Latent Tuberculosis Infection and Revisions in American Thoracic Society/CDC Recommendations, United States 2001 MMWR 50 (No. 34), Aug 31, 2001). Exposure to multidrug-resistant tuberculosis might require prophylaxis with two drugs; consult public health authorities. Possible regimens include pyrazinamide plus either ethambutol or a fluoroquinolone.

³Protection against toxoplasmosis is provided by TMP-SMX, dapsone plus pyrimethamine, and possibly by atovaquone. Atovaquone may be used with or without pyrimethamine. Pyrimethamine alone probably provides little, if any, protection.

⁴See paragraph 9, in section on "Disseminated Infection with *Mycobacterium avium* complex" and references 53-54 for discussion of drug interactions. *During pregnancy, azithromycin is preferred over clarithromycin because of the teratogenicity in animals of clarithromycin.

⁵Vaccination may be offered to persons who have a CD4+ T-lymphocyte count <200 cells/μL, although the efficacy is likely to be diminished. Revaccination 5 years after the first dose or sooner if the initial immunization was given when the CD4+ count was <200 cells/μL and the CD4+ count has increased to >200 cells/μL on HAART is considered optional. Some authorities are concerned that immunizations might stimulate the replication of HIV.

⁶Although data demonstrating clinical benefit of these vaccines in HIV-infected persons are not available, it is logical to assume that those patients who develop antibody responses will derive some protection. Some authorities are concerned that immunizations might stimulate HIV replication, although for influenza vaccination, a large observational study of HIV-infected persons in clinical care showed no adverse effect of this vaccine, including multiple doses, on patient survival (J. Ward, CDC, personal communication). Also, this concern may be less relevant in the setting of HAART. However, because of the theoretical concern that increases in HIV plasma RNA following vaccination during pregnancy might increase the risk of perinatal transmission of HIV, providers may wish to defer vaccination for such patients until after HAART is initiated.

⁷Hepatitis B vaccine has been recommended for all children and adolescents and for all adults with risk factors for hepatitis B virus (HBV). For persons requiring vaccination against both hepatitis A and hepatitis B, a combination vaccine is now available. For additional information regarding vaccination against hepatitis A and B, see CDC. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1991;40 (No RR13).

⁸Oseltamivir is appropriate during outbreaks of either influenza A or influenza B. Rimantadine or amantadine are appropriate during outbreaks of influenza A (although neither rimantadine nor amantadine is recommended during pregnancy). Dosage reduction for antiviral chemoprophylaxis against influenza might be indicated for decreased renal or hepatic function, and for persons with seizure disorders. Physicians should consult the drug package inserts and the annual CDC influenza guidelines for more specific information about adverse effects and dosage adjustments. For additional information about vaccination, antiviral chemoprophylaxis and therapy against influenza, see: CDC. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2001;50(No. RR-4).

⁹In a few unusual occupational or other circumstances, prophylaxis should be considered; consult a specialist.

¹⁰Acyclovir is not protective against CMV. Valacyclovir is not recommended because of an unexplained trend toward increased mortality observed in persons with AIDS who were being administered this drug for prevention of CMV disease.

Source: USPHS/IDSA, 2001. Available at <http://www.aidsinfo.nih.gov>

B. PRESENTATION AND MANAGEMENT OF THE MOST COMMON COMPLICATIONS OF ADVANCED HIV DISEASE (AIDS)

Summaries are presented below. However, specific agents and dosing regimens for acute conditions and secondary opportunistic infection prophylaxis, respectively, can be found at <http://www.aidsinfo.nih.gov>, or in the *2003 Medical Management of HIV Infection* by John Bartlett.

PNEUMOCYSTIS CARINII PNEUMONIA

The diagnosis of PCP can be challenging and requires a heightened index of suspicion. Although there are "classic" symptoms, findings on exam, and chest X-ray manifestations, the presentation of PCP can be subtle and nonspecific. The classic triad of fever, exertional dyspnea, and nonproductive cough occurs in only half of cases, although almost all have at least two of the following: fever, cough, dyspnea, lactate dehydrogenase greater than 460 U/L or an arterial partial pressure of oxygen (PaO₂) less than 75 mm Hg. A careful history may reveal longstanding exertional dyspnea that has worsened incrementally over weeks to months. Physical exam findings are also nonspecific. Fine, dry "cellophane" rales may be heard or auscultation may be entirely normal. In 2–6% of patients, PCP may present as spontaneous pneumothorax. The classic X-ray findings are diffuse interstitial or perihilar infiltrates, but a wide range of X-ray abnormalities is possible and radiography is normal in over one third of cases. Extrapulmonary pneumocystosis is uncommon. PCP is suggested by oxygen desaturation with exercise, easily measured in the office or clinic with a pulse oximeter. This is particularly useful when symptoms are minimal, the patient does not appear acutely ill, and the chest X-ray is unimpressive. Severity of illness is indicated by hypoxemia or a widened alveolar to arterial oxygen difference (A-aDO₂) on blood gas analysis.

Many diseases may have a similar presentation, including mycobacterial, fungal, viral, or bacterial pneumonias, heart failure, pulmonary KS, and pulmonary embolus. The definitive diagnostic test requires bronchoalveolar lavage of affected lung segments that is then concentrated and stained for *P. carinii* organisms. Experienced sites can make a histologic diagnosis from an induced sputum sample that is concentrated and stained, but this less invasive, cheaper diagnostic test should not be attempted where expertise in both obtaining and interpreting the smear is lacking.

Trimethoprim-sulfamethoxazole (TMP-SMX) is the mainstay of treatment for PCP; intravenous or oral administration depends on the severity of the episode. There are a number of alternative regimens for patients who experience treatment-limiting toxicity or who fail to respond to TMP-SMX. PCP should be treated for 21 days. After completing acute therapy, the patient should begin routine daily PCP prophylaxis to prevent recurrence. Patients with PaO₂ less than 70 mm Hg or with an A-aDO₂ greater than 35 on room air should receive adjunctive steroids, which have been shown

to decrease the incidence of ventilatory failure and death. A 21-day course of prednisone (40 mg twice daily for 5 days, then 20 mg twice daily for 5 days, followed by 20 mg once daily for 11 days) is the most popular and cost-effective approach. No additional taper is required.

CANDIDIASIS

The appearance of mucosal candidiasis is often the first clinical indication of impaired T-cell immunity in HIV-infected individuals. Whereas oral and vaginal thrush are almost ubiquitous and *Candida* esophagitis is the second most common OI after PCP, candidemia and tissue-invasive disease are rare. Pharyngitis may be asymptomatic or may cause dysphagia. White plaques can be easily scraped from the pharynx or buccal mucosa; severe cases will involve the tongue, gums, and lips. Vaginitis causes a thick white discharge, pruritus, and sometimes dyspareunia, and has a similar appearance on speculum exam. Intense erythema may be the most prominent finding in some patients with either pharyngitis or vaginitis. Scrapings will be KOH-positive by microscopic exam and will grow readily in culture. These forms of candidiasis may be treated with topical or oral antifungals; topical agents are more cost-effective and avoid the risk of systemic side effects or drug interactions.

Candida esophagitis is a more serious infection that may result in significant weight loss because of odynophagia. Esophagitis should be considered when the patient describes midline substernal chest discomfort with swallowing instead of pain limited to the throat. It may occur in the absence of oropharyngeal thrush, and can be diagnosed by endoscopy or by barium swallow. Topical agents should not be used for esophagitis. Oral fluconazole, 200 mg once daily for 10 days, is the treatment of choice.

Prolonged usage of oral azoles such as fluconazole can result in resistant candidiasis, so it is important to avoid chronic use. Most experts try to use topical antifungals or intermittent courses of azole drugs whenever possible. Prophylaxis for vaginal candidiasis with topical antifungals should be considered when systemic antibiotics are given. Some patients with fluconazole-resistant esophagitis may respond to itraconazole, especially the cyclodextrin solution, oral voriconazole, or to oral amphotericin B solution. However, most patients with resistant infection will ultimately require intravenous (IV) amphotericin for relief.

CRYPTOCOCCAL MENINGITIS

Cryptococcal meningitis may present as nothing more than the worst headache of the patient's life. Fever is common but meningismus may be minimal or absent. Altered mental status and elevated intracranial pressure above 180 mm of water portend a poorer prognosis. Therefore, it is important for patient management to obtain an opening pressure when performing the diagnostic lumbar puncture. Cranial nerve deficits and

seizures are only seen in patients who present very late in the course of their infection and are often antemortem events. The diagnosis is made by detection of cryptococcal capsular antigen in the cerebrospinal fluid (CSF); relying upon a positive India ink stain that demonstrates the organism's thick capsule is too insensitive. *Cryptococcus neoformans* may also be cultured from blood and CSF. Computed tomography (CT) or magnetic resonance imaging (MRI) scans may reveal basilar inflammation, and in patients with intracranial hypertension, the ventricles may be enlarged. Very mild cases may be treated from the outset with oral fluconazole, 400 mg once daily for 10 wk, followed by chronic suppressive therapy (200 mg once daily). Most experts prefer using intravenous amphotericin B at a dose of 0.7–1.0 mg/kg per day for the first 2 wk, with or without flucytosine, and then switching to fluconazole as described above if the patient is responding. Intracranial hypertension can be managed with frequent lumbar punctures to remove large volumes of CSF (20–30 mL at a time). Serum cryptococcal antigen may occasionally be positive before the onset of headache. It may also be detectable when extrameningeal infection occurs, and in the evaluation of a fever of unknown origin. In these situations, oral fluconazole is appropriate therapy.

TOXOPLASMOSIS

Toxoplasmosis manifests almost exclusively as an encephalitis in AIDS patients. The patient presents with a neurologic deficit, and classically one or more ring-enhancing space-occupying lesions can be seen on CT or MRI scan. However, the radiographic appearance of the lesions is not pathognomonic and may mimic other processes such as primary CNS lymphoma. Because serology may be negative and because it is often difficult to obtain a brain biopsy for a definitive diagnosis, the standard approach is a diagnostic trial of antitoxoplasma therapy with pyrimethamine and sulfadiazine for at least 2 wk. Both clinical and radiographic improvement should be evident in response to therapy if the patient has toxoplasmic encephalitis (TE). Clindamycin may be substituted for sulfadiazine if the latter is poorly tolerated. Although TE in AIDS patients results from reactivation of latent infection, a baseline negative IgG test for *Toxoplasma gondii* does not exclude the diagnosis, and seronegative patients will routinely receive a trial of therapy regardless of their serostatus. For this reason, and because PCP prophylaxis with TMP-SMX will also prevent TE, obtaining a *Toxoplasma gondii* IgG may not be very cost-effective. A situation where knowledge of *Toxoplasma gondii* serostatus is helpful is when a patient cannot tolerate TMP-SMX prophylaxis; in this case pyrimethamine should be added to second-line PCP prophylaxis with dapsone to provide protection from TE as well.

HERPES SIMPLEX VIRUS

HIV-infected individuals may have recurrent genital HSV that can be suppressed with oral antiviral drugs such as acyclovir, valacyclovir, and famciclovir. Both treatment and prophylaxis of HSV may require higher

doses and, in the case of treatment, longer administration than is required in the management of HIV-negative patients; this is particularly the case in women with more advanced immunosuppression (see Chapter VI on Gynecologic Problems). Definitive diagnosis is usually made by culturing HSV from the base of the lesion(s), although experienced clinicians will often rely on typical appearance, distribution, and symptoms. When patients develop severe mucocutaneous lesions or ulcers that persist for more than 4 wk, this unusually persistent form of HSV is considered an AIDS-defining illness. Similar to fluconazole-resistant candidiasis, injudicious chronic use of antiherpes drugs may result in drug-resistant infection, which then requires treatment with intravenous foscarnet. Varicella-zoster virus, a related member of the herpesvirus family, causes shingles, which responds to higher doses of antiherpes drugs than those needed for HSV. Shingles can be exquisitely painful and patients may have prolonged postherpetic neuralgia. Secondary bacterial infection may occur, so it is important to keep the lesions clean and to use topical or systemic antibiotics as needed. Control of pruritus and pain is essential for patient comfort. Drug-resistant varicella-zoster virus has been reported and is also treated with IV foscarnet.

CYTOMEGALOVIRUS

Cytomegalovirus (CMV) causes retinitis in 80–85% of AIDS patients with end-organ CMV disease. Gastrointestinal disease anywhere from the mouth to the anus is diagnosed in another 12–15%. Other diagnoses, such as encephalitis and pneumonitis, are uncommon (~1%). CMV retinitis can cause visual loss, and untreated, progresses inexorably to blindness. Because retinitis is a necrotizing process, with effective antiviral treatment the lesions become quiescent and atrophic, but the affected areas do not regain function. Retinitis near critical structures such as the macula or optic nerve may cause catastrophic visual loss even when the total infected area is small. Patients may be completely asymptomatic, or may complain of floaters (due to inflammatory debris), diminished acuity, or visual field defects when the lesion(s) is(are) in the periphery. Diagnosis is made by visual inspection of the entire retina by an experienced ophthalmologist using dilated indirect ophthalmoscopy. Extensive disease may lead to retinal detachment, which may require surgical repair. Treatment is usually begun with oral valganciclovir or with intravenous ganciclovir, foscarnet, or cidofovir for 2–3 wk, followed by chronic suppression with either less frequent IV doses or oral valganciclovir or ganciclovir. Chronic use of these intravenous agents requires the placement of an indwelling catheter for ease of administration, or IV therapy can be used briefly until an intraocular device can be inserted surgically that slowly releases small amounts of ganciclovir directly into the vitreous. Because CMV is a systemic infection with viremia, patients who receive the ganciclovir implant also need chronic suppressive therapy with oral valganciclovir to prevent the development of extraocular CMV disease. CMV can become resistant to antivirals. Refractory disease is often treated with intraocular injections,

which, like the ganciclovir implant, deliver high concentrations of drug to the site of active viral replication. End-organ disease at nonocular sites is treated with 2–3 wk of intravenous induction therapy; oral valganciclovir has not been studied for monocular disease but should be effective. There is no clear agreement that CMV disease at sites outside the eye requires chronic maintenance therapy, but with the availability of oral valganciclovir it seems reasonable to provide continued anti-CMV treatment in patients whose immune systems remain badly damaged (CD4 cells $<100/\text{mm}^3$).

DISSEMINATED MYCOBACTERIUM AVIUM COMPLEX (MAC)

Like CMV, disseminated MAC is one of the OIs that appears at end-stage disease, when the total CD4 cell count is extremely low. It presents nonspecifically with fever, weight loss, diarrhea, anemia, and sometimes abdominal discomfort due to organomegaly and impressive intra-abdominal lymphadenopathy. Mycobacterial blood culture provides a definitive diagnosis; culture of sputum or other specimens is not helpful. Combination oral antimicrobial therapy is required and should include, at a minimum, an azalide (azithromycin or clarithromycin) and ethambutol, 15–25 mg/kg per day. Other drugs, such as ciprofloxacin and amikacin, have been used but do not routinely provide much additional benefit; clofazimine has been shown to have an adverse effect on survival and should not be used.

TUBERCULOSIS

There is a bidirectional interaction between *Mycobacterium tuberculosis* and HIV; each facilitates acquisition of the other, so it is critical to assess all HIV-infected patients for active tuberculosis (TB), and to test all patients with active TB for HIV. Because TB is virulent enough to cause disease in patients with intact immune systems, it may occur in HIV-infected individuals who still have high CD4 cell counts. TB is especially virulent in HIV seropositive individuals. Aspects of this virulence include the high frequency of positive blood cultures and of disseminated (miliary) infection. However, standard combination antimicrobial therapy is effective as long as the patient is adherent and the acquired strain is not multidrug resistant. It is essential to provide directly observed therapy to ensure an adequate course of treatment and conversion of positive sputum cultures to negative. Until susceptibilities are known, all HIV-infected patients should be treated initially with at least four drugs expected to be active according to local susceptibility patterns; for susceptible TB, typically INH, rifampin or rifabutin, pyrazinamide and ethambutol or streptomycin are given for 2 months, followed by INH and rifampin or rifabutin for 4 months. Subsequently, when the results of susceptibility testing are available, therapy for drug-sensitive infection can usually be narrowed to two agents. Patients with advanced HIV disease or a delayed response to TB treatment (symptomatic and/

or culture-positive after 2 months of treatment) should receive a total course of 9 months. Clinicians should work closely with their local health department to ensure that patients receive directly observed therapy, and to track and limit the spread of TB, especially resistant strains. All close contacts – especially young children – must be evaluated for TB so they may be treated promptly for active disease or given prophylaxis as indicated.

CRYPTOSPORIDIOSIS AND MICROSPORIDIOSIS

These enteric protozoa can cause debilitating diarrhea and weight loss in patients with advanced HIV disease. Diagnosis is made by special stool stains. Unfortunately there is no effective therapy (except for *Septata intestinalis*, which may respond to albendazole), so care is supportive. Every effort should be made to optimize the patient's antiretroviral therapy because there are reported cases of clinical resolution (and even clearing of the organism from stool) with potent combination antiretroviral therapy. Patients may develop severe dehydration due to voluminous watery diarrhea. In addition to volume repletion, attempts at slowing the diarrhea should be made as follows by adding (not substituting) each additional agent in a stepwise manner: 1) diphenoxylate or loperamide, increased to their maximum dose, plus 2) tincture of opium or paregoric, with the dose titrated gradually until the desired effect is achieved, and, if additional control is needed, 3) parenteral somatostatin, which is very expensive.

PERIPHERAL NEUROPATHY

Distal, symmetrical polyneuropathy, typically affecting the feet more than the hands, may result from use of the neurotoxic dideoxy nucleoside analogues (didanosine, stavudine, zalcitabine) and much less commonly from dapsone, or may be a consequence of advanced HIV disease itself. Most patients present with paresthesias and/or numbness, but some experience pain that can be disabling. Examination reveals slow or absent ankle jerks, diminished vibratory and proprioceptive responses in both feet, and in patients whose primary complaint is pain, discomfort sometimes even with light touch. If drug toxicity is suspected, the offending agent(s) should be discontinued immediately and replaced. If this is accomplished quickly enough after the onset of symptoms, the syndrome may resolve entirely. When the nerve damage is not attributable to anti-HIV therapy or does not resolve after drug discontinuation, supportive care may be offered. Nonsteroidal antiinflammatory drugs; agents useful in chronic pain syndromes such as amitriptyline, phenytoin, or carbamazepine; the neurotransmitter inhibitor gabapentin; mexilitene, lamotrigine; and, in refractory cases, long-acting narcotics, all have a role in the management of dysesthesias and pain due to peripheral neuropathy.

AIDS DEMENTIA COMPLEX (ADC)/HIV ENCEPHALOPATHY

In the pre-HAART era, frank dementia was the AIDS-defining illness in up to 10% of patients. The initial manifestations may be subtle, and can be uncovered by questioning the patient carefully about short-term memory loss and difficulty concentrating. Useful questions about the latter include the ability to balance a checkbook or to make change. In some patients, a depressed affect may be a prominent finding, and in others, unexplained seizures may bring the patient to medical attention. Psychomotor retardation — slowing of the impulses that match actions to thoughts and intentions — is another hallmark of AIDS dementia complex (ADC). CT and MRI scans show diffuse cortical loss with prominent sulci (“walnut sign”). A good sense of the patient’s level of intellectual functioning can often be obtained at the bedside. In subtle or difficult cases, especially when there is a prior history of depression or subnormal IQ, the patient can be referred for a battery of neuropsychologic tests that may clearly demonstrate the losses characteristic of ADC. There is no specific treatment for ADC other than effective antiretroviral therapy, although symptoms may respond in part to methylphenidate or selegiline. Patients may demonstrate a remarkable degree of recovery with antiretroviral therapy even when they present with advanced dementia, so it is valuable to attempt treatment of all patients, even those initially referred for nursing home care. It may be particularly useful to include agents that achieve good CSF levels.

WASTING SYNDROME (“SLIM DISEASE”)

Weight loss is common in HIV disease, especially in its advanced stages, but the CDC surveillance definition of wasting syndrome specifically refers to involuntary weight loss that exceeds 10% of the patient’s baseline weight in the presence of diarrhea (≥ 2 loose stools per day) or chronic weakness and documented fever (intermittent or constant) for at least 30 days that is not attributable to a condition other than HIV itself. Typically wasting syndrome is accompanied by loss of muscle mass, for example in the temporal areas, and complaints of generalized fatigue and modest weakness. In severe cases the serum albumin level will be very low. Wasting can accompany any of the typical end-stage illnesses, such as disseminated MAC, or may occur by itself in the absence of any evident concomitant illness. Loss of weight, and, especially, of lean body mass, portends poorer survival. Appetite stimulants, such as the progestin megestrol acetate or the marijuana derivative dronabinol, may be used although weight gain with these agents typically consists of fat and water, rather than an increase in lean body mass. However, the psychologic benefit of an improved appetite and some weight gain cannot be underestimated, even if the gain is primarily fat. Recombinant human growth hormone has been used with some short-term success for improvement in lean body mass, but it is very expensive and must

be given parenterally. Other approaches include enteral and parenteral feedings, anabolic steroids such as nandrolone or oxandrolone, and thalidomide or pentoxifylline for cytokine suppression. Men with symptoms of hypogonadism often respond to testosterone replacement, but this approach has not been evaluated in women.

KAPOSI'S SARCOMA

Kaposi's sarcoma (KS) is an endothelial cell tumor that, along with PCP, was the harbinger of the AIDS epidemic. It primarily affects gay and bisexual men, and is fairly uncommon among injecting drug users and women. It is caused by human herpesvirus-8. KS can occur at a range of total CD4 cell counts, but prognosis is poorer at lower values. Most commonly it is limited to mucocutaneous surfaces, where it is a cosmetic problem but not a significant threat to health. KS of the gastrointestinal mucosa is very vascular and may lead to slow, chronic blood loss. KS may also involve the lymphatic system, and may invade the viscera, especially lung parenchyma. Experienced clinicians can generally diagnose mucocutaneous KS by inspection, but a punch biopsy showing typical spindle-shaped cells is easy to obtain and is definitive. Visceral KS, which may occur in the absence of mucocutaneous disease, requires a tissue diagnosis.

Mucocutaneous KS may be treated with a number of local modalities including intralesional vincristine or vinblastine, radiation, and topical retinoids. Gastrointestinal lesions can be cauterized endoscopically. Visceral disease requires systemic chemotherapy. More recently, KS has regressed in patients begun on potent combination antiretroviral therapy alone.

SYSTEMIC LYMPHOMA

Several different types of lymphoma occur at increased frequency among HIV-infected individuals. These too may occur at any CD4 cell count although once again prognosis is worse at lower absolute numbers of CD4 cells. HIV seropositive patients may develop Hodgkin's disease, immunoblastic lymphoma, and Burkitt's lymphoma as well as less common forms, but the most common type is an aggressive non-Hodgkin's B cell lymphoma. There is a marked tendency for extranodal presentations (Stage 1E), and AIDS patients have been described with non-Hodgkin's lymphoma at a range of unusual sites. AIDS-associated lymphoma is diagnosed and staged in the same manner as in seronegative patients, and the same types of combination chemotherapy are used. However, HIV-infected patients typically require lower doses or aggressive support with granulocyte colony-stimulating factor because of their baseline bone marrow fragility.

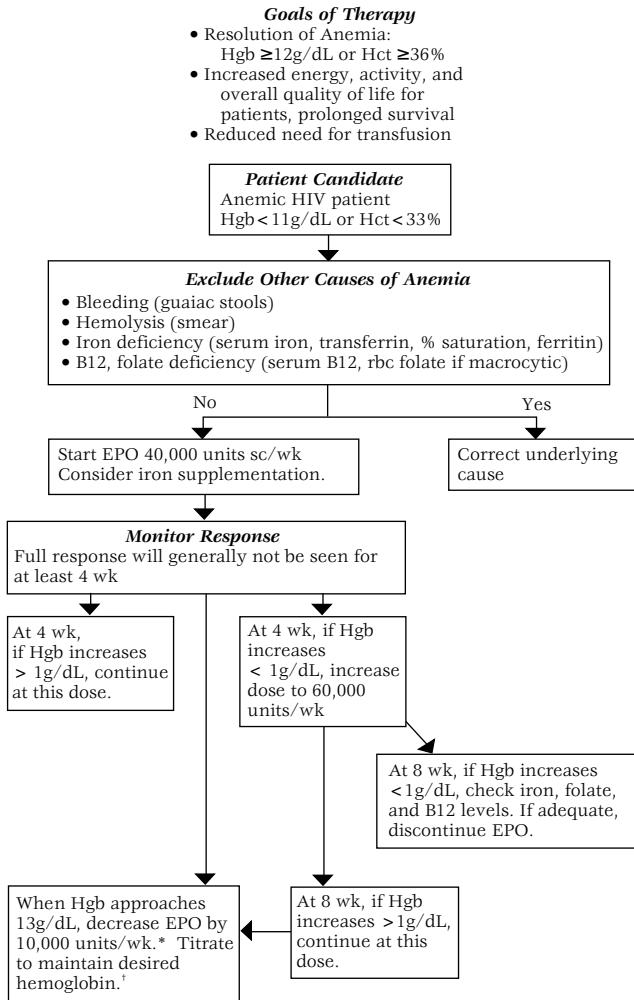
CENTRAL NERVOUS SYSTEM LYMPHOMA

Central nervous system lymphoma occurs at total CD4 cell counts well under 100 cells and is a typical end-stage complication. Definitive diagnosis is made by brain biopsy or CSF cytology in the presence of a space-occupying lesion(s) on CT or MRI scan. A presumptive diagnosis may sometimes be made by nuclear SPECT scan. Because brain biopsy may be difficult to obtain, patients who fail a trial of therapy for toxoplasmosis are often assumed to have CNS lymphoma. There is no effective cytotoxic chemotherapy for this disease, and irradiation is considered palliative. Survival after a diagnosis of CNS lymphoma is usually limited, on the order of a few months.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Progressive multifocal leukoencephalopathy is another end-stage complication of HIV disease, usually presenting as a focal neurologic deficit(s). It is caused by the JC virus, which can be detected by PCR performed on CSF. MRI scan of the brain demonstrates involvement of the white matter that can be focal or fairly diffuse, but is not usually associated with either mass effect or surrounding edema. Most commonly it affects areas adjacent to the cortex, but lesions can be located anywhere. Definitive diagnosis is made by brain biopsy or positive PCR, which is highly specific in the appropriate clinical context. Where these diagnostic modalities are unavailable, the typical MRI picture usually suffices. There is no specific proven therapy for this condition, although a number of case reports describe clinical remission in patients begun on potent combination antiretroviral therapy. In the pre-HAART era, survival was very limited, but now there are patients alive more than a few years after diagnosis.

Figure 4-5: Guidelines for Use of Erythropoietin in the Anemic HIV Patient



* If Hgb \geq 15g/dL at any point, hold erythropoietin (EPO) and restart when Hgb < 12 g/dL, using dose reduced by 10,000/wk.

† During dose adjustment phase, hemoglobin should be monitored every 2-4 wk. Allow at least 4 wk to assess response to dose changes.

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CHRONIC HEPATITIS B AND C

Many of the same behaviors that put women at risk of acquiring HIV also result in hepatitis B and/or C infection. Up to 90% of HIV-infected individuals have evidence of prior exposure to hepatitis B (HBV) and up to 10% have chronic HBV infection (Homann, 1991; Bodsworth, 1991). Risk of developing chronic infection is increased in the presence of HIV co-infection (Bodsworth, 1991; Houssett, 1992); limited data also suggest that HIV-HBV coinfection is associated with higher HBV DNA levels and worse prognosis in terms of liver-related morbidity and mortality (Thio, 2001; Colin, 1999). Persistence of HbsAg for longer than 6 months is indicative of chronic infection; these patients should be tested for HbeAg and anti-Hbe and have periodic assessment (e.g., every 6 months) of transaminases, albumin, prothrombin time, bilirubin, complete blood count, and platelet count. Patients with chronic HBV infection are at increased risk of cirrhosis and end-stage liver disease and hepatocellular carcinoma. Periodic screening every 6–12 months with alfa fetoprotein (AFP) and/or liver ultrasound should be considered in patients with chronic HBV and other high risk characteristics (age >45 years, cirrhosis, family history of liver cancer). Indications for HBV treatment include: HbsAg positive > 6 months, evidence of active viral replication (HbeAg + HBV DNA positive), and moderate or severe liver inflammation on biopsy. The goal of treatment is to prevent or delay the progression of liver disease; eradication of the virus is not possible with current therapies. Agents used to treat HBV include interferon, lamivudine (3TC), tenofovir, adefovir, and emtricitabine; 3TC, tenofovir, and emtricitabine should only be used as part of or in conjunction with a fully suppressive antiretroviral regimen.

A recent cross-sectional analysis of a large heterogeneous group of HIV-infected individuals found that 16% had HCV coinfection (Sherman, 2002). Hepatitis C (HCV) becomes a chronic infection in about 85% of cases. Data from a recent meta-analysis indicate that HIV-HCV coinfecting patients have a 2.9 times higher risk of progressive liver disease than those infected with HCV alone (Graham, 2001). There is some evidence that HCV may accelerate progression of HIV disease as well (Piroth, 2000). Screening for HCV is recommended using a 2nd or 3rd generation HCV enzyme-linked immunosorbent assay with confirmation using HCV RNA testing. Hepatitis C viral loads do not correlate with severity of liver damage on biopsy. Serum transaminases should be monitored, especially ALT, which is more specific for hepatocellular injury. ALT levels may wax and wane, and may be normal or only modestly elevated. Screening for hepatocellular carcinoma with AFP and/or liver ultrasound should be considered, particularly in patients with cirrhosis. Indications for HCV treatment include: detectable HCV RNA, persistently elevated ALT levels, and liver biopsy with portal or bridging fibrosis and at least moderate inflammation and necrosis. The goals of treatment include eradication of HCV infection and prevention or delay of progressive liver disease. Recommended treatment for chronic HCV is pegylated interferon plus ribavirin; preliminary data suggest that HCV virologic response correlates with CD4 cell count in HIV-HCV coinfecting patients (Soriano, 1996).

Patients with either HBV or HCV infection should avoid alcohol consumption, which may increase risk of progressive liver disease. Transplantation of coinfecting patients with end-stage liver disease has been successful and is being evaluated further.

ANEMIA

Modest anemia (≥ 9 –10 g/dL) is a hallmark of chronic HIV infection and may be complicated by menstrual losses in women of childbearing age. Severe anemia (≤ 9 g/dL) may occur as part of certain opportunistic diseases, especially MAC, disseminated histoplasmosis, and lymphoma, and may also be the result of drug toxicity. Although severe anemia has been shown to be associated with a poorer prognosis for survival in a number of studies, diagnosis and treatment of the opportunistic process is often sufficient to improve anemia in these cases.

Patients who are symptomatic with exertional dyspnea and dizziness can be transfused acutely. Most HIV-infected patients become anemic gradually, and unconsciously limit their activities to control symptoms. These individuals can be managed with changes of antiretroviral or OI therapies known to be toxic to red blood cells, such as AZT (zidovudine) and TMP-SMX. In patients refractory to conservative management, red blood cell production can be stimulated by using recombinant erythropoietin along with sufficient iron replacement to stimulate production of new red cells (see Figure 4-5).

C. OPPORTUNISTIC DISEASE IN THE HAART ERA

The impact of highly active antiretroviral therapy on the natural history of opportunistic diseases has been profound, and the clinician must be familiar with at least the broad outline of these changes. There may be sufficient immune restoration that even patients with end-stage disease become capable of mounting an inflammatory response to opportunistic pathogens. This can result in worsening of the clinical manifestations of an OI that has been under treatment or atypical presentation of a new acute OI, generally within the first couple of months after initiating potent antiretroviral therapy, after CD4 cell counts have begun to improve. For example, in the case of MAC lymphadenitis, there may be the acute focal development of a tender, enlarged lymph node with negative blood cultures, whereas in the pre-HAART era the typical presentation would have been diffuse, with widespread nontender adenopathy and high-grade mycobacteremia. This seemingly paradoxical development of an OI with rising CD4 cell counts is likely due to an inflammatory response to an OI that was subclinical when HAART was begun. Similarly, immune reconstitution syndromes have been described for TB, PCP, toxoplasmosis, cryptococcal infection, and PML, when these infections have been under treatment. Management includes continuation of antiretroviral therapy while making sure there has been no recrudescence of the underlying OI, plus addition of NSAIDs or corticosteroids to alleviate the inflammatory reaction.

Patients who recover pathogen-specific immunity in addition to the overall increase in CD4 cells may be able to discontinue chronic suppressive (maintenance) therapy, because the patient's immune system is now capable of containing the infection. Thus far this has been best demonstrated for discontinuing chronic suppression for CMV retinitis. Similar phenomena have been described for other OIs, such as disseminated MAC, and there is no reason to think that other OIs will behave differently. Last, patients with previously untreatable opportunistic processes, such as PML or cryptosporidiosis, have had clinical remissions after initiating HAART.

A number of studies have shown that patients receiving primary prophylaxis for PCP and MAC are at very low risk of developing these OIs if prophylaxis is withdrawn after total CD4 cell counts have improved above the threshold levels for risk of each specific OI for at least 3–6 mo. Most of these studies have been performed among patients with reasonably well controlled HIV viral loads, with the majority undetectable or at most, less than 10,000 copies. At this point, it is clear that specific prophylaxis can be safely stopped for any OI when CD4 cell counts have increased above the threshold of risk \geq 3 months. The 2002 revision of the USPHS guidelines on OI prophylaxis describes the data and rationale for discontinuing suppressive therapy and prophylaxis in the appropriate patient. These guidelines are revised periodically just as the ones for treatment and HIV are, so it is wise to check www.aidsinfo.nih.gov.

VI. ALGORITHMS FOR DIAGNOSIS AND MANAGEMENT OF SYMPTOMS

Figure 4-6: Fever of Unknown Origin in Patients with AIDS

Figure 4-7: Acute Diarrhea in Patients with AIDS

Figure 4-8: Chronic Diarrhea (CD4 Count $<$ 300/mm³)

Figure 4-9: Cough, Fever, Dyspnea

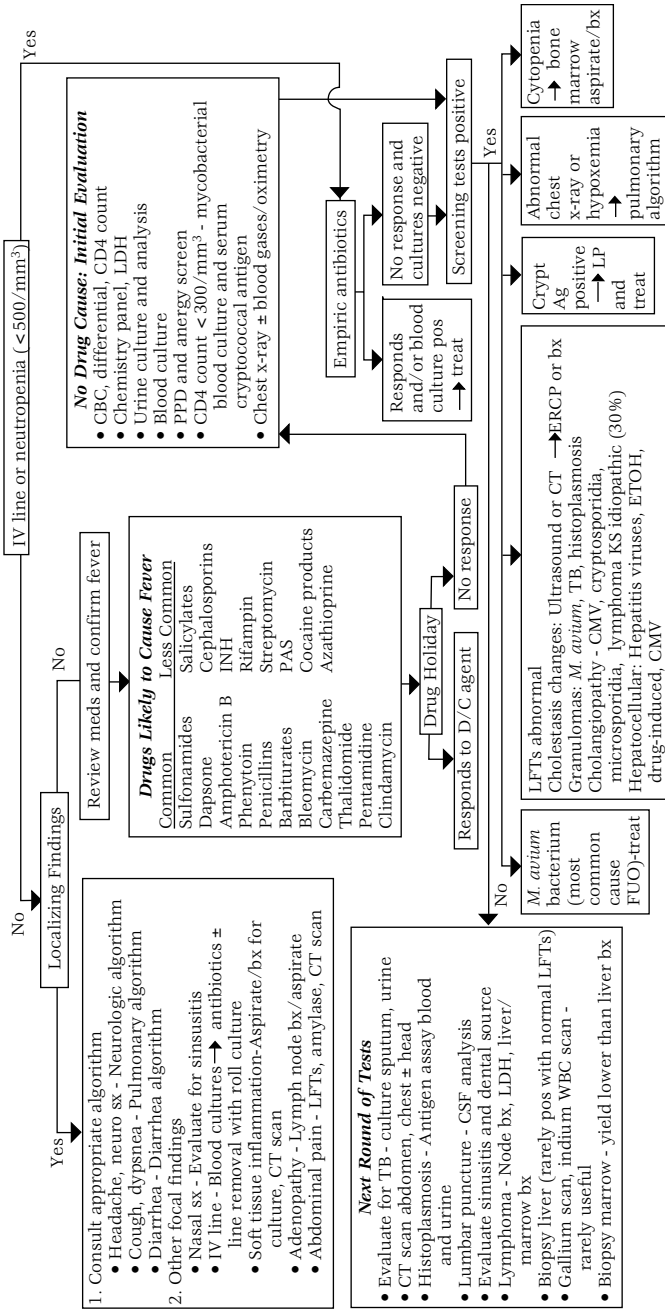
Figure 4-10: Headache in Patients with AIDS

Figure 4-11: Advanced HIV Infection Plus Altered Status, New Seizures, Headache (Severe or Persistent), or Focal Neurologic Deficits

Figure 4-12: Sensory Neuropathies in Patients with AIDS

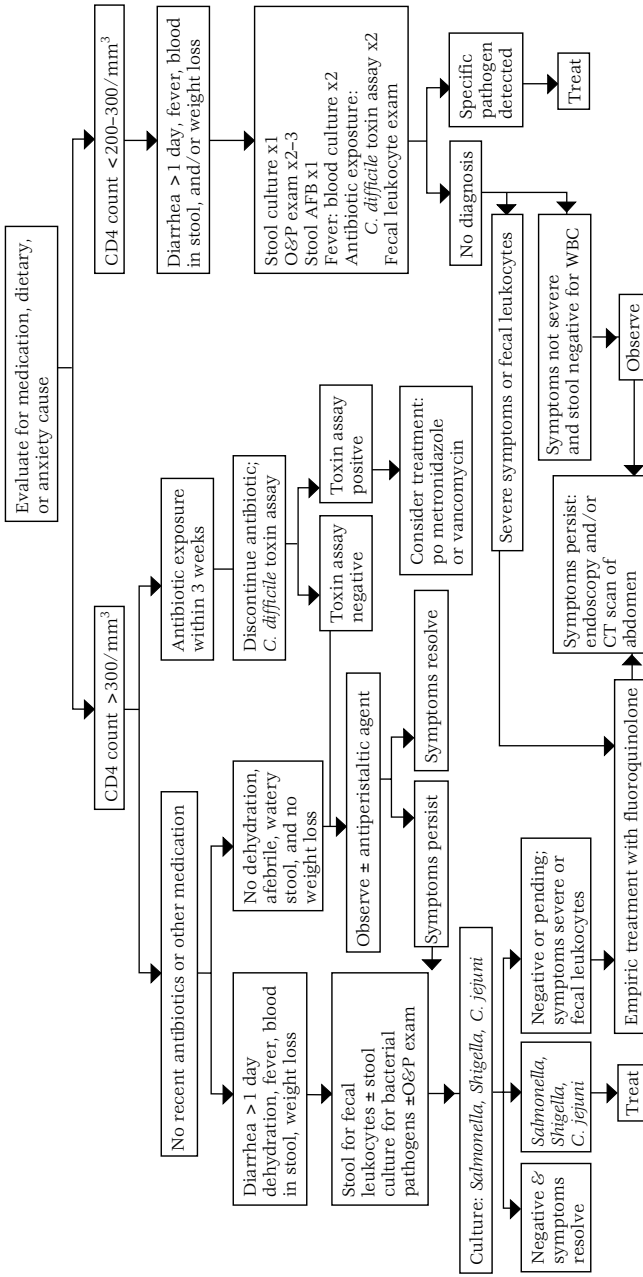
Figure 4-13: Odynophagia in Patients with AIDS

Figure 4-6: Fever of Unknown Origin in Patients with AIDS



Source: Bartlett, 2001. Reprinted with permission.

Figure 4-7: Acute Diarrhea in Patients with AIDS



Source: Bartlett, 2001. Reprinted with permission.

Figure 4-8: Chronic Diarrhea (CD4 Count < 300/mm³)

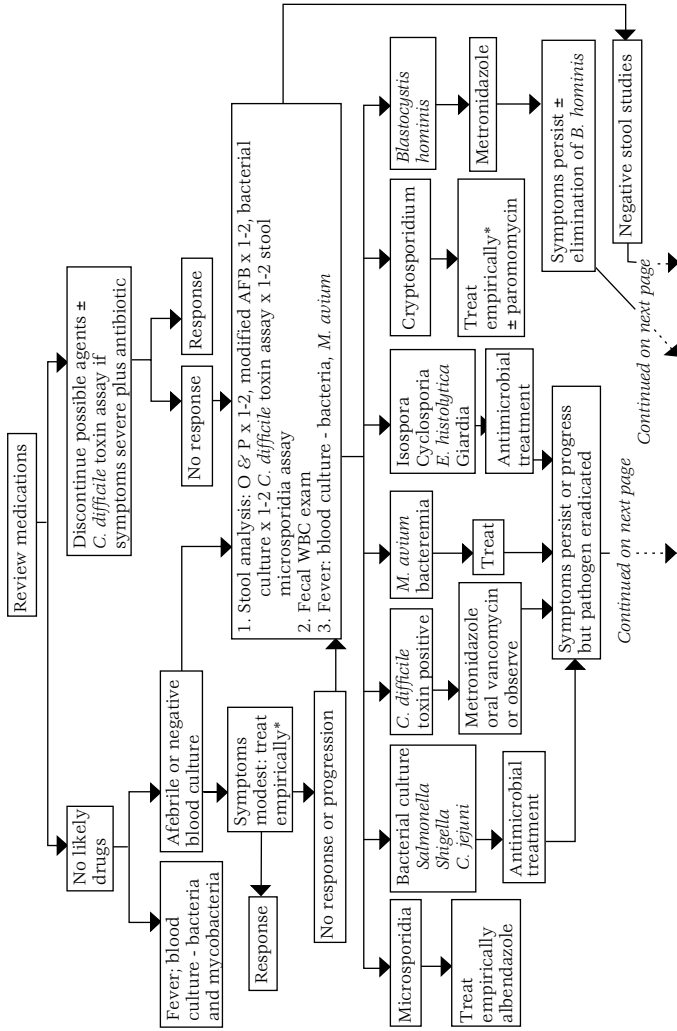
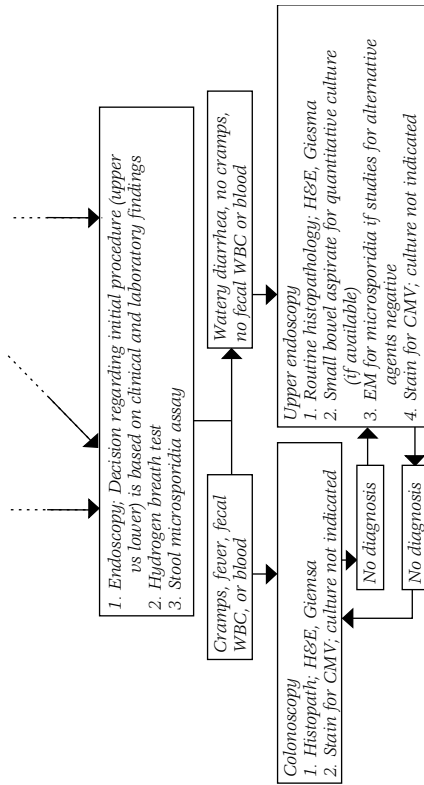


Figure 4-8: Chronic Diarrhea (CD4 Count < 300/mm³) (continued)



* Frequent small feedings, bland foods, avoid caffeine, low-lactose, low-fat, high-fiber diet. Supplement with polymeric formulas and antiperistaltic agents (loperamide or Lomotil) progressing to tincture of opium octroide) as necessary.

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Figure 4-9: Cough, Fever, Dyspnea

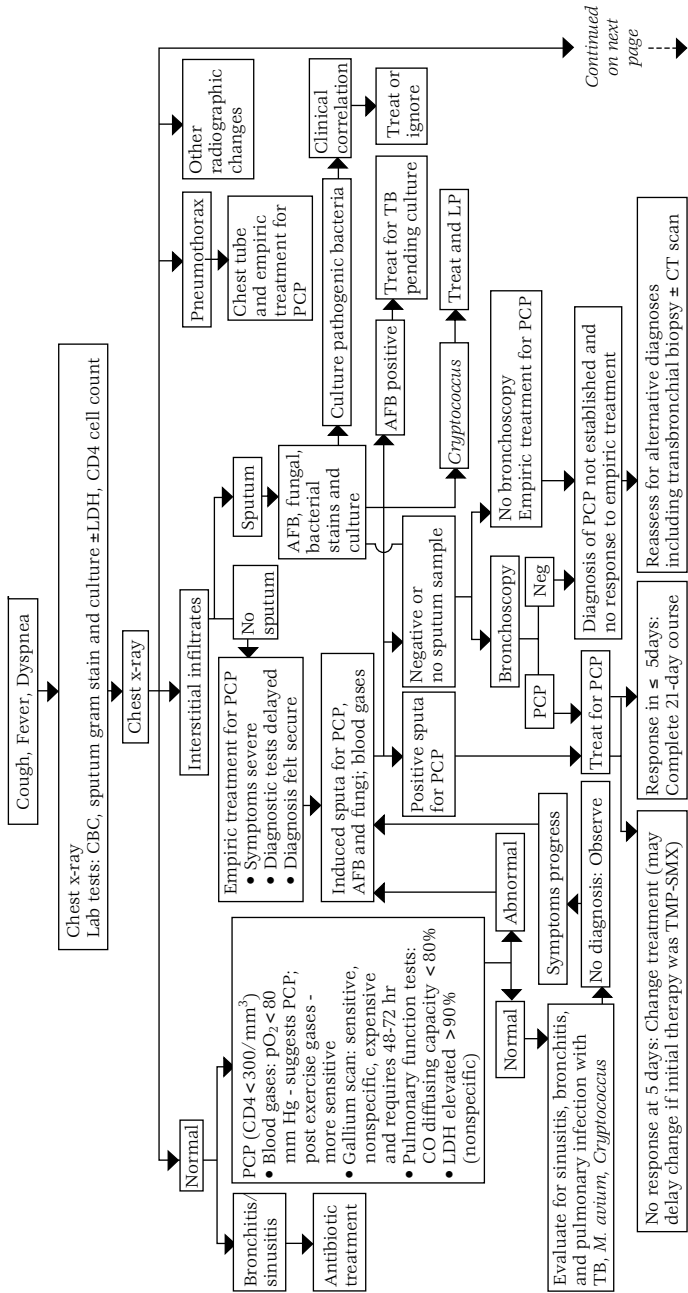
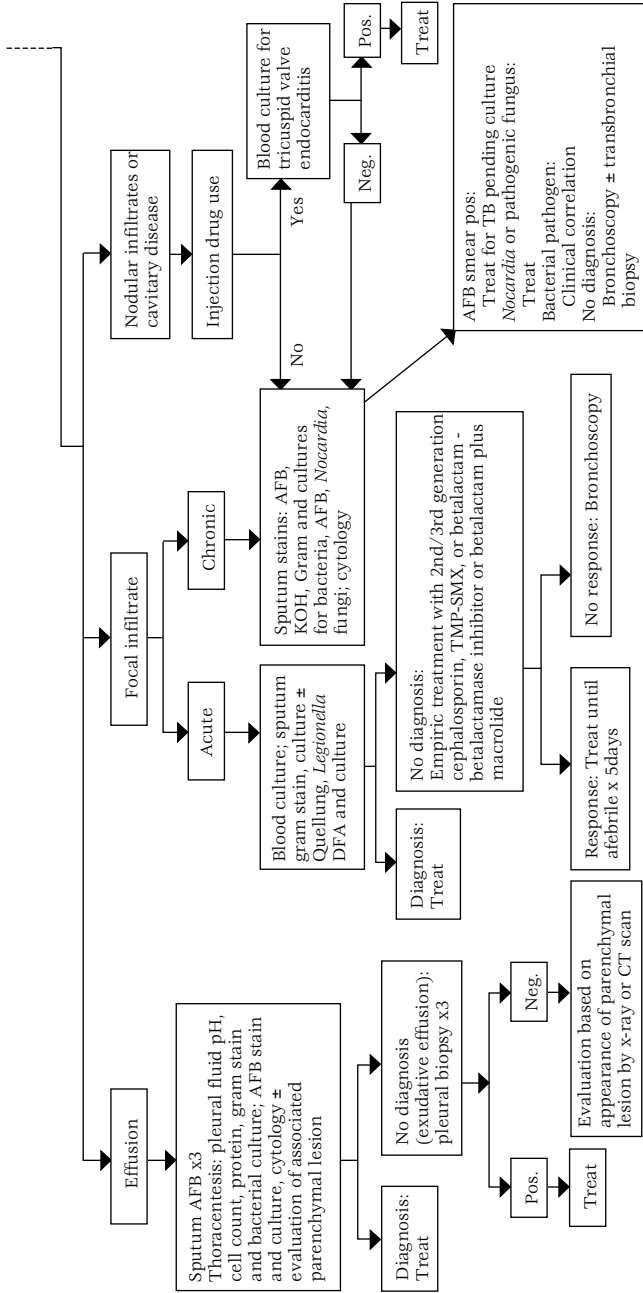
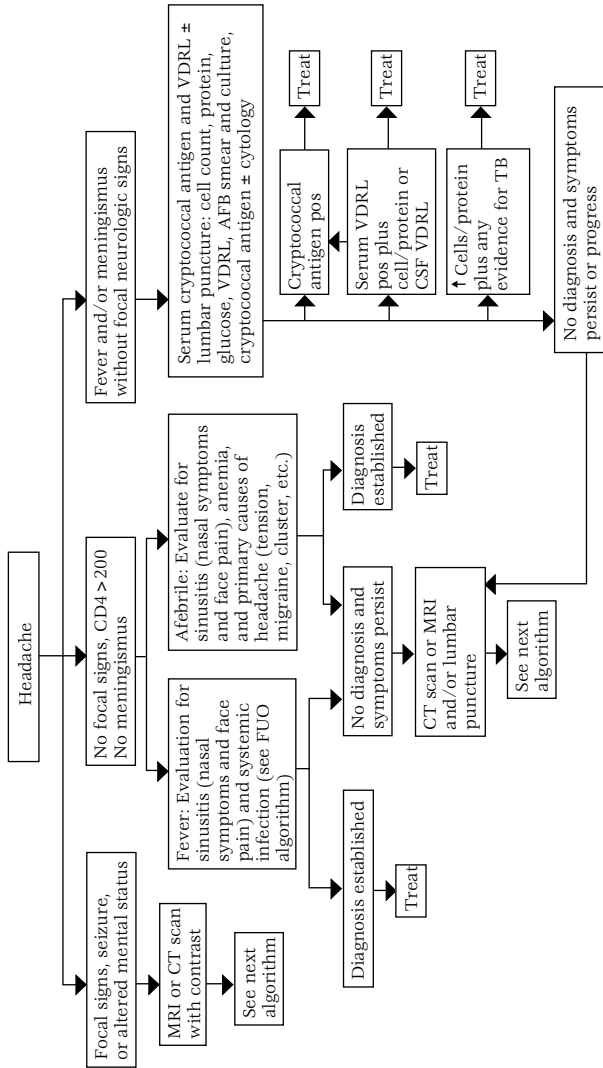


Figure 4-9: Cough, Fever, Dyspnea (continued)



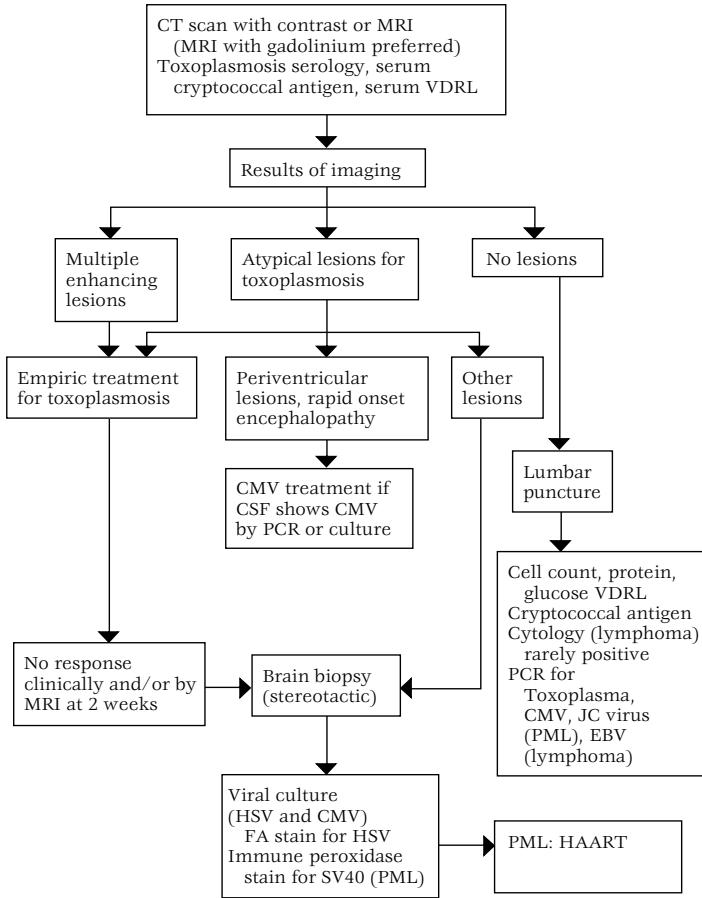
Source: Bartlett, 2003. Reprinted with permission.

Figure 4-10: Headache in Patients with AIDS



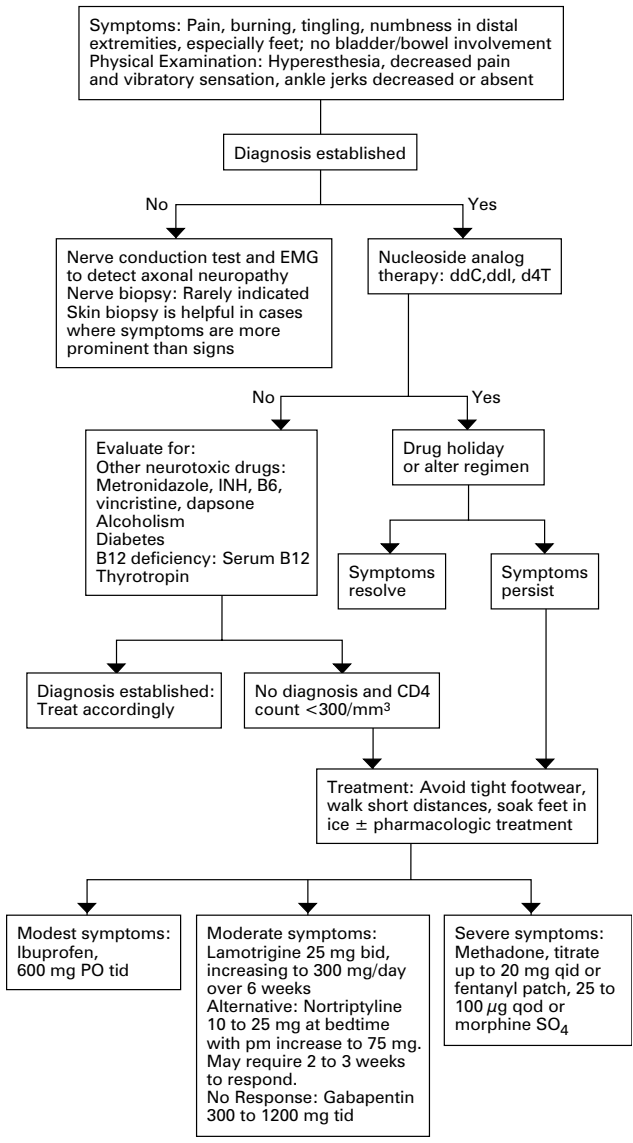
Source: Bartlett, 2001. Reprinted with permission.

Figure 4-11: Advanced HIV Infection Plus Altered Status, New Seizures, Headache (Severe or Persistent), or Focal Neurologic Deficits



Source: Adapted from Bartlett, 2001. Reprinted with permission.

Figure 4-12: Sensory Neuropathies in Patients with AIDS



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Figure 4-13: Odynophagia in Patients with AIDS

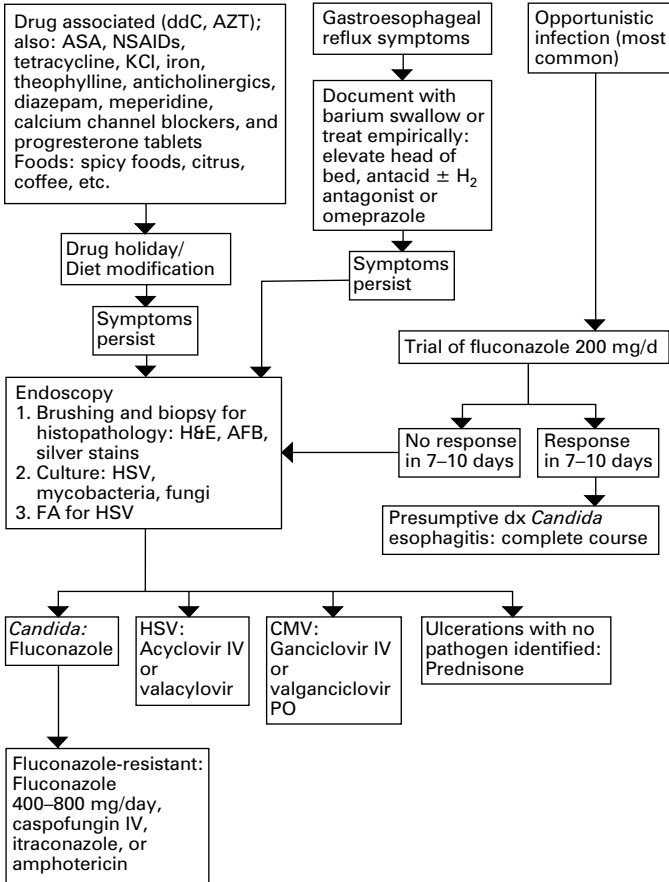
Evaluation

1. Medication or food related
2. Gastroesophageal reflux disease: (heartburn ± regurgitation and dysphagia)
3. Opportunistic infection or tumor

Common: *Candida* sp.

Less common: HSV, CMV, idiopathic (aphthous)

Rare: TB, *M. avium*, histoplasmosis, PCP, cryptosporidia, Kaposi's sarcoma, lymphoma



Source: Bartlett, 2003. Reprinted with permission.

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V. ADHERENCE TO HIV THERAPIES

Laura W. Cheever, MD

I. INTRODUCTION

Adherence to HIV therapies is critical if patients are to achieve and maintain undetectable viral loads and avoid preventable opportunistic infections. Initial clinical trials of highly active antiretroviral therapy (HAART) demonstrated that 80–90% of patients receiving protease inhibitor therapy could achieve viral loads <400 copies/mL (Gulick, 1997). However, currently in real-world clinical practice only 50% of patients achieve this goal (Lucas, 1999). The primary reason is nonadherence with therapy. Adherence with medications in any chronic disease is a challenge for most patients. As a general rule, only 50% of patients with chronic illnesses maintain “good adherence” (taking >80% of medication doses) over time. Patients with HIV infection have similar rates of adherence. Unfortunately in this infection, “good adherence” is not good enough, and the consequences of nonadherence are severe. Nonadherence with antiretroviral therapy is strongly associated with HIV disease progression and mortality (Hoggs, 2002).

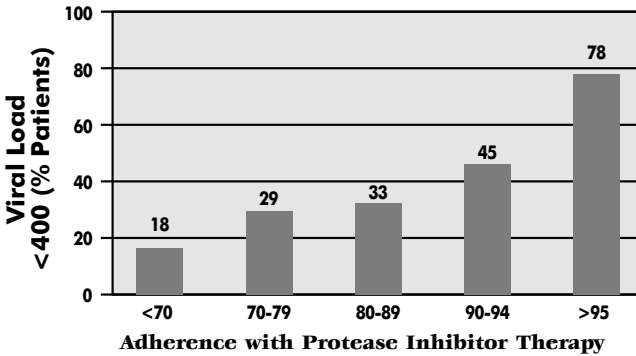
This chapter addresses the important issues regarding adherence with HIV medications. Beyond this specific issue, there are other aspects of adherence with medical care, including adherence with recommendations for laboratory monitoring for toxicity and clinical response and adherence with appointment keeping, that are also critical factors in successful HIV treatment.

II. THE UNFORGIVING NATURE OF HIV AND THE MEDICATIONS TO TREAT IT

Adherence with medications is critical in HIV infections for several reasons involving both the nature of the virus and the drugs to combat it. First, the virus has a very high replication and mutation rate. If drug doses are intermittently missed, the virus quickly begins to replicate. In the presence of low levels of drug, viral mutations that confer drug resistance will thrive. Second, the most potent drugs, both protease inhibitors and nonnucleoside reverse transcriptase inhibitors, have broad class resistance. That is, when resistance to one drug in the class occurs, often resistance has developed to many other drugs in that class. Thus, nonadherence to one regimen can result in virus resistant to many antiretrovirals.

Finally, a patient needs to have near-perfect adherence, as shown in Figure 5-1, to achieve the undetectable viral load necessary to prevent the development of resistant virus (Paterson, 2000). For most chronic diseases, 80% adherence is considered “good adherence.” However, only 49% of patients achieved undetectable viral load with this level of adherence.

Figure 5-1: Adherence Rates Predict Viral Load Responses



Source: Adapted from Paterson, 2000. Modified with permission from American College of Physicians.

Thus, in HIV infection, patients must have exceptionally high levels of adherence to therapy to prevent the emergence of resistant virus. Additionally, unlike other chronic diseases, such as hypertension, if HIV-infected patients are nonadherent, even for a few weeks, they may severely limit their future treatment options because of broad class resistance.

III. PREDICTORS OF ADHERENCE

Adherence is a complex behavior. In analyzing predictors of adherence, it is important to consider factors related to the patient, the treatment regimen, the doctor-patient relationship, and the system of medical care. Several patient-related factors are consistently predictive of adherence or nonadherence among HIV-infected individuals. Depression and active substance abuse (including alcohol, cocaine, or heroin) correlate with nonadherence, whereas the patient's belief that they can both make HIV medication regimens fit into their life and be adherent with the regimen is predictive of adherence (Table 5-1, Cheever, 1999). In addition, one of the best predictors of adherence is adherence with previous therapy.

In most chronic diseases, demographic characteristics, such as sex, race, income, education, and age, are not predictive of adherence (Haynes, 1979). However, in the initial studies of these factors of HIV-infected patients, the data are inconclusive. In the HIV Cost and Services Utilization Study, a national probability sample survey, the investigators found that women, African Americans, Hispanics, younger adults, and patients with higher CD4 counts reported lower rates of adherence (Wenger, 1999). Other studies report conflicting results, and the relationship between these demographic variables and adherence needs further exploration.

Table 5-1: Patient Factors Associated with Adherence
<i>Strongly Associated</i>
• Lack of depression
• Lack of active alcohol/substance abuse
• Self-efficacy (belief in one's ability to take medication as instructed)
• Belief medications can be fit into their day
• Understanding the relationship of viral resistance and adherence
• Previous adherence
<i>Inconsistently Associated</i>
• Sex (males more adherent than females)
• Race (whites more adherent than blacks)
• Age (older patients more adherent than younger patients)
• Stage of disease (patients with lower CD4 counts more adherent than patients with higher CD4 counts)
<i>Not Generally Associated</i>
• Education, income, employment
• HIV risk factor
• Belief that medications will improve health

In terms of the treatment regimen, side effects are a major cause of nonadherence (Heath, 2002). Adherence decreases as the number of doses per day, pills, or medications increase. Likewise, medications with food restrictions are harder to take as directed. Length of time on therapy also impacts medication adherence. Adherence tends to wane over time, which is a compelling reason to delay therapy until the risk of progression to AIDS is significant. Pharmacy and social work counseling of patients whenever HAART is initiated or the regimen is changed can be helpful in ensuring that patients understand dosing and side effects and can assist in developing strategies to avoid missing doses.

The doctor-patient relationship is also an important variable in adherence and should not be overlooked. Several studies have shown that patients who trust their doctor are more likely to adhere to therapy, including studies among HIV-infected patients (Altice, 2001). Most medical providers believe that they can predict which patient will be able to adhere to a medical regimen. However, studies have repeatedly shown that physicians, nurse practitioners, and nurses cannot predict with reliability which patients will adhere to therapy (Paterson, 2000). Table 5-2 lists the most common reason patients say they miss their medication (Chesney, 1997; Eldred, 1998). These reasons vary significantly from the reasons that providers cite as reasons their patients miss doses (Gallant, 1998).

Table 5-2: Reasons Patients Cite for Missing Medication

• Did not have medication at the time of the dose
• Simply “forgot” to take it
• Asleep at time of dose
• Too busy at the time
• Off usual daily schedule/routine
• Ran out of medication
• Using drugs/alcohol
• Pills too difficult to take (too many, too big, schedule too complicated)
• Didn’t want to be reminded of HIV/AIDS
• Didn’t want to take pills in front of others

The system of care can affect adherence to a medication regimen. Situations that facilitate patients' access to medication, in terms of refill requests, reminders to refill medication, and mechanisms to obtain medications when gaps in medication insurance occur, can significantly affect a patient's ability to adhere. Similarly, systems that help patients overcome barriers to seeking medical care, including problems with transportation, childcare, and paying for services, also assist in the patient's adherence efforts. Finally, patient education is a critical part of improving adherence. Within the system of care, personnel and resources need to be dedicated to this important endeavor.

IV. ADHERENCE IN SPECIAL POPULATIONS

A. INCARCERATED PATIENTS

Incarcerated patients have unique challenges to medication adherence. Medical regulations vary significantly among correctional systems, and these regulations influence patients' medication adherence. Correctional institutions may provide directly observed therapy of each dose of medication, which may result in excellent medication adherence. On the other hand, lockdowns and other security concerns supercede medical concerns and may result in missed doses. In correctional systems where HIV-infected inmates are identified and called by name to receive medications, many patients forego treatment rather than risk disclosure of their HIV infection. Additionally, the incarceration process itself provides many opportunities for potential disruption in access to medications. Most patients do not immediately access their antiretroviral medication on entry to the system or at times of transfer within the system. When patients are discharged from the penal system, they are provided with a limited supply of medication; often patients run out of medication before they can establish medical care in their communities, resulting in nonadherence with their regimen.

B. HOMELESS PATIENTS

It is often assumed that homeless patients face insurmountable barriers to adherence with medications. Certainly, homelessness itself creates many challenges to adherence. Additionally, many homeless patients have mental illness or substance abuse that may further contribute to nonadherence. However, homeless patients can be successful in taking HAART. In a study of homeless and marginally housed patients from San Francisco, 38% of the 32 homeless patients taking protease inhibitors had high levels of adherence (Bangsberg, 2000). However, the group appears to be highly selected since only 34 of 153 patients in this marginally housed cohort were prescribed HAART.

C. CHILDREN AND ADOLESCENTS

Young children are dependent on the adults around them for their medication adherence. As with many HIV-infected adults, HIV-infected children may be in tenuous social situations due to poverty and unstable housing, in addition to illness among their parents. Many children are unable or unwilling to swallow unpalatable medication or pills, making dosing administration take hours each day. In one study, gastric tubes were placed in children who had extreme problems with taking medication. These children subsequently showed improvement in adherence, viral load, time necessary to administer doses, and interpersonal relationships with the persons administering the medication (Shingadia, 2000). Adolescents who have not disclosed their HIV status may miss doses because of lack of a private place to take their medication. Furthermore, adolescence is a time of testing limits and feelings of invulnerability, both of which may contribute to the likelihood of nonadherence.

V. MEASURING ADHERENCE

There are many methods to measure adherence including electronic devices, pill counts, and drug assays. However, in clinical practice, the most efficient method to measure adherence is simply to ask the patient (Icovicks, 1997). It is critical to ask over time as patients' adherence will vary, for example, in response to re-initiation of substance abuse.

When asked in a nonjudgmental way, most patients (80% in several studies) are truthful about their medication taking (Sackett, 1976). To get the most reliable information, patients should be given permission to have missed doses, asked in a nonjudgmental way, and given a specific time frame. For example, *"Everyone misses doses some of the time. In the last 2 weeks, how many doses have you missed?"*

Computer assisted self-interviewing (CASI) technology is increasingly used to assess adherence and improves the reliability of patient self report (Turner, 1998, Bangsberg, 2002). The technology is also used to simultaneously collect information on side effects and high risk behaviors that might be missed in a less structured format of a patient-clinician interaction.

Pharmacy records can also give important information regarding adherence when available to the clinical staff. Serum drug level tests are now commercially available. These are most useful when patients professing adherence are not responding well to therapy; however, low drug levels may also be due to poor absorption or drug-drug interactions as well as to nonadherence.

VI. IMPROVING ADHERENCE

Given the importance of adherence in HIV infection and the relatively low rates of adherence in any chronic disease, it is of utmost importance to support efforts to increase patient adherence. Many interventions have been shown to increase adherence with pill taking in chronic disease. However, most interventions only have a modest effect on adherence. Those that work best are *multifaceted* (working on more than one aspect of the pill taking behavior) and *repetitive* (having the intervention reapplied over time) (McDonald 2002, Roter, 1998). With antiretroviral medication, it is critical to start the intervention before nonadherence, and viral resistance, have occurred.

In initiating a successful regimen, the most important thing to consider is whether the patient is ready to start antiretroviral therapy. The patient is usually the best judge of when to start therapy as long as she is well informed regarding the rigors of antiretroviral therapy and the consequences of nonadherence. Thus, the bulk of patient education efforts should be made before initiation of therapy. Given that the patient's "first shot [of antiretrovirals] is the best shot," most patients benefit in the long run by delaying therapy if they are not ready to start. The urgency of therapy increases as the CD4 count falls and the viral load increases. Many physicians feel pressured by practice guidelines for starting therapy. The best time to start therapy is when the patient is ready.

There are, however, a few "antiretroviral emergencies," pregnancy being one of them. Clearly, for the pregnant woman, the cost benefit considerations are different, as outlined in Chapter VII on HIV and Reproduction. In the case of pregnant women, the time permitted for the patient to prepare to start therapy may be considerably compressed. Thus, even more intensive educational efforts are needed in this population.

Patient education is clearly important, with high returns on the investment made before starting therapy. Group education generally works better than one-on-one education, probably because of the support and practical peer advice that is shared (Roter, 1998). Many patients resist groups, but many find them beneficial if they can be convinced to go. Specific interventions to improve adherence are outlined in Table 5-3.

Many intervention trials in HIV infection are on-going or completed. The Health Resources and Services Administration funded the evaluation of 14 U.S. based adherence programs. For antiretroviral naïve patients, programs that included readiness training, that is spending time with the patient before the initiation of therapy to prepare them to start, were most effective. For both naïve and experienced patients, programs that included peer support, whether in one-on-one or group sessions, were also highly effective.

Table 5-3: Interventions to Improve Adherence	
<i>Intervention</i>	<i>Comments</i>
<i>The Patient</i>	
Start when the patient is ready	<ul style="list-style-type: none"> • For pregnant women, the cost-benefit analysis of treatment is different.
Treat substance abuse and depression before initiating antiviral therapy	<ul style="list-style-type: none"> • If there is no antiretroviral emergency, patients with active substance abuse and depression should have these comorbidities addressed before initiation of antiretrovirals.
Engage the patient in medication tailoring	<ul style="list-style-type: none"> • Discuss with the patient in detail how the medications will fit into their daily routine, i.e., when (and if) meals are eaten, what the patient does on a daily basis that can be linked to dosing times.
Educate (group/individual) regarding: <ul style="list-style-type: none"> • The regimen • Side effects management • Consequences of nonadherence 	<ul style="list-style-type: none"> • Patient education is essential—both group and one-on-one education. • Involve caretakers and patient support network in educational efforts. • Patients need to know exactly how to take their medication. A daily calendar with pills on it will help a patient to visualize the regimen. • Before initiating therapy, patients should know which side effects to expect, what they can do to manage them, and when to call the medical practice. • Patients need to understand the serious consequences of nonadherence and what to do in the event of a late or missed dose.
Increase support	<ul style="list-style-type: none"> • Patients should enlist the aid of family and friends to promote their adherence. The HIV health care team can provide support through office visits, home visits, and telephone calls, especially in the first days and weeks of antiretroviral therapy.
Use skill-building exercises as part of readiness training	<ul style="list-style-type: none"> • Have the patient use a trial of jellybeans in a pill box to accustom themselves to their pill-taking schedule before initiating therapy.
Address barriers to adherence	<ul style="list-style-type: none"> • Have the patient consider when medications are likely to be missed and make plans to decrease these events. • Some patients store a few doses in places where they spend a lot of time, such as at the houses of friends and relatives.
Use reminders	<ul style="list-style-type: none"> • Alarm clocks, in the form of watch alarms or pill boxes, can decrease missed doses due to simply forgetting. • Patients can place medications in locations they will notice them at dosing times, such on the breakfast table.
Simplify as much as possible	<ul style="list-style-type: none"> • Once or twice daily regimens are easiest for patients. • Use as few pills and medications as possible. • Try to use regimens that can be taken without regard to food intake.
Anticipate potential medications side effects	<ul style="list-style-type: none"> • Discuss potential side effects, their likely duration and ways to prevent or manage them.
<i>The Regimen</i>	
Tailor the regimen to the patient's lifestyle (and not the patient's lifestyle to the regimen).	<ul style="list-style-type: none"> • Ask the patient about her daily routine, comfort in taking medications in front of others and at work. • Construct a regimen that works for the patient.
Use pill boxes	<ul style="list-style-type: none"> • Use of pill boxes allows the patient to carry her daily medication. • Pill boxes allow for patients to easily recognize when they have missed a dose.
Make refills accessible	<ul style="list-style-type: none"> • Develop policies to allow patients ready access to refills.

Table 5-3: Interventions to Improve Adherence (continued)	
The Doctor-patient Relationship	
Develop a trusting relationship	<ul style="list-style-type: none"> • Rarely is initiation of antiretrovirals required at the first visit. Invest in the doctor-patient relationship before initiating therapy.
Ask about adherence	<ul style="list-style-type: none"> • Medical providers cannot predict adherence; you must ask the patient. • Ask in a nonjudgmental way, with a specific time frame, to get good information. • Give permission for missed doses before asking. • Ask repetitively over time.
Use positive reinforcement	<ul style="list-style-type: none"> • Share viral load and CD4 results and reinforce the relationship to adherence.
Listen to the patient	<ul style="list-style-type: none"> • Individualize therapy based on patient preferences regarding fear of specific side effects or specific medication. Negotiate the regimen with the patient.
The System of Care	
Maintain close follow-up at initiation	<ul style="list-style-type: none"> • Have telephone, office, or home contact with patient within first few days of therapy to assess for side of regimen effects and accurate understanding of regimen.
Develop patient education program	<ul style="list-style-type: none"> • Consider use of nurses, case managers, pharmacists, and peers in patient education. • Have written materials accessible.
Incorporate the adherence message throughout the medical practice	<ul style="list-style-type: none"> • All staff members need to understand and promote the importance of adherence. • Have pill boxes, alarms, and other adherence aids available to patients.

Source: Adapted from Cheever, 1999.

VII. CONCLUSION

Adherence with medications is critical in HIV infection. Whenever medications are prescribed, special emphasis must be placed on patient readiness and adherence. Many types of interventions can improve adherence, and it is vital that these are employed to give patients the best chance at an optimal response to HIV therapies.

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VI. GYNECOLOGIC PROBLEMS

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I. INTRODUCTION

Gynecologic problems are common among HIV-positive women and are frequently present at the time of initial presentation for evaluation and care. Minkoff et al. found that 46.9% of 262 HIV-infected women had a least one incident gynecologic condition with serial assessment (Minkoff, 1999). In a study of women admitted to an inpatient AIDS service, although only 9% were admitted with a primary gynecologic problem, 83% had coexisting gynecologic disease when evaluated (Frankel, 1997). Some gynecologic issues are unrelated to the patients' serologic status, whereas others are directly related to HIV disease and associated immunosuppression. Still others are associated epidemiologically with HIV because of common risk factors, such as sexual behavior or substance abuse.

In 2002, women accounted for 26% of the adult AIDS cases and 32% of the adult cases of HIV infection reported in the United States (CDC, 2002). Moreover, women have had the greatest increase in AIDS incidence in recent years when compared with other US population groups. With this background and the fact that HIV infection primarily affects women during their reproductive years, gynecologic and reproductive health care will play an increasingly important role in the overall care of the HIV-infected woman. With improved longevity and quality of life, gynecologic problems may be encountered more commonly or may be more prominent. With these issues in mind, the goal of this chapter is to use a problem-oriented approach in reviewing the most common gynecologic complaints together with their differential diagnosis, evaluation, management, and relationship to HIV.

II. ABNORMAL UTERINE BLEEDING/AMENORRHEA

A. WHAT IS CONSIDERED "ABNORMAL" BLEEDING?

A normal menstrual period should occur every 21 to 35 days and last between 2 and 6 days. The average blood loss during menses is 20 to 60 mL, but up to 14% of healthy women have blood loss greater than 80 mL and are more likely to be anemic because of this (Mishell, 1997a).

Amenorrhea represents a sort of abnormal bleeding in that it is the lack of menstruation. Primary amenorrhea is defined as the absence of menses by age 16. Secondary amenorrhea is the absence of menses for a variable period of time, for at least 3 mo and usually 6 mo or longer, in a woman who has previously menstruated.

B. RELATIONSHIP TO HIV DISEASE

Menstrual disorders are frequently reported by HIV-positive women. However, controlled studies have yielded conflicting evidence regarding whether HIV or HIV-related immunosuppression exerts a clinically significant direct effect on these reported disturbances (Chirgwin, 1996; Ellerbrock, 1996; Shah, 1994) and more definitive studies are needed. A recent large study of HIV-positive and high-risk HIV-negative women from the HERS and WIHS prospective cohorts found that HIV serostatus has little overall effect on amenorrhea or menstrual cycle length or variability. However, higher viral loads and lower CD4 counts were associated with increased cycle variability and polymenorrhea. (Harlow, 2000). Clark et al, using measurement of serum progesterone and follicle-stimulating hormone (FSH) levels, found higher than expected occurrence of anovulation and premature menopause in a small study of women 20-42 years old who participated in selected ACTG protocols.(Clark, 2001). Although numbers were too small to reach statistical significance, these menstrual disorders were more common among women with lower CD4 cell counts.

In the setting of HIV infection, menstrual disorders may be related to confounding variables, such as weight loss, chronic disease, substance abuse, or use of psychotherapeutic medications (Harlow, 2003) and progestational agents used for appetite stimulation or contraception. The impact of antiretroviral therapy on menstruation has not been well studied but hypermenorrhea, or excessive menstrual blood loss, has been reported with ritonavir (Nielsen, 1999). The effect of HIV-RNA levels on menstrual function is unknown.

C. HISTORY

- **Characteristics of bleeding:** date of last normal menstrual period, duration and frequency of menses, amount of bleeding (number of pads/tampons used per day); presence of clots or associated pain/cramping; duration and pattern of menstrual irregularities or amenorrhea; presence of intermenstrual or postcoital bleeding.
- **Other bleeding sources:** gastrointestinal (GI) or bleeding from the urinary tract (vs. from a gynecologic source); history of easy bruising, nose or gum bleeds.
- **History of gynecologic problems/other symptoms:** abnormal Pap smears; uterine fibroids or polyps; prior ectopic pregnancy; abnormal vaginal discharge.
- **Medical history:** timing of diagnosis of HIV/AIDS and existing comorbid conditions; clinical symptoms of HIV; CD4 count and viral load; history of platelet disorders (thrombocytopenia is frequently diagnosed in HIV infection, particularly in individuals with more advanced stages of disease (Sloand, 1992); medications; history of substance abuse.
- **Sexual history:** last sexual intercourse and use of contraception and condoms.

D. PHYSICAL EXAM

A careful and comprehensive abdominal and pelvic examination should be performed. The presence of abdominal tenderness or mass should be noted. The external genitalia, vagina, and cervix should be inspected for evidence of actively bleeding lesions (e.g., lacerations, condylomata, polyps) or inflammation. Bimanual and rectovaginal examinations assess the presence of pelvic tenderness, enlarged uterus, or other pelvic mass.

E. DIFFERENTIAL DIAGNOSIS

- **Pregnancy.** Pregnancy must be considered in any woman of reproductive age with irregular bleeding or amenorrhea. Pregnancy may be either intrauterine or ectopic (usually tubal); bleeding with an intrauterine pregnancy may indicate threatened or incomplete abortion or miscarriage or a serious obstetric complication in later pregnancy.
- **Anovulation.** Anovulation is the most common cause of abnormal uterine bleeding among reproductive-aged women. Typically, the woman has a history of menstrual irregularity and may go several months with no bleeding, followed by the onset of prolonged and heavy bleeding. Anovulatory bleeding is a diagnosis of exclusion, and organic, systemic, and iatrogenic causes of bleeding must be ruled out. Anovulation and oligoovulation are more common among perimenopausal women and adolescents soon after menarche.
- **Perimenopause.** In addition to anovulation/oligoovulation, women in perimenopause may have irregular menses because of declining estrogen levels.
- **Uterine fibroids.** Fibroids are common benign uterine tumors that are most often asymptomatic, but may cause heavy and/or prolonged periods.
- **Cancer.** Malignant processes in every part of the female genital tract (vulva, vagina, cervix, uterus, fallopian tubes, and ovaries) can potentially present with abnormal bleeding; most common in postmenopausal women.
- **Genital tract infections.** Cervicitis, endometritis, and even vaginitis and vulvitis may present with abnormal vaginal bleeding or spotting. Associated symptoms, including pain/tenderness, discharge, fever, and other signs and symptoms of infection, will aid in making the diagnosis. In very immunosuppressed patients, consider opportunistic processes, including tuberculous or cytomegalovirus (CMV) endometritis.
- **Medical conditions.** Thyroid disorders (hypothyroidism or hyperthyroidism), coagulopathy (including platelet disorders), cirrhosis, chronic illness/wasting.

- **Substance abuse.** Drug use (including methadone) can lead to disturbances of the hypothalamic-pituitary axis, with resulting irregular bleeding or amenorrhea.
- **Medications.** Progestational agents, such as those used for contraception (e.g., Depo-Provera, Norplant) or for appetite stimulation (e.g., Megace) frequently cause irregular vaginal bleeding. Consider antiretroviral agents as a potential cause of abnormal bleeding. Medications that can affect prolactin concentrations and possibly result in amenorrhea include psychotropic drugs (tricyclic antidepressants, phenothiazines, opiates) and metoclopramide. Thalidomide has been also been associated with development of secondary amenorrhea (Frances, 2002).

F. EVALUATION

The basic evaluation includes the following:

- **Pregnancy test (urine or serum):** perform on all women with abnormal bleeding/amenorrhea within reproductive age range
- **Laboratory tests:**
 - Complete blood count (CBC), platelet count
 - Thyroid-stimulating hormone, prolactin levels — consider with any irregular bleeding/amenorrhea without apparent cause
 - Follicle-stimulating hormone (FSH), estradiol — with oligomenorrhea/amenorrhea and/or signs/symptoms of decreased estrogen production (hot flashes, vaginal atrophic changes). These tests are particularly helpful in distinguishing ovarian failure (low estradiol, high FSH) and hypothalamic amenorrhea (e.g., with wasting) (low estradiol, low/normal FSH)
 - Coagulation profile — if evidence of systemic bleeding, to rule out coagulopathy
- **Cervical testing:** for gonorrhea and chlamydia
- **Pelvic ultrasound:** with abnormal exam (uterine enlargement, adnexal mass, significant tenderness) or positive pregnancy test; ultrasound using the transvaginal approach is used commonly in the evaluation of abnormal bleeding to assess endometrial thickness, especially in peri- and postmenopausal women, or to look for other possible abnormalities (e.g., polyps, fibroids)
- **Endometrial biopsy:** indicated with postmenopausal bleeding, prolonged amenorrhea followed by onset of irregular or heavy bleeding, persistently irregular bleeding. Used liberally with any form of abnormal bleeding if no cause is found otherwise and bleeding does not respond to conservative (e.g., progestins, oral contraceptives) management. It is helpful in diagnosing endometritis, endometrial hyperplasia, and uterine cancer; endometrial tissue necessary to diagnose CMV or tuberculosis (TB) endometritis—alert your pathologist if these are considerations

- **Pap smear:** do not perform with active bleeding; if cervical lesion seen, biopsy is required.

Further evaluation or referral is indicated based on results of these tests, severity of the problem, and response to basic management.

G. MANAGEMENT

Management depends on the diagnosis and results of testing. All women with a positive pregnancy test require referral to a specialist. If anovulatory bleeding is suspected, medical management may be attempted with oral contraceptive pills or cyclic progestins (medroxyprogesterone acetate 10 mg po qd for 10–14 days each month). These therapies help restore regular menstruation, reduce possible anemia, and protect the endometrium from prolonged estrogenic stimulation, which can cause hyperplasia or neoplasia. Oral contraceptive pills will also provide effective contraception, but are contraindicated in heavy smokers over the age of 35, with hypertension or other cardiovascular disease, and in diabetics and women with markedly abnormal liver function.

With severe bleeding and anemia, pelvic mass, findings suspicious for malignancy, or bleeding that is not resolved with conservative measures, referral is indicated.

III. ABNORMAL PAP SMEAR

In the setting of HIV infection 30–60% of Pap smears exhibit cytologic abnormalities and 15–40% have evidence of dysplasia; these rates are 10–11 times greater than those observed among HIV-negative women (Maiman, 1998).

A. INTERRELATIONSHIP OF HIV AND HUMAN PAPILLOMAVIRUS

- Human papillomavirus (HPV) infection plays a causative role in lower genital intraepithelial and invasive neoplasia. The spectrum of HPV disease includes subclinical disease, classic genital warts and other HPV-related skin lesions, lower genital tract intraepithelial neoplasia, and invasive cancers of the lower genital tract. There are over 100 HPV subtypes, which are divided into low, intermediate, or high risk, based on oncogenic potential; nevertheless, these categories are not exclusive and “low-risk” HPV types have been described in cervical carcinomas.
- HPV is an extremely common infection; current evidence suggests that over 50% of sexually active adults have been infected with one or more genital HPV types, but most HPV infections are transient (Evander, 1995; Ho, 1998). Studies have shown that HIV-infected women have higher prevalence of HPV, higher incidence of HPV (Branca, 2003; Ahdieh, 2001), higher HPV viral load (Jamieson, 2002), longer persistence of HPV (Ahdieh, 2000; Sun, 1997), higher likelihood of multiple HPV subtypes (Jamieson, 2002), and greater

prevalence of oncogenic subtypes (Minkoff, 1998; Uberti-Foppa, 1998) than HIV-uninfected women. HPV viral load is independently associated with HPV persistence (Ahdieh, 2001).

- In HIV-positive women the prevalence and persistence of HPV infection increases with decreasing CD4 count and increasing HIV RNA levels (Palefsky, 1999) and some studies show that oncogenic HPV types may be more common with lower CD4 counts and/or higher viral loads. (Luque, 1999; Minkoff, 1998). Higher HPV viral loads are also associated with lower CD4 counts (Heard, 2000).
- Sun et al. (Sun, 1995) have suggested that the presence of immunosuppression shifts the ratio of latent:clinically expressed HPV infections from 8:1 in the general population to 3:1 in HIV-positive women with CD4 >500/mm³ to 1:1 in HIV-positive women with CD4 <200/mm³.

B. HIV AND CERVICAL DYSPLASIA

- Abnormal cervical cytology is more common among HIV-infected women and is associated with the presence of HPV infection and the degree of immunosuppression. Both frequency and severity of abnormal Pap smears and histologically documented dysplasia increase with declining CD4 counts and have also been associated with higher HIV-RNA levels (Garzetti, 1995; Shah, 1996; Davis, 2001). Incidence of abnormal Pap smears is increased in HIV-infected as compared to -uninfected women, and is associated with lower CD4 counts; progression and regression of Pap smear abnormalities have been associated with level of immunosuppression and plasma viremia, as reflected in CD4 count and HIV viral load (Massad, 2001; Schuman, 2003). Increased HPV viral load, seen in women with more advanced HIV, is also associated with increased frequency, severity, and incidence of cervical dysplasia (Heard, 2000; Weissenborn 2003; Cohn, 2001).
- In HIV-positive women dysplasia is associated with more extensive cervical involvement and is more likely to involve other sites in the lower genital tract, such as the vagina, vulva, and perianal region (Hillemanns, 1996; Korn, 1995; Maiman, 1990; Petry, 1996; Williams, 1994) as compared with HIV-negative women.
- Recent studies have shown increased incidence of oncogenic HPV types (Minkoff, 1998) and increased incidence of biopsy-proven cervical dysplasia (Ellerbrock, 2000) in HIV-positive women compared with HIV-negative controls. A French study found an increased likelihood of progression of cervical abnormalities in HIV-positive women, although analysis was based on Pap smear results only (Six, 1998). A recent study also found an association between progression of abnormal Pap smears and high plasma HIV RNA levels (>100,000 c/mL) (Sewell, 2000). Presently there is little evidence for increased rates of progression to invasive cancer, particularly if adequate screening and treatment programs are in place.

C. HIV AND ANAL HPV/DYSPLASIA

- Anal HPV-DNA has been reported in up to 76% of HIV+ women and, when concurrent anal and cervical HPV data were available, anal HPV was more prevalent in both HIV-infected and high-risk HIV-uninfected women (Palefsky, 2001a). Anal HPV is more common with lower CD4 counts and with presence of cervical HPV. Multiple HPV types and oncogenic types are common (Lacey, 1999).
- Abnormal anal cytology or anal squamous intraepithelial lesions (ASIL) are reported in up to 26% of HIV-infected women; risk factors include lower CD4 count, increased HIV viral load, high HPV viral load, history of receptive anal intercourse, and concurrent abnormal cervical cytology (Holly, 2001; Kiviat, 1993).
- Sensitivity of anal Pap smears appears to be similar to cervical cytology, although grade of anal dysplasia may not correlate well with histology (Palefsky, 1997)
- Risk for invasive anal cancer is increased in patients with HIV/AIDS (Grulich, 2000).

D. INVASIVE CERVICAL CANCER IN HIV DISEASE

- In 1993, the CDC expanded the case definition of AIDS to include invasive cervical cancer.
- Oncogenic HPV types play a central role in the relationship between HIV and cervical cancer. Recent African data found that without high-risk HPV present, the risk ratio for cervical cancer between HIV-positive and HIV-negative women was approximately 1 (Hawes, 2003).
- Although there is little evidence that HIV infection is having a large effect on cervical cancer rates, linking of US AIDS and cancer registries has found that observed cervical cancer cases in HIV-infected women are up to 9-fold higher than the expected number of cases ; however, the likelihood of cervical cancer was not related to CD4 count (Mbulaiteye, 2003). In an analysis of women in the HER study, the rate of invasive cervical cancer was 1.20/1000 person-years in HIV-infected women as compared to 0/1000 person-years in high-risk HIV-negative women (Phelps, 2001). Mean CD4 cell count was 443 cells/mm³ at time of diagnosis of cervical cancer in women with HIV. Women with HIV and cervical cancer tend to be younger and less immunosuppressed compared with HIV-positive women with other AIDS-indicator conditions. Women with HIV and cervical cancer tend to be younger than HIV-negative women with cervical cancer (Lomalisa, 2000). A prospective cohort study from Italy found that the incidence of invasive cervical cancer as a first AIDS-defining condition continued to increase after the introduction of HAART, possibly due to the decrease seen in incidence of other AIDS-defining diseases after HAART (Dorrucchi, 2001).

- HIV-positive women with invasive cervical cancer appear to present at more advanced stages (especially with CD4 < 200/mm³), may metastasize to unusual locations (e.g., psoas muscle, clitoris, meningeal involvement), have poorer responses to standard therapy, and have higher recurrences and death rates, as well as shorter intervals to recurrence or death, compared with HIV-negative women of similar stage (Klevens, 1996; Maiman, 1990).

E. SCREENING TESTS

- A single Pap smear is associated with false-negative rates of 10–25%; accuracy is significantly improved with regular periodic screening. Controlled studies have not demonstrated a decrease in sensitivity or specificity with standard cervical cytology in HIV-positive women compared with HIV-negative controls (Adachi, 1993; Spinillo, 1998). However, a prospective cohort study found that HIV-infected women were significantly more likely to have abnormal biopsy results with normal Pap smears as compared with high-risk HIV-uninfected women; predictors of discordant histology and cytology included presence of HPV by PCR and CD4 count < 500/mm³. In this study 17 of 19 women with discordant results had abnormal Paps within one year of these results, using current guidelines for Pap smear screening (Anderson 2002).
- Newer Pap smear screening techniques using liquid-based media appear to increase sensitivity, decrease inadequate smears, and reduce, but not eliminate, false-negative results; they also offer the possibility of direct HPV testing on collected specimens. They are more expensive than conventional Pap tests. A recent review of over 400 HIV-infected women who underwent both conventional and liquid-based cytologic screening found a significant decrease in the proportion of smears diagnosed as ASCUS/AGUS as well as the ASCUS/SIL ratio, with liquid-based preparations (Swierczynski, 2002).
- HPV testing can identify both oncogenic and nononcogenic viral types; HPV testing for cancer-associated types can play an important role in the evaluation of women with atypical squamous cells on Pap smear (Solomon, 2001).
- The role of HPV DNA testing as an alternative or addition to the Pap smear in HIV-positive women is unknown. One analysis suggested that adding HPV testing to standard Pap smear screening may be a cost-effective strategy if this allows modification of screening intervals (Goldie, 2001). A recent German study examining HPV DNA testing as a primary screening method for cervical dysplasia in 94 HIV-positive women found that HPV DNA testing identified high-grade cervical dysplasia more accurately than Pap smear (Petry, 1999).
- Pap smear results are reported according to the Bethesda System (Solomon, 2002) (Table 6-1).

Table 6-1: Pap Smear Report for Bethesda System

Specimen adequacy	<ul style="list-style-type: none"> • Satisfactory for evaluation (note presence/absence of endocervical transformation zone component) • Unsatisfactory for evaluation (specify reason)
General categorization	<ul style="list-style-type: none"> • Negative for intraepithelial lesion or malignancy • Epithelial cell abnormality • Other
Interpretation/result	<ul style="list-style-type: none"> • Negative for intraepithelial lesion or malignancy <ul style="list-style-type: none"> - infections - reactive changes (inflammation, radiation) - atrophy • Epithelial cell abnormalities <ul style="list-style-type: none"> - atypical squamous cells (ASC) <ul style="list-style-type: none"> - of undetermined significance (ASC-US) - cannot exclude HSIL (ASC-H) - low-grade squamous intraepithelial lesion, including HPV changes and mild dysplasia CIN1 - high-grade squamous intraepithelial lesion, including moderate and severe dysplasia, CIN2, CIN3 - squamous cell carcinoma - glandular cell abnormalities • Other <ul style="list-style-type: none"> - endometrial cells in a woman ≥ 40 years of age

CIN, cervical intraepithelial neoplasia.



F. RECOMMENDATIONS FOR PAP SMEAR SCREENING AND COLPOSCOPY

- HIV-infected women should have a complete gynecologic evaluation, including a Pap smear and pelvic exam, as part of their initial evaluation (US Public Health Service (USPHS)/ Infectious Diseases Society of America (IDSA) 2001 accessed at <http://www.aidsinfo.nih.gov>).
- A Pap smear should be obtained twice in the first year after diagnosis of HIV infection. If these results are normal, annual examinations are then indicated.
- More frequent Pap smears should be considered:
 - with previous abnormal Pap smear
 - with HPV infection
 - after treatment for cervical dysplasia
 - in women with symptomatic HIV infection (including CD4 counts < 200/mm³)
- The American College of Obstetricians and Gynecologists recommends Pap smears every 3–4 mo for the first year after treatment of preinvasive cervical lesions, followed by Pap smears every 6 mo (ACOG, 1993). Vaginal Pap smears should be obtained after hysterectomy for persistent or recurrent cervical dysplasia.

- Women receiving gynecologic and primary HIV care at the same location are more likely to have had Pap smear screening within the previous year (Stein, 2001).
- The role of anal cytology remains unclear and recommendations for routine anal Pap smear screening are not currently part of standard guidelines. However, the approach suggested by experts in this field is similar to recommendations for cervical Pap smear screening:
 - perform anal Pap as part of initial evaluation and, if normal, repeat in 6 months
 - if these results are normal, repeat annually
 - more frequent anal Pap smears should be considered:
 - with $CD4 < 500/mm^3$*
 - presence of cervical dysplasia*
 - with previous abnormal anal Pap smear*
 - after treatment for anal dysplasia*
 - anal Pap smears with ASCUS or SIL should be evaluated with anoscopy and biopsy
- Anal Pap smears are performed by inserting a moistened Dacron swab 1–1.5 inches into the anal canal and rotating as it is slowly withdrawn over 15–20 seconds, maintaining contact with the mucosa; both rectal columnar and anal squamous cells must be obtained to have an adequate specimen. The swab should then be vigorously shaken in liquid-based cytology media.
- Indications for colposcopy are outlined in Table 6-2.

Table 6-2: Indications for Colposcopy

- | |
|--|
| • Cytologic abnormality (atypia or greater, including ASC, AGC) |
| • History of untreated abnormal Pap smear |
| • Consider periodic colposcopy after treatment of cervical dysplasia |
| • Consider with evidence of HPV infection |
| • Consider screening colposcopy with $CD4 < 200/mm^3$ |

ASC, atypical squamous cells;
AGC, atypical glandular cells.

- ASC (atypical squamous cells) represents the mildest cytologic abnormality in the Bethesda system; however, in the general population 5–17% of women with ASC have underlying CIN2-3 and approximately 0.1% have invasive cancer (Solomon, 2001). The 2001 Bethesda system stratifies ASC into two categories: atypical squamous cells of undetermined significance (ASC US) and atypical squamous cells-cannot exclude HSIL (ASC-H), with 24–92% of women with ASC-H having CIN2-3 confirmed with biopsy (Wright, 2002). In a study of women with ASCUS, Wright (Wright, 1996) found that HIV-positive women were approximately twice as

likely to have underlying dysplasia compared with HIV-negative women; a recent cross-sectional analysis of 761 Pap smears from HIV-positive women found that 27% were diagnosed as ASCUS; 15% had underlying high-grade dysplasia (Holcomb, 1999a). Immunosuppression did not appear to increase the frequency of dysplasia associated with ASCUS on Pap smear. Incidence of ASCUS is increased in HIV-infected women (Massad, 2001). Referral for colposcopy is recommended for all HIV-infected women with ASC, irrespective of CD4 cell count, HIV viral load, or antiretroviral therapy (Wright, 2002).

Table 6-3: Suggested Frequency of Pap smears

<i>Clinical Scenario</i>	<i>Screening Frequency</i>
Normal Pap	1 yr
Symptomatic infection / CD4 <200	6 mo
ASC/LSIL (evaluated and followed without treatment)	4–6 mo
Following treatment of preinvasive lesions	3–4 mo for first year, then 6 mo lesions

ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion.

- The risk of underlying pathology with a diagnosis of atypical glandular cells (AGC) is significant. The 2001 Bethesda system stratifies AGC into 3 categories: atypical glandular cells, either endocervical, endometrial, or “not otherwise specified” (NOS); atypical glandular cells, favor neoplastic; and endocervical adenocarcinoma-in-situ (AIS). Overall, various studies have found that 9–54% of women with AGC have CIN on biopsy, 0–8% have AIS on biopsy, and up to 9% have invasive cancer (Wright, 2002). The risk of a significant abnormality increases with the severity of the AGC reading. Colposcopy is indicated with any AGC on Pap, as well as endocervical sampling. Endometrial sampling is indicated with presence of atypical endometrial cells or AGC-NOS, in women older than 35 years, and in younger women with AGC who have unexplained vaginal bleeding (Wright, 2002). Because of the significant risk of invasive disease with AGC, favor neoplasia or endocervical AIS, women with these results should undergo diagnostic cervical conization if initial evaluation is negative for invasive cancer (Wright, 2002).
- Biopsies should be obtained at the time of colposcopy to confirm cytologic abnormalities and/or if abnormal areas are visualized.
- Because of the multicentric nature of lower genital tract intraepithelial neoplasia in the setting of immunosuppression, it is recommended that the entire lower genital tract (vagina, vulva, and perianal region) be examined at the time of colposcopy.

G. MANAGEMENT OF CERVICAL AND OTHER LOWER GENITAL TRACT LESIONS

Management of abnormal Pap smears is outlined in Table 6-4. Documentation of a high-grade cervical lesion requires treatment. Standard excisional or ablative treatment is recommended, although HIV-positive women have an increased incidence of recurrence after treatment (over 50% recurrence rate), correlated with degree of immunosuppression (Fruchter, 1996; Holcomb, 1999b). Cryotherapy has had the highest rate of recurrences and should be avoided, if other treatment methods are available. Hysterectomy as treatment for recurrent or persistent cervical dysplasia has also been associated with significant recurrence rates in the vagina (Tate, 2002). Recurrences have been associated with detectable HIV RNA in plasma and higher mean HIV RNA levels (Keller, 2002) and may also be related to positive surgical margins with excisional treatment, which appear to be more common in HIV-positive women compared with HIV-negative women (Boardman, 1999). Abstinence should be emphasized until complete healing has occurred after treatment for cervical dysplasia, since the treatment has been shown to dramatically increase genital tract HIV shedding (Wright, 2001) and may increase risk of sexual transmission of HIV.

<i>Pap Smear Result</i>	<i>Management</i>
Unsatisfactory	Repeat Pap smear
Partially obscuring - inflammation	Evaluate for infection; consider repeat Pap
Epithelial cell abnormality	
- atypical glandular cells	- colposcopy, endocervical sampling; endometrial sampling if > 35 yrs. or with abnormal bleeding; cervical conization if initial evaluation negative and cytology favors neoplasia
- atypical squamous cells (ASCUS and ASC-H)	- colposcopy, biopsy if indicated; endocervical sampling if unsatisfactory colposcopy; follow with Pap every 6 months, consider repeat colposcopy annually if Pap unchanged
- low-grade squamous intraepithelial lesion (LSIL, CIN1)	- colposcopy, biopsy if indicated; endocervical sampling if unsatisfactory colposcopy; follow with Pap every 6 months, consider repeat colposcopy annually if Pap unchanged
- high-grade squamous intraepithelial lesion (HSIL, CIN2-3, carcinoma-in-situ)	- colposcopy, biopsy, endocervical sampling; treat with loop excision or conization
- invasive carcinoma	- colposcopy with biopsy or conization; treat confirmed invasive disease with surgery or radiation (referral to gynecologic oncologist needed)

*Management should be based on histologic findings when biopsy is performed.

Topical vaginal 5-fluorouracil (5-FU) cream (2 g biweekly for 6 mo) was shown to reduce recurrence rates after standard treatment for high-grade cervical dysplasia in HIV-positive women in a recent clinical trial; over 18 mo of follow-up, 31% of women who were only observed developed a recurrent high-grade lesion compared with 8% of women receiving 5-FU. Disease recurred more slowly in women who had received antiretroviral therapy, compared with those who were antiretroviral-naïve (Maiman, 1999).

5-FU may play a role in secondary prophylaxis of preinvasive cervical lesions in some cases. However, clinical experience with this therapy is too limited to provide a recommendation for routine use. 5-FU may have significant mucosal toxicity and concerns have been raised about the potential for increased risk for transmission of HIV or other sexually transmitted infections (STIs) with this therapy.

Women with documented vaginal, vulvar, or anal dysplasia should be managed in consultation with a gynecologic specialist. Treatment options include observation, excisional biopsy, use of cavitation ultrasonic surgical aspiration, or laser vaporization; 5-FU has been used successfully for treatment of vulvar and vaginal lesions and recent small studies suggest a possible role for topical 1% cidofovir gel with lower genital tract HPV-related lesions (Koonsaeng, 2001; Snoeck, 2001a; Snoeck, 2001b). Regardless of type of treatment, recurrence rates are increased in HIV-infected women and close follow-up is needed (Chang, 2002).

The role of highly active antiretroviral therapy (HAART) and immune reconstitution in the management of lower genital tract precancerous lesions remains unclear. In one study use of HAART was associated with increased likelihood of regression of cervical dysplasia after treatment for 12 months (Heard, 2002). In the Women's Interagency HIV Study (WIHS), after adjustment for CD4 count and Pap status, use of HAART was associated with increased regression and decreased risk of progression of cervical cytologic abnormalities (Minkoff, 2001). On the other hand, Palefsky found no effect of 6 months of HAART on anal HPV or ASIL (Palefsky, 2001b). With 15 months of follow-up, persistence of high-risk HPV and progression of SIL were comparable among women without antiretroviral treatment, those treated with nucleoside analogues only, and those treated with HAART (Lillo, 2001). Duerr and colleagues found no differences in regression of abnormalities on Pap smear, HPV acquisition or persistence after up to 24 mo on HAART compared with untreated women or women receiving non-HAART treatment. However, new abnormal Pap smear results were less likely in the HAART group (Duerr, 2000).

At the current time, HIV-positive women should continue to be followed closely for evidence of lower genital tract neoplasia, regardless of antiretroviral therapy or viral load.

IV. GENITAL ULCERS

A. HISTORY

Duration and location of lesion(s); previous history of genital ulcers, syphilis, or genital herpes; associated symptoms (pain, pruritus, fever, etc.); medications and timing of ulcers relative to initiation of new medication; sexual history (including condom use); and CD4 counts and HIV RNA levels.

B. PHYSICAL EXAM

Dimensions and location of lesion(s); presence of pigmentation, edema, erythema, or induration; presence of associated exudate or tenderness; presence of oral lesions; associated lymphadenopathy or rash.

C. EVALUATION

- Syphilis serology or darkfield examination
- Culture or antigen test for herpes simplex virus (HSV)
- Biopsy: with unclear diagnosis, lack of response to treatment; consider special stains, if indicated (CMV, acid-fast bacillus)
- Culture for *Haemophilus ducreyi*: not widely available commercially; diagnosis of chancroid generally made with typical clinical presentation, after excluding syphilis and HSV

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

(See recent review Rosen, 2003)

INFECTIONS

HERPES SIMPLEX VIRUS

- most prevalent infectious cause of genital ulcers in the United States
- two distinct serotypes of HSV (HSV-1 and HSV-2), most cases of recurrent genital herpes (60–95%) are caused by HSV-2
- Since the late 1970s, the seroprevalence of HSV-2 infection has increased by 30%; infection is now detectable in 21.9% of people aged 12 or older nationwide (Fleming, 1997). Most people with HSV-2 do not know that they are infected, since they have mild or unrecognized symptoms; however, they may shed virus intermittently in the genital tract and transmit infection to their sexual partners. Age-adjusted HSV-2 prevalence is significantly higher among women than in men (Xu, 2002).
- typically lesions present as painful vesicles that ulcerate and heal without scarring
- primary infection often associated with systemic symptoms (fever, photophobia, headache); duration of lesions and viral shedding more prolonged with primary infection; after primary episode latency established in sacral dorsal root ganglia

- nonprimary first episode herpes occurs in individuals with antibodies to HSV-2 or HSV-1 but no previous clinical symptoms of HSV; milder, shorter episode
- recurrent episodes occur at variable frequency; more localized lesions, shorter duration compared with first episodes (primary or nonprimary)
- viral shedding and sexual transmission can occur during asymptomatic periods
- HIV-positive patients:
 - more frequent, prolonged, and/or severe episodes common with progressive immunosuppression; lesions may be atypical in appearance or location
 - HSV viral shedding increases with declining CD4 counts (Augenbraun, 1995) and higher plasma HIV viral load (Wright, 2003); may be more common in oral contraceptive or Depo-Provera users and in women with severe vitamin A deficiency (Mostad, 2000); most viral shedding asymptomatic
 - HSV is associated with increased risk for HIV transmission/acquisition (Heng, 1994). Higher levels of cervical HSV have been associated with increased HIV shedding in the genital tract (McClelland, 2002) and plasma HIV viral load is increased during HSV reactivation (Schacker, 2002).
- Treatment: See Table 6-5.
 - HIV-positive women often need higher doses and longer treatment courses, particularly with more advanced immunosuppression, and may benefit from suppressive therapy.
 - Daily suppressive therapy reduces the frequency of recurrences by $\geq 75\%$ among patients who suffer from frequent HSV episodes (i.e., six or more recurrences per year). Suppressive treatment reduces but does not eliminate viral shedding. Safety and efficacy with daily acyclovir for over 10 years.

	<i>Drug</i>	<i>Dose</i>
First clinical episode	Acyclovir Acyclovir Famciclovir Valacyclovir	400 mg po three times a day for 7–10 days 200 mg po five times a day for 7–10 days 250 mg po three times a day for 7–10 days 1 g po twice a day for 7–10 days
Recurrent episodes	Acyclovir Acyclovir Famciclovir Valacyclovir	400 mg po three times a day for 5–10 days 200 mg po five times a day for 5–10 days 500 mg po twice a day for 5–10 days 1 g po twice a day for 5–10 days
Daily suppressive therapy	Acyclovir Famciclovir Valacyclovir	400–800 mg po twice to three times a day 500 mg po twice a day 500 mg po twice a day
Severe disease	Acyclovir	5–10 mg/kg body weight IV every 8 hr for 2–7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days total therapy
Acyclovir-resistant HSV	Foscarnet Topical Cidofovir gel 1%	40 mg/kg body weight IV every 8 hr or 60 mg/kg IV every 12 hr for 3 wk applied to lesions once a day for 5 consecutive days

Source: CDC, 2002.

- Acyclovir-resistant HSV: Usually cross-resistant to famciclovir, valacyclovir. The prevalence of resistant HSV in immunocompromised patients has remained stable at approximately 4–7% (Bacon, 2003). Most of these isolates are susceptible to foscarnet IV or topical cidofovir. Factors associated with acyclovir resistance are low CD4 counts and long-term exposure to acyclovir.

SYPHILIS

- systemic disease caused by *Treponema pallidum*
- definitive methods for diagnosing early syphilis are darkfield examination and direct fluorescent antibody test of lesion exudate or tissue
- presumptive diagnosis is possible using two types of serologic tests for syphilis: VDRL or RPR (nontreponemal) and a confirmatory FTA-ABS or MHA-TP (treponemal)
- nontreponemal test antibody titers usually correlate with disease activity and are used to assess treatment response; serial assessment during follow-up after treatment should use the same type of nontreponemal test
- HIV-infected patients may have abnormal serologic test results (e.g., unusually high titers, false negatives or delayed seroreactivity). However, generally serologic tests can be interpreted in the usual manner. If clinical findings suggest syphilis but serology is nonreactive, biopsy, darkfield examination, or direct fluorescent antibody staining of lesion material should be considered. The clinical presentation of syphilis is very variable at all stages; atypical manifestations may be seen in the setting of HIV disease. Neurosyphilis should be considered in the differential diagnosis of neurologic signs or symptoms in HIV-infected individuals (CDC, 2002).
- Treatment: See Table 6-6.

Table 6-6: Recommended Management For Syphilis

<i>Stage</i>	<i>Treatment</i>
Primary and secondary syphilis and early latent syphilis	Benzathine penicillin G 2.4 million units IM (single dose); additional treatment recommended by some (i.e., three weekly doses of penicillin); some specialists recommend CSF examination before treatment and follow-up CSF examination after treatment in persons with initial abnormalities
If penicillin-allergic (nonpregnant patients only)	Doxycycline 100 mg po twice a day for 2 wk, OR tetracycline 500 mg po 4 times a day for 2 wk
Late latent syphilis or syphilis of unknown duration (including tertiary syphilis)	Examination of the CSF must be performed before initiating treatment. If the CSF examination is negative, patients should be treated with 7.2 million units of benzathine penicillin G (three weekly doses of 2.4 million units each) IM
Neurosyphilis	Aqueous crystalline penicillin G 18–24 million units a day (administered as 3–4 million units IV every 4 hr) for 10–14 days (every 4 hr or continuous infusion) Administration of benzathine penicillin 2.4 million units IM once per week for up to 3 weeks after completion of the IV regimen recommended by some

Table 6-6: Recommended Management For Syphilis (continued)

Recommended Follow-Up	
Stage	Treatment
Primary and secondary syphilis	HIV-infected patients require clinical and serologic evaluation for treatment failure at 3, 6, 9, 12, and 24 mos after treatment. Treatment failures necessitate a CSF examination and retreatment (three weekly doses of 2.4 million units of benzathine penicillin G if CSF examination is negative). The latter regimen should also be considered for patients whose titers do not decrease fourfold within 6–12 mo.
Latent syphilis	HIV-infected patients require clinical and serologic evaluation at 6, 12, 18, and 24 mos after treatment. The CSF examination should be repeated and appropriate treatment instituted if clinical symptoms develop, titers rise fourfold, or if titers fail to decline by >75% between the evaluations at 12 and 24 mo.
Neurosyphilis	CSF examination should be repeated every 6 mo until the cell count is normal. Retreatment should be considered if the cell count has not decreased after 6 mo or if the CSF is not entirely normal after 2 yr.

CSF, cerebrospinal fluid

Source: CDC, 2002

CHANCROID

- caused by *H. ducreyi*
- endemic in some areas of the United States; also occurs in discrete outbreaks
- 10% of patients with chancroid have coinfection with *T. pallidum* or HSV
- initial presentation typically consists of a tender papule that becomes pustular and then ulcerative; the ulcer is usually well demarcated, with ragged undermined edges
- probable diagnosis can be made if the patient has one or more painful ulcers, there is no evidence of *T. pallidum* or HSV infection, and the clinical presentation appearance of ulcers and regional lymphadenopathy is typical for chancroid
- Response to treatment may be diminished in the HIV-infected patient; may require longer courses of therapy, increased risk for treatment failure
- Treatment:
 - Azithromycin 1 g po (single dose), OR
 - Ceftriaxone 250 mg IM (single dose), OR
 - Ciprofloxacin 500 mg po twice a day for 3 days, OR
 - Erythromycin base 500 mg po four times a day for 7 days.
 - Note
 - In HIV-positive patients use single-dose therapies only if follow-up can be ensured;
 - Some experts recommend the 7-day erythromycin regimen in the setting of HIV infection.

CYTOMEGALOVIRUS

- should be suspected in severely immunocompromised patients
- diagnosis requires biopsy of lesion with immunohistochemical stains
- cervical shedding of cytomegalovirus is associated with low CD4 counts (Clark, 1997)
- Treatment:
 - Ganciclovir 5 mg/kg IV twice a day for 2–3 wk, OR
 - Foscarnet 60 mg/kg IV q 8 hr or 90 mg/kg q 12 hr for 2–3 wk.

OTHER INFECTIOUS CAUSES OF GENITAL ULCERS

- **Lymphogranuloma venereum:** rare in United States; associated with tender, usually unilateral inguinal or femoral lymphadenopathy, proctocolitis, rectal fistulas/strictures; diagnosis with serology and exclusion of other causes; treatment: doxycycline or erythromycin for 3 wk; HIV-positive individuals may require more prolonged treatment
- **Granuloma inguinale (donovanosis):** rare in United States; painless, progressive ulcers which bleed easily on contact, without regional lymphadenopathy; diagnosis with biopsy or tissue crush preparation; treatment trimethoprim-sulfamethoxazole or doxycycline for 3 wk or until all lesions healed; CDC recommends adding aminoglycoside to regimen in HIV-positive patients
- **Tuberculosis (Giannacopoulos, 1998):** genital TB is generally a secondary manifestation of primary (usually pulmonary) disease. In the United States, the incidence of genital disease is < 1 % diagnosis is established by biopsy. Genital tuberculosis should be treated as is extrapulmonary disease; expert consultation is necessary.

INFLAMMATORY CONDITIONS

CROHN'S DISEASE

- This disease may be easily misdiagnosed because its principal clinical features (i.e., fever, abdominal pain, diarrhea, fatigability, weight loss) are often found in patients with HIV disease. Crohn's disease may also present with genital ulcers, rectal fissures, perirectal abscesses, or intestinal fistulas. Sigmoidoscopy or barium enema is essential in making this diagnosis. Manage with expert consultation.

BEHÇET'S SYNDROME

- This is a multisystem disorder that presents with recurrent oral and genital ulcerations as well as uveitis, arthritis, and vasculitis. Vaginal ulcers are usually painless, whereas lesions on the external genitalia are generally painful. Ulcers range between 2 and 10 mm in diameter, and they can be shallow or deep with a central yellowish necrotic base; either a single lesion or crops of lesions may be evident. Diagnosis is established based on the clinical presentation and biopsy. Treatment consists of topical or systemic corticosteroids.

HIDRADENITIS SUPPURATIVA (DROEGEMUELLER, 1997)

- This is a chronic, refractory condition involving the skin, subcutaneous tissues, and apocrine glands. Lesions are painful and are associated with a foul-smelling discharge. Eventually, a deep-seated chronic infection of apocrine glands develops, with multiple draining abscesses and sinuses. A biopsy is necessary to establish the diagnosis. In the early stages of disease, treatment options include antibiotics, topical steroids, antiandrogens, and isotretinoin. Treatment of advanced disease requires surgical intervention.

NEOPLASTIC

- any nonhealing genital ulcer must be biopsied to rule out a neoplastic process
- squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, melanoma, lymphoma, Kaposi's sarcoma
- refer to oncologist

DRUG REACTION

- has been described as rare side effect of treatment with zalcitibine and foscarnet

APHTHOUS GENITAL ULCERATIONS (ANDERSON, 1996)

- no specific etiology (typical or opportunistic organism) is identifiable
- similar to aphthous ulcers seen in the gastrointestinal tract
- most patients are significantly immunosuppressed (median CD4 count 50/mm³)
- lesions can be painful, multiple, deep, and extensive (size 1–6 cm)
- associated morbidity includes immobility, bleeding, and superinfection
- most have been reported to be chronic and/or recurrent or relapsing
- oroesophageal ulcers coexist in about one third of cases and one fifth were associated with genital fistula formation
- Treatment:
 - Consider empiric therapy for HSV.
 - If empiric therapy fails, systemic steroids (prednisone 40–60 mg/day for 1–2 wk, then taper) have been moderately successful.
 - Thalidomide (200 mg/day for 2–4 wk) has been used in similar ulcers in the oropharynx or esophagus with complete healing in 55–73% of these ulcers (Jacobson, 1997, 1999); there has been similar success anecdotally in genital aphthous ulcers. (Warning: this drug is a powerful teratogen and should only be used in women of reproductive age after appropriate counseling and pregnancy testing and in the setting of reliable contraception or abstinence.)

TRAUMA

- history of traumatic injury
- consider possibility of sexual violence

V. VAGINAL DISCHARGE

A. HISTORY

Duration and characteristics of discharge, associated symptoms (e.g., pruritus, malodor, burning, pelvic pain), sexual history (including condom and other contraceptive use), history of sexually transmitted diseases, history of douching, recent antibiotic use, CD4 counts and HIV-RNA levels, medications.

B. PHYSICAL EXAM

Complete genital inspection and bimanual pelvic examination; document the characteristics and amount of discharge as well as the presence of erythema, edema, and tenderness.

C. EVALUATION

- saline wet mount
- 10% potassium hydroxide (KOH) preparation
- vaginal pH determination
- testing for gonorrhea and chlamydia
- fungal culture, if indicated (signs/symptoms of yeast infection with negative findings on microscopy; chronic/recurrent yeast infections)

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

BACTERIAL VAGINOSIS (BV)

- most prevalent cause of vaginal discharge or malodor
- results from replacement of normal *Lactobacillus* dominant vaginal flora with increase in prevalence and concentration of mixed flora, including anaerobic bacteria, *Gardnerella vaginalis*, and *Mycoplasma hominis*
- 18–42% prevalence among HIV-infected women; BV is more prevalent and persistent as compared with HIV-negative controls and prevalence, persistence and severity increase with lower CD4 counts (Cu-Uvin, 1999; Greenblatt, 1999; Jamieson, 2001). Use of antiretroviral drugs has been associated with lower prevalence of BV (Warren, 2001).

- Some studies suggest that BV or BV-associated organisms (or lack of vaginal lactobacilli) may enhance HIV transmission (Martin, 1999; Olinger, 1999). BV has been associated with increased HIV expression in the genital tract (Cu-Uvin, 2001).
- associated with increase in several obstetric and gynecologic complications, including pelvic inflammatory disease (PID), postabortion and posthysterectomy infections, preterm labor
- standard diagnosis by clinical criteria; requires three of the following: 1) a homogeneous grayish or yellowish discharge (may coat vaginal walls); 2) clue cells on microscopic examination; 3) vaginal pH >4.5; 4) a positive whiff test (i.e., fishy odor of discharge before or after addition of 10% KOH)
- Treatment: See Table 6-7.

Table 6-7: Recommended Management For Bacterial Vaginosis
Metronidazole 500 mg po twice a day for 7 days
Clindamycin cream 2%, 5 g intravaginally at bedtime for 7 days
Metronidazole gel 0.75%, 5 g intravaginally once a day for 5 days
Note: Clindamycin cream is oil based and may weaken latex condoms and diaphragms. Alternative regimens: metronidazole 2 g po in single dose or clindamycin 300 mg po twice a day for 7 days or clindamycin ovules 100 g intravaginally at bedtime for 3 days

Source: CDC, 2002

VULVOVAGINAL CANDIDIASIS

- Most commonly caused by *Candida albicans*; the prevalence of infections due to non-*albicans* species is increasing
- 75% of all women will have at least one episode of candidiasis, and 40–45% will have two or more episodes; less than 5% of women experience recurrent episodes of candidiasis
- Typical symptoms: thick, white discharge and pruritus; other symptoms include vulvar burning, vaginal soreness, dyspareunia, and external dysuria
- Prevalence among HIV-infected women is 3–15%; most studies suggest no significant difference in prevalence of infection between relatively immunocompetent HIV-positive women and HIV-negative controls; recent longitudinal analysis from the HER Study found that vulvovaginal candidiasis occurred with higher incidence and greater persistence, but not greater severity, among HIV-infected as compared to high-risk HIV-uninfected women. Lower CD4 count and higher viral load were associated with vulvovaginal candidiasis (Cu-Uvin 1999; Duerr, 2003).

- Possible confounding factor for HIV-positive women is more frequent use of antibiotics; pregnancy is also a predisposing factor for candidiasis irrespective of HIV status.
- Most studies show increased rates of vaginal (also rectal, oral) colonization in HIV-positive women, particularly with declining immune function.
- In HIV-positive women 26–27% of vaginal isolates are non-*albicans* strains (Schuman, 1998); available studies are conflicting on the proportion of non-*albicans* strains in HIV-positive compared with HIV-negative women; most common is *Candida glabrata*. No association found to date between strain diversity and HIV progression. In general conventional antifungal therapies are not as effective against non-*albicans* species and 10–14 days of therapy with a non-fluconazole azole drug is recommended as first-line therapy.
- Diagnosis is made by identifying budding yeast or pseudohyphae on a wet mount or KOH preparation or Gram stain of vaginal discharge; positive identification can also be accomplished by means of culture
- **Treatment:** See Table 6-8.
 - **Special considerations in HIV-positive women:**
 - Topical therapies may be more effective when given for at least 7 days; fluconazole may be more effective when given in two sequential 150 mg doses 3 days apart.
 - Consider prophylactic use of topical antifungals when antibiotics are given
 - Randomized, placebo-controlled trial of fluconazole 200 mg po weekly for prophylaxis of candidiasis in women with CD4 <300/mm³ (median CD4 15/mm³): effective in preventing oropharyngeal candidiasis (relative risk .50, p < .001) and vaginal candidiasis (relative risk .64, p = .05), but not esophageal candidiasis (Schuman, 1997). Consider in selected cases with recurrent vaginal candidiasis.
 - Recent study found that ritonavir and indinavir (and possibly other protease inhibitors) strongly inhibited secretory aspartyl proteinase (proteolytic enzyme produced by pathogenic *Candida* species, considered a virulence factor) activity and production in a dose-dependent fashion, and exerted a therapeutic effect in an experimental model of vaginal candidiasis, with efficacy similar to fluconazole (Cassone, 1999).
 - **Azole resistance:**

Concerns have been raised about extensive use of oral azoles and promotion of azole resistance, possibly limiting use of these agents for other HIV-related indications. Current information about development of resistance is limited.

 - ACTG 816: annual incidence of clinical failure to fluconazole (persistence of oral candidiasis after 200 mg/day or higher dose for 14 days) 5.8% (median CD4 15/mm³); *C. albicans* primary etiology
 - Community Programs for Clinical Research on AIDS—randomized, placebo-controlled trial of fluconazole 200 mg weekly for prophylaxis of candidiasis (described above) (median CD4 15/mm³): after median 29 mo follow-up, fluconazole resistance <5% resistance in both fluconazole and placebo groups (Schuman, 1997a)

Table 6-8: Recommended Management for Vulvovaginal Candidiasis
Topical Azoles
• Butoconazole 2% cream 5 g PV for 3 days*
• Butoconazole 2% cream 5 g (sustained release) PV application x 1
• Clotrimazole 1% cream 5 g PV for 7–14 days*
• Clotrimazole 100 mg vaginal tablet for 7 days
• Clotrimazole 100 mg vaginal tablet, 2 tablets for 3 days
• Clotrimazole 500 mg vaginal tablet x 1
• Miconazole 2% cream 5 g PV for 7 days*
• Miconazole 200 mg vaginal suppository for 3 days*
• Miconazole 100 mg vaginal suppository for 7 days*
• Tioconazole 6.5% ointment 5 g PV x 1*
• Terconazole 0.4% cream 5 g PV for 7 days
• Terconazole 0.8% cream 5 g PV for 3 days
• Terconazole 80 mg vaginal suppository for 3 days
* Available over the counter. PV, vaginally. Note: These creams are oil-based and may weaken latex condoms and diaphragms.
Oral agent[†]
• Fluconazole 150 mg po x 1
† Avoid concomitant use with terfenadine, astemizole, cisapride secondary to cardiotoxicity.
Others
• Nystatin 100,000 unit vaginal tablet, one tablet for 14 days (less effective)
• 1% Gentian violet applied to vagina 4 times at intervals of approximately 7 days‡
• Boric acid 600 mg intravaginal capsules bid for 2 wk‡
‡ May be useful in chronic/recurrent cases; gentian violet messy, causes mucosal exfoliation; encourage abstinence during treatment; reinforce condom use.

Source: CDC, 2002.

- HIV Epidemiology Research Study (HERS): overall fluconazole resistance rare among *C. albicans* isolates with no evidence for progressive reduction in susceptibility over time; however, resistance frequent in non-*albicans* isolates from vagina and oral cavity; fluconazole resistance with non-*albicans* species more likely in HIV-positive women (Sobel, 2001). There was a trend towards more in vitro azole resistance in non-*albicans* species (all *C. glabrata*) in women with CD4 < 300/mm³ who were receiving weekly fluconazole prophylaxis vs placebo. (Vazquez, 2001).
- 139 isolates from vulvovaginal candidiasis in HIV-positive women: 95–98% susceptibility of *C. albicans* to fluconazole, itraconazole, clotrimazole; *C. glabrata*: 44% resistance to fluconazole, 72% resistance to itraconazole and clotrimazole. Twenty percent of 90 relapses/persistence were with same organism; emergence of drug resistance was not observed between sequential isolates. Twelve percent had recurrent infection with different strains or species (Li, 1997).

There are no current data to suggest that intermittent therapy with a single dose of fluconazole increases development of azole resistance. Similarly, weekly prophylaxis with fluconazole was associated with infrequent development of resistance, which was not significantly different from placebo recipients. Nevertheless, long-term use of fluconazole may select for more resistant and difficult-to-treat non-*albicans* species and should be used with caution. Further study is needed.

- **Recurrent candidiasis** (four or more symptomatic episodes per year):
 - Evaluation:
 1. *establish diagnosis — fungal culture may be needed*
 2. *identify/eliminate predisposing factors, if possible: uncontrolled diabetes, corticosteroid use, topical or systemic antibiotics, spermicides (conflicting data), tight-fitting synthetic underwear, douching, pregnancy, immunosuppression*
 3. *speciation/susceptibility testing*
 - Management options:
 1. *longer duration of standard treatment regimen*
 2. *chronic intermittent therapy (e.g., with perimenstrual episodes)*
 3. *restriction of orogenital/anogenital sexual contact (anecdotal evidence only); double-blind, placebo-controlled trials of topical therapy for male sexual partners showed no benefit (Sobel, 1999)*
 4. *possible role for boric acid vaginal capsules, gentian violet*
 5. *maintenance therapy: initial intensive regimen (e.g., 7–14 days of topical therapy or a 150 mg oral dose of fluconazole repeated 3 days later) followed by a maintenance regimen for at least 6 mo:*
 - a. fluconazole* 100–150 mg po every wk
 - b. itraconazole* 400 mg po every month or 100 mg po every day
 - c. clotrimazole 500 mg suppository per vagina every wk
 - d. ketoconazole* 100 mg po every day (associated with rare but significant hepatotoxicity-monitor liver function; significant drug interactions with some antiretrovirals (see Chapter XIV on Pharmacologic Considerations in HIV-infected Pregnant Patients)
 6. *immune reconstitution; potential benefit with protease inhibitors*

* Note: avoid concomitant use with terfenadine, astemizole, cisapride secondary to cardiotoxicity.

TRICHOMONIASIS

- Caused by *Trichomonas vaginalis*
- HIV-positive women: 5–23% prevalence; incidence in HIV-positive women 10–17% (Minkoff, 1999; Sorvillo, 1998). Studies have not shown increased prevalence, incidence, persistence or recurrence compared with HIV-negative women or with lower CD4 counts (Cu-Uvin, 2002).
- Clinical features: profuse, malodorous, often frothy, yellow-green discharge and vulvar irritation; may have urinary symptoms or dyspareunia; signs of inflammation — vaginal erythema, “strawberry” vagina, cervix with punctate hemorrhages; may be asymptomatic in chronic cases

- Diagnosis: saline wet mount (motile trichomonads seen in 50–70% culture-positive cases); Pap smear (60–70% sensitivity, false positives not uncommon); culture (95% sensitivity); DNA probes; monoclonal antibodies
- *T. vaginalis* cysteine proteases degrade and render nonfunctional secretory leukocyte protease inhibitor, a substance thought to protect mucosal surfaces from HIV transmission by inhibition of HIV protease activity necessary for infection of monocytes and macrophages (Draper, 1998)
- **Treatment** (CDC, 2002):
 - Metronidazole 2 g po (single dose), OR
 - Metronidazole 500 mg po twice a day for 7 days
 - Note:
 - No change in treatment based on HIV status
 - Sex partners should be treated with the same regimen (>90% cure rates can be expected if partner is treated simultaneously); intercourse should be avoided until therapy is complete and patient and partner are asymptomatic
 - Topical metronidazole less effective
 - Metronidazole resistance is rare; organisms with decreased susceptibility usually respond to higher doses of metronidazole. If treatment failure occurs with either regimen, retreat with metronidazole 500 mg po twice a day for 7 days. If treatment failure occurs repeatedly, treat with metronidazole 2 g po once a day for 3–5 days. Patients with documented infection (with reinfection excluded) who have not responded to these measures should be managed in consultation with an expert.

GONORRHEA

- caused by *Neisseria gonorrhoeae*
- clinical presentation: commonly asymptomatic; vaginal discharge may be present; if untreated, 10–20% develop PID; urethra is primary site of colonization after hysterectomy and should be sampled with culture or DNA probe for testing in these patients; gonorrhea may also cause rectal infection, pharyngitis, and (rarely) disseminated infection
- diagnosis: culture, DNA probe, polymerase chain reaction (PCR) or ligase chain reaction (LCR). PCR/LCR can be used with cervical, urethral, or urine specimens; may detect gonorrhea and chlamydia simultaneously; sensitivity 93–98%, specificity >99%; able to detect 15–40% more infections than culture (Hook, 1999)
- prevalence/clinical presentation/diagnosis/treatment in HIV-positive patients: no difference compared with HIV-negative patients
- **Treatment** (CDC, 2002): Uncomplicated gonococcal infections of the cervix, urethra, and rectum
 - Cefixime 400 mg po (single dose), OR
 - Ceftriaxone 125 mg IM (single dose), OR
 - Ciprofloxacin 500 mg po (single dose), OR

- Ofloxacin 400 mg po (single dose)
- Levofloxacin 250 mg po (single dose), OR
- **Alternative regimen:**
 - Spectinomycin 2 g IM (single dose)
- Note:
 - It is recommended that women be presumptively treated for chlamydia, particularly in areas with high rates of coinfection, absence of chlamydial testing, and/or when patient may not return for results
 - Sex partners should be treated for both gonorrhea and chlamydia if their last sexual contact was within 60 days before the diagnosis or onset of symptoms. If a patient's most recent sexual contact occurred more than 60 days before the onset of symptoms, her most recent partner should be treated. Intercourse should be avoided until treatment is completed and symptoms have resolved.
 - Culture and susceptibility testing recommended after apparent treatment failure with standard regimen
 - Due to the increased prevalence of quinolone-resistant gonorrhea in Hawaii, California, or with infections acquired in Asia or the Pacific, the use of fluoroquinolones in these locations or circumstances is not advisable (CDC, 2002)
 - Avoid use of quinolones and tetracyclines in pregnancy

CHLAMYDIA

- caused by *Chlamydia trachomatis*
- clinical presentation: asymptomatic infection common; abnormal discharge; symptoms of urethritis; if untreated, 10–40% develop PID
- diagnosis: culture (cell based), antigen detection, DNA probe, PCR/LCR (90–100% sensitivity — see above) (Stamm, 1999)
- prevalence/clinical presentation/diagnosis/treatment in HIV-positive women: no differences compared with HIV-negative women
- **Treatment (CDC, 2002):**
 - Azithromycin 1 g po (single dose), OR
 - Doxycycline 100 mg po twice a day for 7 days
 - Alternative regimens:
 - Erythromycin base 500 mg po four times a day for 7 days, OR
 - Erythromycin ethylsuccinate 800 mg po four times a day for 7 days, OR
 - Ofloxacin 300 mg po twice a day for 7 days, OR
 - Levofloxacin 500 mg po for 7 days
 - Note:
 - Recommendations for the management of sex partners are the same as for gonorrhea (see above)
 - Avoid use of doxycycline or quinolones in pregnancy
 - Rescreening for chlamydia 3–4 months after treatment is recommended.

OTHER

- Atrophic vaginitis: related to estrogen deficiency; irritative symptoms, vaginal dryness, and dyspareunia; the vaginal epithelium appears thin and a watery discharge may be present; treat with either topical or oral estrogen.
- Foreign body (retained tampon, toilet paper, etc.)
- Local irritants (spermicides, vaginal medications, toilet paper dye, hygiene sprays, soap, detergent, douches, etc.)

VI. PELVIC/ABDOMINAL PAIN

Abdominopelvic pain can be classified as acute, chronic, or cyclic. **Acute pain** is typically sudden in onset and short in duration, whereas **chronic pain** is of at least 6 mo duration. **Cyclic pain** is associated with the menstrual cycle.

A. HISTORY

Characteristics of pain: onset (rapid or gradual), character (crampy, colicky, sharp or dull), location (generalized or localized pain), and duration; associated symptoms: abnormal vaginal bleeding or discharge, gastrointestinal symptoms (e.g., nausea/vomiting, anorexia, constipation, diarrhea), and urinary (e.g., dysuria, frequency, urgency, hematuria) symptoms, fever or chills; history of other medical conditions; surgical history; gynecologic history: date of last menstrual period, use of contraception and condoms, history of STIs; medications; CD4 counts and HIV-RNA levels.

B. PHYSICAL EXAM

A complete set of vital signs should be obtained. The physical exam should focus on abdominal and pelvic findings. A complete abdominal exam should evaluate the presence and character of bowel sounds, distention, suprapubic or costovertebral angle tenderness, other abdominal tenderness (including rebound and guarding), and presence of masses. The pelvic exam should determine the presence of abnormal bleeding or discharge; reproducibility and location of tenderness (e.g., uterine, adnexal, or cervical motion tenderness); presence of a palpable abdominal or pelvic mass should be ruled out.

C. EVALUATION

- Pregnancy test
- Laboratory tests: CBC with differential, sedimentation rate, chemistry panel, others as indicated
- Wet mount/STI testing
- Urinalysis and urine culture

- Stool studies (cultures, evaluation for ova and parasites, *C. difficile* toxin assay) — if indicated by GI symptomatology
- Pelvic ultrasound, computed tomography (CT) scans — if indicated
- Blood cultures — bacteria, *Mycobacterium avium*, if indicated

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

Includes but is not limited to:

- **Pregnancy:** refer; with pain and pregnancy ± bleeding, must suspect ectopic pregnancy, and urgent evaluation is indicated.
- **Pelvic inflammatory disease:** PID is an upper genital tract infection, usually polymicrobial in nature. Sexually transmitted organisms, including *N. gonorrhoea* and *C. trachomatis*, are implicated in most cases of PID; bacterial vaginosis-associated organisms are also commonly present. Symptoms may be virtually absent or mild and nonspecific (e.g., abnormal bleeding, dyspareunia, vaginal discharge; less commonly right upper quadrant pleuritic pain secondary to perihepatitis). Current CDC-recommended criteria for diagnosis of PID are (CDC, 2002):

- **Minimum criteria:**

- uterine/adnexal tenderness
- cervical motion tenderness

Because of difficulty in diagnosis and the potential for long-term complications, empiric therapy should be initiated if these criteria are present and no other cause for symptoms is identified.

- **Additional criteria:**

- oral temperature >101°F (>38.3°C)
- abnormal mucopurulent cervical or vaginal discharge
- elevated erythrocyte sedimentation rate
- elevated C-reactive protein
- documented cervical gonorrhea or chlamydia infection
- white blood cells on saline wet mount of vaginal secretions

These criteria enhance specificity.

- **Definitive criteria:**

- endometritis on endometrial biopsy
- tuboovarian complex or thickened, fluid-filled tubes on transvaginal ultrasound or magnetic resonance imaging (MRI)
- laparoscopic abnormalities consistent with PID

Warranted in patients who are severely ill and/or when diagnosis is uncertain.

- **PID in the HIV-positive woman:** Several studies have found increased seroprevalence of HIV in hospitalized PID patients (Hoegsberg, 1990; Sperling, 1991). A recent analysis of hysterectomy specimens from HIV-positive women and HIV-negative women, matched for surgical indication, found chronic endometritis twice as commonly in the HIV-positive specimens;

some degree of abnormal uterine bleeding had occurred in all cases (Kerr-Layton, 1998). Moreover, the clinical presentation among these women may be more severe or otherwise altered (e.g., lower white blood cell counts than HIV-negative women) (Barbosa, 1997; Cohen, 1998; Kamenga, 1995, Irwin, 2000); in African studies, more severe illness, including tuboovarian abscess, and longer hospital stays were found with significant immunosuppression. The microbiology of infection and response to standard antibiotic regimens are similar to HIV-uninfected women, although one study found mycoplasmas and streptococci were more likely to be isolated from HIV-positive women (Irwin, 2000). Some studies have reported a greater need for surgical intervention (Korn, 1993). CMV and tuberculosis may cause upper genital tract infection in rare cases and should be considered in appropriate clinical situations. A recent study from Kenya found similar efficacy of oral ambulatory therapy in HIV-positive and HIV-negative women with PID (Bukusi, 1999). Decisions about oral vs. parenteral therapy should be individualized.

• Inadequate response to outpatient therapy
• Uncertain diagnosis; surgical emergency cannot be excluded
• Pregnancy
• Inability to tolerate or follow outpatient regimen
• Immunosuppression (low CD4 counts, clinical AIDS, on immunosuppressive drugs, other significant comorbidity)
• Tuboovarian abscess or other evidence of severe illness, nausea and vomiting, or high fever

- Treatment (CDC, 2002):

• **Parenteral regimens:**

Cefotetan 2 g IV every 12 hr, PLUS doxycycline 100 mg PO or IV, OR

Cefoxitin 2 g IV every 6 hr, PLUS doxycycline 100 mg PO or IV, OR

Clindamycin 900 mg IV every 8 hr, PLUS gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hr. Single daily dosing of gentamicin may be substituted.

• **Oral regimens:**

Ofloxacin 400 mg po twice a day for 14 days OR levofloxacin 500 mg po once daily for 14 days WITH or WITHOUT metronidazole 500 mg po twice a day for 14 days.

Ceftriaxone 250 mg IM, OR cefoxitin 2 gm IM once and probenecid 1 g po in a single dose concurrently, OR other parenteral third-generation cephalosporin (ceftizoxime or cefotaxime) PLUS doxycycline 100 mg po twice a day for 14 days WITH or WITHOUT metronidazole 500 mg po twice a day for 14 days.

For alternative oral and parenteral regimens, please see the CDC 2002 Guidelines for Treatment of Sexually Transmitted Diseases.

Parenteral therapy may be discontinued 24 hr after there is evidence of clinical improvement. Oral therapy with doxycycline 100 mg every 12 hr (consider the addition of metronidazole 500 mg every 12 hr, particularly with presence of tuboovarian abscess) or clindamycin 450 mg four times a day should then be instituted to complete a 14-day treatment course. Sexual partners of women diagnosed with PID should be evaluated and treated presumptively for gonorrhea and chlamydia if they have had sexual contact within the 60 days preceding the onset of symptoms.

- **Ruptured/hemorrhagic ovarian cyst:** can cause acute abdominal pain; bleeding associated with rupture is usually self-limited but may require surgical intervention.
- **Ovarian torsion:** acute, severe, unilateral lower abdominal/pelvic pain, often with history of previous similar episodes; palpable adnexal mass often present. Surgical intervention required.
- **Uterine leiomyomas (fibroids):** may cause pain with rapid enlargement, degeneration, or torsion; referral indicated
- **Endometriosis:** cause of acute or chronic pain, usually includes secondary dysmenorrhea and/or dyspareunia; referral to gynecologic specialist indicated if endometriosis suspected
- **Dysmenorrhea:** affects about half of all menstruating women; cyclic pain with menses. Primary dysmenorrhea is menstrual pain in the absence of pelvic pathology; secondary dysmenorrhea is associated with underlying pathology (such as endometriosis). Treatment of primary dysmenorrhea consists of nonsteroidal anti-inflammatory drugs (NSAIDs) (80% effective) or oral contraceptive pills (90% effective). Treatment of secondary dysmenorrhea is directed at the specific underlying problem.
- **Mittelschmerz:** pain with ovulation, generally self-limited; manage with NSAIDs
- **Gastrointestinal pathology:** includes appendicitis; diverticulitis (pain generally localizes to the left lower quadrant; usually seen at older ages); irritable bowel syndrome (pain is usually intermittent, cramp-like, and more common in the left lower quadrant; exacerbated by certain foods); inflammatory bowel disease; infectious enterocolitis (pain, cramping, diarrhea); obstruction (colicky pain, distention, vomiting, obstipation). Opportunistic infections, including cryptosporidia, CMV, and *M. avium* may be causes of chronic diarrhea in patients with AIDS, and clinical features usually include abdominal pain.
- **Urinary tract pathology:** renal/ureteral stones, cystitis, and pyelonephritis
- **Medication-related:** indinavir (renal stones); didanosine (pancreatitis)

VII. PELVIC MASS

A. HISTORY

Presence and duration of associated symptoms: pain, abnormal vaginal bleeding or discharge, urinary symptoms (e.g., frequency, urinary retention), gastrointestinal symptoms (e.g., nausea, vomiting, constipation, diarrhea), or constitutional symptoms (e.g., fever, chills, weight loss or gain).

B. PHYSICAL EXAM

A complete abdominal and pelvic examination should be performed, with particular attention given to the size, location, mobility, and characteristics of the mass (if palpable) as well as to signs of ascites; lymph node survey. With functional ovarian cysts, a normal ovary may be up to 5–6 cm in size for a woman in the reproductive age range. A palpable ovary in a postmenopausal woman may be abnormal and requires further evaluation.

C. EVALUATION

- Pregnancy test: if premenopausal
- Laboratory tests: CBC with differential; chemistry panel; tumor markers, if indicated (e.g., CEA, Ca-125; frequent false positives and false negatives, should only be used in conjunction with other diagnostic procedures)
- Radiologic studies: pelvic ultrasound (transabdominal/transvaginal), CT, and magnetic resonance imaging (MRI), as indicated. Ultrasound is generally the first diagnostic modality employed in evaluating pelvic anatomy; concerning characteristics include complex or solid mass, presence of ascites. CT/MRI are better at imaging GI tract, retroperitoneal lymphadenopathy, liver

Additional evaluation involving procedures such as laparoscopy, colonoscopy, etc., require referral to appropriate specialists.

D. DIFFERENTIAL DIAGNOSIS

- **Ectopic pregnancy:** the primary consideration in the setting of an adnexal mass and a positive pregnancy test, urgent evaluation indicated.
- **Ovarian functional cyst:** Functional cysts are the most common ovarian masses found among women of reproductive age; resolution occurs spontaneously in 1–3 mo.
- **Uterine leiomyomas (fibroids):** often asymptomatic, but may be associated with heavy and/or prolonged menses, urinary frequency.
- **Endometrioma:** consider in women with a documented or suspected history of endometriosis.

- **Hydrosalpinx/pyosalpinx and tuboovarian abscess:** consider with history suggestive of PID; initial management with broad-spectrum antibiotics, even if patient asymptomatic.
- **Benign or malignant ovarian neoplasm:** Surgical intervention is required. No evidence of increased prevalence in HIV-positive women; anecdotal reports suggest ovarian cancer may present at more advanced stage, with poorer response to cytoreductive surgery and chemotherapy (Rojansky, 1996). Non-Hodgkins lymphoma of ovary described in an HIV-positive woman (Neary, 1996).
- **Retroperitoneal lymphadenopathy:** may present as pelvic mass; possible causes include tuberculosis, lymphoma
- **Gastrointestinal masses:** includes diverticular abscess, bowel malignancy

In general, the presence of a pelvic or abdominal mass requires expert consultation and referral to an appropriate specialist.

VIII. URINARY SYMPTOMS

A. HISTORY

Duration and severity of urinary symptoms; specific symptoms: dysuria, frequency, urgency, hematuria, nocturia, incontinence; associated symptoms, including pain (suprapubic or flank), fever, chills, and weight loss; other medical conditions (e.g., diabetes, sickle cell disease); surgical history; medications; CD4 count and HIV-RNA level

B. PHYSICAL EXAM

Vital signs; document presence of suprapubic tenderness or flank or costovertebral angle tenderness

C. EVALUATION

- Microscopic exam of urine
- Urine culture and sensitivity
- Gonorrhea/chlamydia testing, if indicated
- Urine cytology: consider in woman over age 50 who presents with irritative symptoms or hematuria and negative culture
- Urine for acid-fast bacillus (AFB) culture, purified protein derivative (PPD): if indicated, urinary TB suspected
- Intravenous pyelogram (IVP): if indicated; consider if stones, urinary tract anomalies, or urinary TB suspected
- Other tests: cystoscopy, urodynamics — refer to appropriate specialist

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

- **Bacterial urinary tract infection:** lower tract (cystitis) or upper tract (pyelonephritis); may be asymptomatic and clinical signs and symptoms cannot reliably distinguish between upper and lower tract infection. Classically cystitis characterized by the presence of dull, suprapubic pain; typical associated symptoms include dysuria, urinary frequency and urgency, and occasionally hematuria. Pyelonephritis associated with flank or costovertebral pain and tenderness to percussion, as well as systemic signs/symptoms, including fever, chills, nausea, vomiting, tachycardia. Treat with appropriate antibiotics; severe pyelonephritis requires hospitalization for IV antibiotics and hydration.
- **Urethral syndrome:** dysuria, frequency with negative urine culture; rule out urethritis due to gonorrheal or chlamydial infection
- **Renal/ureteral stones:** severe, colicky pain; usually associated with urinary stasis or chronic infection, although may be related to metabolic abnormalities, such as gout or problems with calcium homeostasis; a significant side effect associated with indinavir therapy.
- **Interstitial cystitis:** symptoms include severe urinary frequency and urgency (urinating as often as every 15 minutes daytime and nighttime) as well as suprapubic or perineal discomfort before, during, and after urination; refer for definitive evaluation
- **Urinary tuberculosis:** one of the most common sites of extrapulmonary TB; gross or microscopic hematuria and pyuria with negative bacterial culture should lead to consideration; manage with expert consultation
- **Tumors:** most common presenting complaint is gross or microscopic hematuria; hematuria without identifiable etiology (e.g., infection) requires referral to urologist
- **Urinary incontinence:** can be caused by many factors, including anatomic displacements related to aging and childbearing; bladder muscle (detrusor) instability; neurologic disease; infection; fistulas secondary to surgical injury, radiation, or cancer; and some medications. Rule out infection with culture and “overflow” incontinence (secondary to overdistended bladder) with postvoid catheterization for residual urine determination. Further evaluation requires referral to urogynecologist or urologist
- **Urinary retention:** may be caused by obstruction, neurologic disorders, or certain medications (e.g., antihistamines, antidepressants, antipsychotics, opiates, antispasmodics, terbutaline, over-the-counter cold remedies)

IX. GENITAL WARTS

Genital warts are a common manifestation of HPV infection. HPV types 6 and 11 are usually the cause of visible genital warts. Oncogenic types (i.e., 16, 18, 31, 33, and 35) are occasionally found in visible warts and have been associated with squamous intraepithelial neoplasia of the external genitalia (see section on abnormal Pap smear, above).

A. HISTORY

Location of warts, duration, and the presence of associated symptoms (itching, irritation, pain, bleeding); history of prior occurrences of similar lesions and their treatment; history of abnormal Pap smear results

B. PHYSICAL EXAM

Complete examination of the external genitalia as well as of the cervix, vagina, and perianal region should be performed; location and size of warts should be documented. Genital warts can present as cauliflower-shaped growths (condyloma acuminata); smooth, dome-shaped, skin-colored papules; keratotic warts with a thick horny layer; or flat or slightly raised flat-topped papules.

C. RELATION TO HIV

HIV-infected women are more likely to have HPV coinfection and both prevalence and incidence of genital warts are increased compared with HIV-negative women (Silverberg, 2002; Conley, 2002). Both prevalence and clinical expression of HPV increase with progressive clinical disease and immunologic decline. Immunosuppressed women may not respond as well to treatment and have more frequent recurrences after therapy. Squamous cell carcinomas that arise in or resemble genital warts may occur more commonly in the setting of immunosuppression, making confirmation of diagnosis with biopsy more frequently necessary.

D. EVALUATION

- **Biopsy:** Typical condyloma acuminata are diagnosed by inspection and do not require biopsy, although current CDC guidelines suggest biopsy when the patient is immunocompromised. A biopsy of the lesion and histopathologic confirmation of the diagnosis are always indicated in the following situations:
 - diagnosis is uncertain
 - warts do not respond to therapy
 - lesions worsen during therapy
 - warts are pigmented, indurated, fixed, or ulcerated
- **Colposcopy:** Colposcopy and directed biopsies of the entire lower genital tract should be considered in HIV-positive women with evidence of HPV infection. Colposcopy should be performed to rule out the presence of high-grade squamous intraepithelial lesions before initiating treatment of cervical warts.

- **Treatment:** The primary goal of treatment is the removal of symptomatic lesions. When left untreated, visible warts may resolve spontaneously, may remain unchanged, or may increase in number or size. There is no evidence that currently available therapies eradicate HPV, have an effect on the natural history of infection, or affect the subsequent development of cervical cancer. Infectivity may or may not be decreased by the removal of visible warts.

The treatment modality depends on the number, size, and location of the warts. When there are a small number of lesions and they are fairly small, a topical agent may be employed. Table 6-10 displays provider-applied and patient-administered regimens recommended by the CDC (CDC, 2002).

Most treatment modalities are associated with mild to moderate discomfort and local irritation. Persistent hypo- or hyperpigmentation is common after ablative therapies and scarring or chronic pain at the treatment site can occur but is rare. Intralesional interferon is an additional alternative treatment but is expensive and associated with a high frequency of systemic side effects. Treatment method should be changed if there is not substantial improvement after three provider-administered treatments or if there is not complete clearance after six treatments. Combining modalities does not appear to increase efficacy but may increase complications. Recurrence rates are significant with all modalities; frequent follow-up will allow retreatment when new warts are small and few in number. When the number of warts is large or the lesions are very extensive, referral for possible laser surgery should be considered. In one study relapse rates of treated genital warts in HIV-positive patients was lower in those on combination antiretroviral therapy and was correlated with HIV-RNA levels (Giovanna, 1998).

<i>Provider-applied</i>	<i>Patient-applied</i>
80–90% trichloroacetic or bichloroacetic acid (weekly if necessary) Cryotherapy with liquid nitrogen or cryoprobe—repeat every 1–2 wk. Remove excess acid with talc powder, baking soda, or liquid soap.	Podofilox .5% solution or gel applied twice a day for 3 days followed by 4 days of no therapy. May repeat application for up to 4 cycles; application should be limited to .5 mL per day and <10 cm ² area of warts
10–25% podophyllin resin (weekly if necessary). Application should be limited to <.5 mL of podophyllin or <10 cm ² of warts per session and preparation should be thoroughly washed off 1–4 hr after application to reduce local irritation. Because of concern about potential systemic absorption and toxicity, avoid use on mucosal surfaces.	Imiquimod 5% cream applied three times per wk for as long as 16 wk. The treated area should be washed with mild soap and water 6–10 hr after application.
Surgical removal (laser or excision)	

Note: Avoid use of podophyllin, podofilox, and imiquimod during pregnancy.
 Source: CDC, 2002.

X. GENITAL MASSES/NODULES

A. HISTORY

Duration; changes in size or appearance; associated symptoms (e.g., pain/tenderness, itching, edema); history of similar nodules and their treatment; sexual history (including presence of similar lesions on genitals of partner); medications; CD4 count and HIV-RNA level

B. PHYSICAL EXAM

Document anatomic location, number, and size of the nodules; presence of associated edema, erythema, induration, fluctuance, tenderness, discharge, or bleeding

C. EVALUATION

Biopsy indicated if etiology is unclear; culture of abscess contents

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT (ROSEN, 2003)

- **Bartholin's abscess:** Bartholin's glands are normally nonpalpable and located deep in the perineum at the 5 and 7 o'clock positions in the entrance to the vagina. Obstruction of a Bartholin's duct by nonspecific inflammation, infection (e.g., gonorrhea or chlamydia) or trauma can lead to the formation of an abscess; exquisitely tender. Treatment consists of incision and drainage.
- **Molluscum contagiosum:** an asymptomatic viral disease that primarily affects skin of the vulva, although it can present as a generalized skin disease in immunosuppressed individuals; spread by close contact, both sexual and nonsexual. Clinical features: small nodules or domed papules, usually 1–5 mm in diameter; the more mature nodules appear to have an umbilicated center. This disease tends to be self-limited; however, disease course may be complicated by repeat infection and autoinoculation of the virus. Treatment consists of serial applications of liquid nitrogen or of removal of the nodules with a dermal curet and chemical cauterization of base with 85% trichloroacetic acid or ferric subsulfate. Molluscum contagiosum affects 5–10% of HIV-positive patients; extensive, severe lesions that show poor response to therapy are common; such unresponsive lesions, however, have been found to regress with HAART (Calista, 1999).
- **Tumors, other masses:** biopsy required; expert consultation indicated.

XI. GENITAL ITCHING/IRRITATION

A. HISTORY

Duration, location, and severity of pruritis/irritation; associated symptoms (erythema, edema, vulvar burning, dysuria, dyspareunia); prior episodes of similar symptoms and treatment; exposure to particular agents (e.g., soaps, sprays, vaginal contraceptives, douches, colored toilet tissue, etc.) coincident with the beginning of symptoms; presence of similar symptoms in close contacts; medications, including antibiotics; CD4 count and HIV-RNA level

B. PHYSICAL EXAM

Physical appearance and distribution of the irritated area (e.g., diffuse rash, papular or vesicular lesions, skin burrows, etc.); associated findings, including erythema, edema, and tenderness, vaginal discharge; if a more generalized process is suspected (e.g., allergic reaction to detergent, scabies, etc.) more thorough inspection of the skin throughout the body may be indicated.

C. EVALUATION

- Fungal culture/KOH preparation: indicated if a fungal infection is suspected.
- HSV culture: herpes may appear atypically and should be ruled out in the presence of vesicular lesions, unexplained abrasions, or fissuring, or if warranted by history.
- Skin scrapings: scraping of skin papule is with a needle, and the crust is placed under a drop of mineral oil on a slide; eggs, parasites, or fecal pellets microscopically visualized by this technique are diagnostic of scabies or pubic lice.

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT (ROSEN, 2003)

- **Fungal infection:** Although the primary symptom associated with fungal infections is itching, women also complain of vulvar burning, dysuria, and dyspareunia, particularly with involvement of vulvar skin. Examination often reveals edema, erythema, and excoriation; pustular lesions may be found to extend beyond the line of erythema when extensive skin involvement is present. Diagnosis is established by means of a KOH preparation or fungal culture. Treatment is topical application of an antifungal preparation. (See vulvovaginal candidiasis in the Vaginal Discharge section above.)
- **Allergic/irritative reaction:** Contact dermatitis frequently affects the vulvar skin, particularly the intertriginous areas; etiologic agents include urine or feces, latex, semen, cosmetic or therapeutic agents (including vaginal contraceptives, lubricants, sprays, perfumes, douches, fabric dyes, fabric softeners, synthetic

fibers, bleaches, soaps, chlorine, dyes in toilet tissues, and local anesthetic creams); severe cases of dermatitis may be due to poison ivy or poison oak. Typical symptoms are itching, vulvar burning, and tenderness. Examination of the skin reveals erythema, edema, and inflammation; the skin may be weeping and eczematoid. Secondary infection may occur.

Treatment involves removing the offending agent. Severe lesions may be treated with wet compresses of Burow's solution diluted 1:20 for 30 min several times a day. If possible, the vulva should be dried with cool air from a hair dryer following the compresses. Lubricating agents such as Eucerin cream or petroleum jelly can help reduce the itching. Nonmedicated baby powders can be used to facilitate vulvar dryness. Symptomatic relief can be achieved with hydrocortisone (0.5% to 1%) or fluorinated corticosteroid (Valisone 0.1% or Synalar 0.01%) lotions or creams into the skin two to three times a day for a few days. Dermatitis due to poison ivy or poison oak may require treatment with systemic corticosteroids. The use of white cotton undergarments is advisable, and tight-fitting clothing should be avoided.

- **Scabies/lice:**

- Scabies is a parasitic infection produced by the itch mite, *Sarcoptes scabiei*. The main symptom reported is severe, intermittent itching that tends to be more intense at night. Lesions can present as vesicles, papules, or burrows; any area of skin may be affected: the hands, wrists, breasts, vulva, and buttocks are most often affected. HIV-infected and other immunosuppressed patients are at increased risk for Norwegian scabies, a disseminated dermatologic infection; this can appear classically as hyperkeratotic, nonpruritic lesions; as crusting with pruritis; a pruritic, papular dermatitis; or lesions resembling psoriasis (Schlesinger, 1994).

- CDC-recommended treatment for scabies (CDC, 2002):

Permethrin cream (5%) applied to all areas of the body from the neck down and washed off after 8–14 hr.

- Alternative regimens:

Lindane (1%) 1 oz of lotion or 30 g of cream applied to all areas of the body from the neck down and washed off thoroughly after 8 hr OR ivermectin 200 ug/kg po, repeated in 2 weeks.

Lindane should not be used by pregnant or lactating women or after a bath.

Itching may persist for days following treatment; antihistamine therapy should be considered for symptomatic relief. Bedding and clothing should be decontaminated (machine washed or dry-cleaned) or removed from body contact for at least 72 hours. Norwegian scabies should be managed in consultation with an expert.

- Pediculosis pubis is due to infestation by the crab louse, *Phthirus pubis*, or pubic louse. Transmission is by close contact, but the louse can also be acquired from bedding or towels. This infection is usually confined to the hairy areas of the vulva (eyelids are occasionally infested). The presenting symptom is constant itching in the pubic area. Eggs, adult lice, and fecal material

can be seen upon close examination (without magnification). The diagnosis can be definitively established by microscopic visualization, as described above.

- The CDC-recommended treatment (CDC, 2002) is permethrin 1% cream rinse applied to affected areas and washed off after 10 min or, lindane 1% shampoo (applied for 4 min and thoroughly washed off; lindane not recommended for pregnant or lactating women) OR pyrethrins with piperonyl butoxide (applied to the affected area and washed off after 10 min). If symptoms do not resolve, patients should be reexamined in 1 wk; if lice or eggs are seen at the hair-skin junction, the patient should be retreated. All clothing and bedding must be decontaminated. Close household contacts and sexual contacts (within the previous month) should be treated.

XII. BREAST LUMP

A. HISTORY

If palpable by the patient, duration of the lump; any associated symptoms (e.g., tenderness, nipple discharge, cyclic pain); changes in the characteristics of the lump (e.g., increase in size); history of previous breast lumps; family history of breast disease or cancer or history of genetic screening showing BRCA-1 or BRCA-2 mutation.

B. PHYSICAL EXAM

Symmetry, contour, and appearance of the skin; presence of edema, erythema, skin dimpling, or nipple retraction; presence and size of dominant masses, nodularity, tenderness; nipple discharge (including color); and lymphadenopathy (axillary and supraclavicular).

C. EVALUATION

- Mammogram: should be performed with any persistent palpable mass or other suspicious changes in the breast (e.g., bloody nipple discharge, skin retraction). A negative mammogram alone is not sufficient to rule out malignant pathology in a patient with a palpable breast mass or bloody nipple discharge; further evaluation and possible biopsy are indicated.
- Ultrasound: most helpful to distinguish cystic and solid masses; useful initial test in younger women when simple cyst suspected.
- Needle aspiration: for cystic lesion; fluid can be discarded if clear and if mass disappears; otherwise send fluid for cytology, and biopsy may be needed.
- Biopsy: indicated in cases of dominant mass (even with normal mammographic findings) or suspicious nonpalpable mammographic findings.

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

- **Fibrocystic change:** Typically found among women who are 30–50 yr old. Fibrocystic changes usually present as breast nodularity associated with cyclic bilateral pain or tenderness, which is worse premenstrually. Breast engorgement, increased density, and cyst formation are common and vary with menstrual cycle phase. The pain/discomfort associated with this condition can be relieved wearing a brassiere that gives adequate support. Analgesics can aid in symptomatic relief; some women have reported improvement of symptoms with vitamin E (400 IU a day) and decrease in caffeine consumption. Oral contraceptives are known to decrease benign breast disease. The appearance of a persistent dominant mass requires biopsy.
- **Fat maldistribution syndrome:** HIV or antiretroviral treatment may affect breast tissue, resulting in gynecomastia or increased fatty deposition (Pantanowitz, 2002)
- **Breast abscess/mastitis:** Usually presents with tender breasts with evidence of inflammation (redness, swelling); if abscess present, may palpate fluctuant mass; fever may be present. Generally bacterial etiology, but consider tuberculous mastitis/abscess in appropriate circumstances. Treatment includes antibiotics, incision and drainage of abscess. Consider biopsy and/or other diagnostic tests with non-response.
- **Benign breast tumor:** Most frequently diagnosed benign tumors of the breast are fibroadenomas, usually found in women aged 20–35. Typically, most masses are about 2–3 cm in diameter, although they can become much larger. Examination reveals a firm, smooth, rubbery mass that is freely mobile. Inflammation, skin dimpling, and nipple retraction are absent. On mammographic examination, the mass appears smooth with well-defined margins. Definitive diagnosis is established by means of biopsy. A fibroadenoma may simply be observed; however, a large, growing, or otherwise suspicious mass should be surgically excised.
- **Breast cancer:** Incidence of breast cancer increases with age; risk factors include positive family history, early menarche, late menopause, and nulliparity or late childbearing. If a palpable mass is present, it is usually firm and nontender with irregular margins; it may be fixed to skin or underlying tissue. Definitive diagnosis is established by means of biopsy, and referral to a surgeon is indicated. Although there is no apparent increase in incidence of breast cancer among HIV-positive women and most cases occur with CD4 counts above 200/mm³, breast cancer in the setting of HIV infection tends to occur at a relatively early age, is more likely to be bilateral and to have unusual histology, and is more aggressive, with early metastatic spread and poor outcome. Kaposi's sarcoma and non-Hodgkins lymphoma may also be localized to the breast in women with AIDS. (Pantanowitz, 2002; Voutsadakis, 2002).

XIII. MENOPAUSE

As HIV-positive women live longer and more women nearing menopause or postmenopausal become infected, menopausal issues become more important to consider and address. The association between HIV/AIDS and premature ovarian failure remains unclear.

Menopause is defined as the permanent cessation of menstruation caused by the loss of ovarian function. The mean age at which women undergo menopause is genetically predetermined and in the United States averages between 51 and 52 yr of age. Certain medical conditions, such as osteoporosis and cardiovascular disease, have been linked to estrogen deficiency and women with HIV may be at increased risk for these conditions, particularly if they are on potent antiretroviral therapy (see Chapter IV Primary Medical Care); associations have also been proposed between menopause and Alzheimer's disease and colon cancer (Hurd, 1996; Mishell, 1997b).

A. HISTORY

Last menstrual period and recent menstrual pattern (cycle length, duration, and amount of flow); any irregular or intermenstrual bleeding or spotting; hot flashes; genitourinary dryness/atrophy; decreased libido; anxiety, irritability, sleep disturbances, and depression; difficulty with memory; urinary symptoms

B. PHYSICAL EXAM

Vagina appears smoother in contour, "drier"; may be more easily traumatized and more vulnerable to infection.

C. EVALUATION

If indicated, confirmation of menopause can be provided by an elevated serum follicle-stimulating hormone level and a low estradiol level.

D. MANAGEMENT

- Hormone Replacement Therapy (HRT) (combined estrogen-progestin replacement therapy)

The benefits and risks associated with HRT have been extensively studied among women who are HIV-negative. HRT is known to ameliorate symptoms of vasomotor instability (e.g., hot flashes, sleep disturbances, irritability, etc.) and urogenital atrophy (e.g., vaginal dryness, dyspareunia, etc.). HRT also is associated with decreased risk of osteoporosis and osteoporosis-related fractures and colon cancer (Women's Health Initiative, 2002). However, results of a recent large randomized, placebo-controlled study of combined estrogen-progestin therapy found a small but statistically significant increase in incidence of breast cancer, dementia, stroke, pulmonary embolism, and cardiovascular disease (Rousouw,

2002; Shumaker, 2003; Chlebowski, 2003). HRT should no longer be given for primary or secondary prevention of cardiovascular disease. A recent prospective cohort study found increased breast cancer risk from even brief exposures to both estrogen only and estrogen-progestin combination hormone replacement (Beral, 2003), although risk was substantially greater for combination HRT. Given current data, the primary indication for HRT is for the short-term management of menopausal symptoms. It is unclear whether lower doses of combined estrogen-progestin therapy or estrogen alone are associated with similar spectrum or magnitude of risks, although there is an increased risk of endometrial cancer in women treated with estrogen only. Because of the higher prevalence of active liver disease in hepatitis B or C coinfecting patients and the potential increase in risk for cardiovascular disease associated with metabolic changes of long-term antiretroviral therapies, HRT may be associated with increased risk in the setting of HIV infection.

- Alternatives to HRT
 - Progestin-only regimens (medroxyprogesterone acetate 10–30 mg or norethindrone 1–5 mg daily) may help relieve hot flashes in women; effect of long-term therapy on breast cancer risk unknown.
 - Nonhormonal lubricants and/or moisturizers or Estring (vaginal ring with estradiol reservoir that is changed every 90 days – minimal systemic absorption) for the management of urogenital atrophy.
 - Bisphosphonates (e.g., Fosamax) for the prevention or treatment of osteoporosis.
 - Selective estrogen receptor modulators (raloxifene 60 mg po every day) offer bone and cardiovascular benefit without evidence of breast or endometrial stimulation; no effect on hot flashes, small increase in risk of venous thromboembolism.

XIV. HEALTH MAINTENANCE ISSUES (HILLIARD, 1996)

- **Gynecologic evaluation:** annually and as indicated by presence of symptoms, follow-up of ongoing problems, exposure to STIs, development of abnormal Pap smear, or other need for referral based on primary care evaluation
- **Pap smears:** twice within the first year of diagnosis and then annually; more frequent screening indicated with history of abnormal Pap, HPV infection, after treatment for cervical dysplasia, and with symptomatic HIV disease
- **STI screening:**
 - annual syphilis screening or with development of neurologic signs/symptoms

- gonorrhea/chlamydia screening: offer annually at time of routine gynecologic visit, if sexually active; perform as indicated by the presence of relevant symptoms or findings on exam, with recent change in sexual partners, history of STI in sexual partner, periodically as indicated by sexual practices (commercial sex workers, multiple partners, inconsistent use of condoms), or with patient request
- **Mammography:** The American Cancer Society recommends annual mammography beginning at age 40 (Smith, 2003a); women at increased risk (e.g., first-degree relative(s) with breast cancer, BRCA 1 or BRCA 2 mutation) may benefit from earlier initiation of screening or the addition of screening modalities other than mammography, such as ultrasound or MRI. Mammogram should be performed with presence of persistent palpable mass or other suspicious findings on exam
- **Screening for colorectal cancer:** begin screening at age 50 with annual fecal occult blood testing OR flexible sigmoidoscopy every 5 years OR double contrast barium enema every 5 years OR colonoscopy every 10 years; women with colorectal cancer or adenomatous polyp in any first-degree relative before age 60 or in two or more first-degree relatives at any age should have colonoscopy every 5-10 years beginning at age 40 or 10 years before youngest case in immediate family. Women with certain conditions (familial polyposis, personal history of inflammatory bowel disease, adenomatous polyps, or colon cancer) have altered recommendations for screening. Please refer to American Cancer Society Guidelines for the Early Detection of Cancer, 2003 (Smith, 2003b).
- **Osteoporosis prevention:** 1000–1200 mg/day calcium in premenopausal women; 1200–1500 mg/day in postmenopausal women; regular performance of weight-bearing exercise. Periodic bone density screening should be considered in postmenopausal women, in particular those with risk factors for osteoporosis (e.g., Caucasian or Asian race/ethnicity; alcohol abuse; smoking; low body mass index; chronic steroid use). Women are at increased risk for osteoporosis as compared to men, and risk increases after menopause. Recent studies suggest an association between HIV infection and possibly antiretroviral therapy and loss of bone density (Thomas, 2003); therefore, women with HIV may be at additional risk for osteopenia and osteoporosis.
- **Lipid screening:** Assess risk factors for hyperlipidemia at initial visit and periodically: history of cardiovascular, peripheral vascular, or cerebrovascular disease; age >55; family history; smoking; diabetes; hypertension; obesity; physical inactivity. Periodic lipid profile screening based on risk factors, baseline results, and antiretroviral regimen and/or ongoing treatment for hyperlipidemia.

XV. GUIDELINES FOR GYNECOLOGIC REFERRAL

In general, referral to an obstetric-gynecologic specialist should be considered under the following circumstances:

- Uncertain diagnosis with gynecologic condition part of differential diagnosis
- Diagnosis of pregnancy
- Inadequate response to standard treatment regimens for gynecologic conditions
- Possible need for surgical intervention
- A premalignant or malignant condition is suspected

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COLOR PLATES

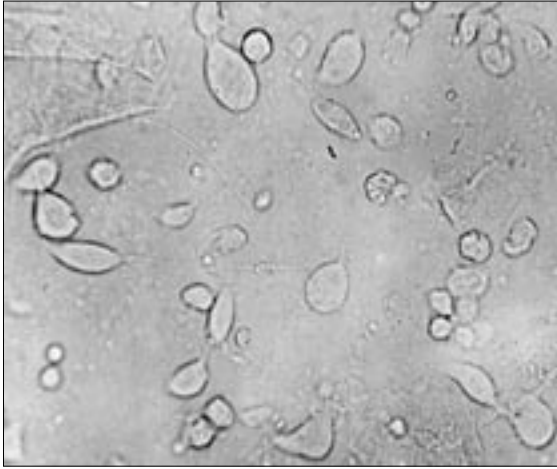


PLATE 1

Trichomonads in a saline wet mount (high power) (Monif, 1982; Fig. 22-2; reprinted with permission from Harper & Row.)

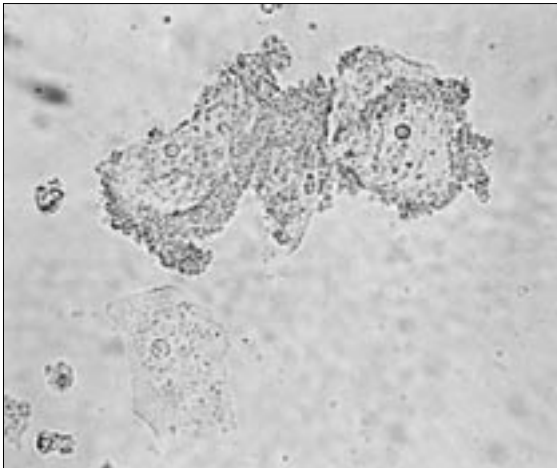


PLATE 2.

Clue cells of *G. vaginalis* vaginitis on a saline wet mount (high power) (Monif, 1982; Fig. 22-3; reprinted with permission from Harper & Row.)

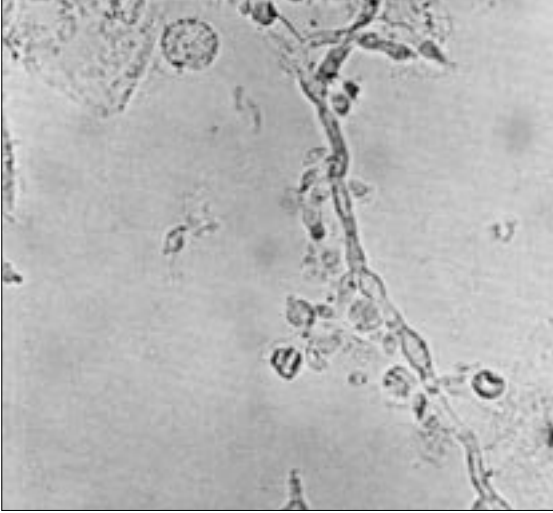
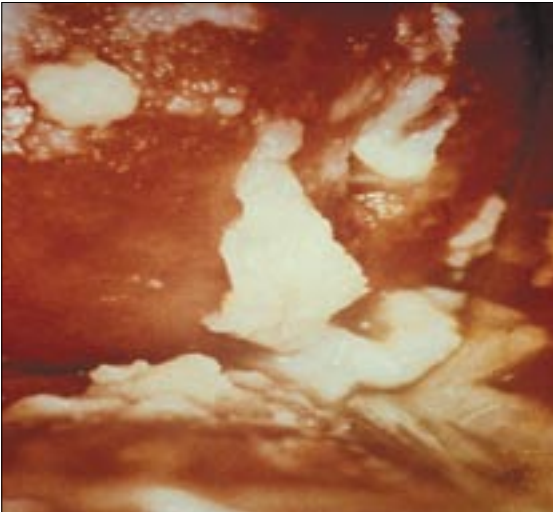


PLATE 3.

Candida in a saline wet mount (high power) (Monif, 1982; Fig. 22-4B; reprinted with permission from Harper & Row.)



COLOR PLATE 4.

Vaginal candidiasis: thrush patches on the vaginal wall of a patient with candidiasis (courtesy J. Anderson, MD).



COLOR PLATE 5.

Severe vulvar intraepithelial neoplasia (VIN3) (Wilkinson and Stone, 1995; Fig 6.27; reprinted with permission from Williams & Wilkins.)



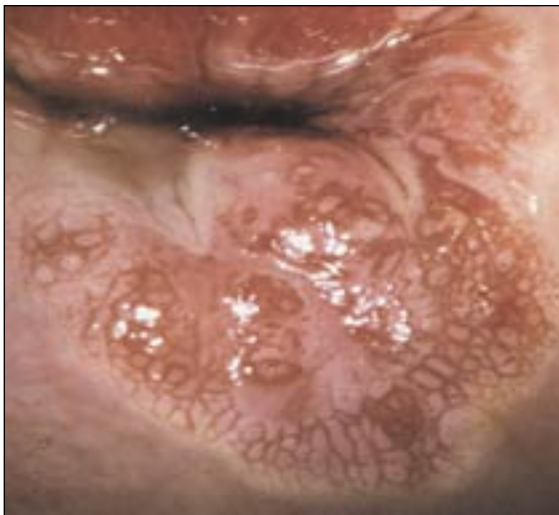
COLOR PLATE 6.

Nontender chancres (kissing lesions) in a woman with primary syphilis (Wilkinson and Stone, 1995; Fig 8.46; reprinted with permission from Williams & Wilkins.)



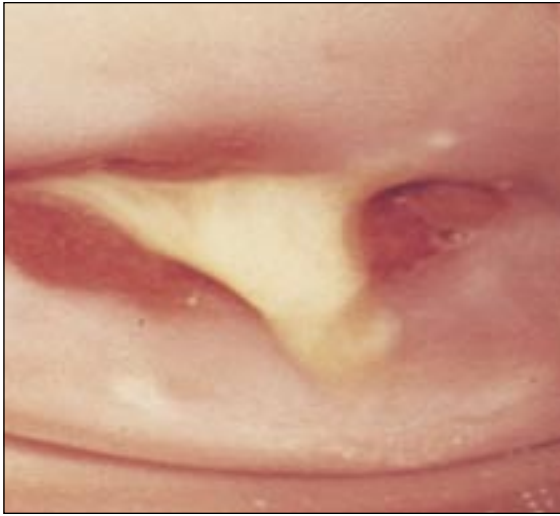
COLOR PLATE 7.

Extensive vulvar condylomata acuminata (human papillomavirus) (Wilkinson and Stone, 1995; Fig 9.3; reprinted with permission from Williams & Wilkins.)



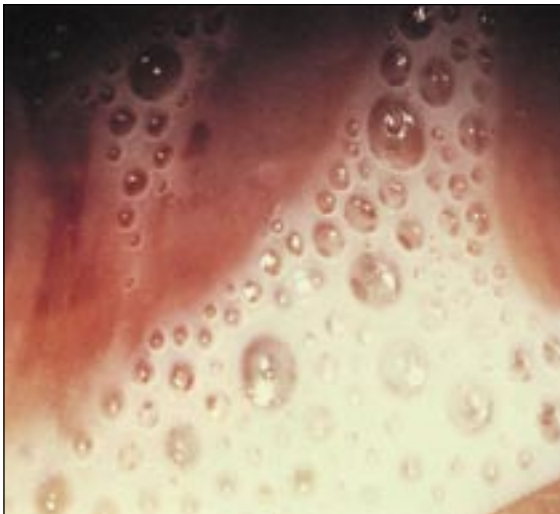
COLOR PLATE 8.

Cervical intraepithelial neoplasia (CIN3) demonstrating coarse mosaicism and punctuation on posterior lip (Burghardt, 1991; Fig. 11.37; reprinted with permission from Thieme Medical Publishers.)



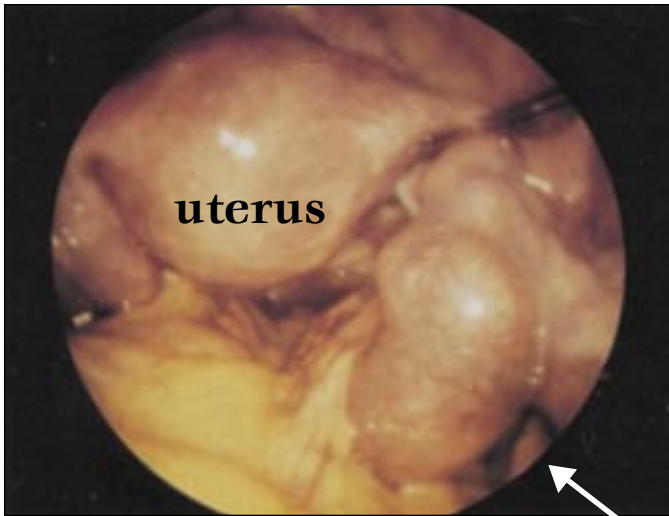
COLOR PLATE 9.

Mucopurulent cervicitis caused by *C. trachomatis* (Holmes, 1999; Plate 16; reprinted with permission from McGraw Hill.)



COLOR PLATE 10.

Profuse purulent frothy vaginal discharge due to trichomonas (Holmes, 1999; Plate 21; reprinted with permission from McGraw Hill.)



COLOR PLATE 11.

Pelvic inflammatory disease, proven chlamydial pyosalpinx. Right tube is swollen and tortuous (arrow) (Holmes, 1999; Plate 17; reprinted with permission from McGraw Hill.)



COLOR PLATE 12.

Chancroid (Holmes, 1999; Plate 32; reprinted with permission from McGraw Hill.)



COLOR PLATE 13.

Condyloma latum in secondary syphilis (Holmes, 1999; Plate 47; reprinted with permission from McGraw Hill.)



COLOR PLATE 14.

Lesion of herpes simplex (courtesy J. Anderson, MD).



COLOR PLATE 15.

Herpes simplex in woman with AIDS, CD4 < 50
(courtesy J. Anderson, MD).



COLOR PLATE 16.

Aphthous genital ulceration (courtesy J. Anderson, MD).



COLOR PLATE 17.

Aphthous oral ulceration (courtesy J. Anderson, MD).

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VII. HIV AND REPRODUCTION

Jean Anderson, MD

I. INTRODUCTION

The ability to become pregnant and to bear children is uniquely female. With increasing numbers of HIV-infected women, 80% of whom are of childbearing age, and concerns about perinatal transmission of HIV, pregnancy in the setting of HIV infection has been a focus of much interest, research, and often discrimination. From 1989 to 1994 it was estimated that 1.5 to 1.7/1000 U.S. childbearing women were HIV-positive (Davis, 1998); however, this number may grow as more women become infected through sexual exposure, often unaware of their risk, and as more women who know they are infected choose to become pregnant because of therapeutic advances in care and prevention of vertical transmission. Almost one-third of HIV-infected men and women receiving medical care in the US desire children in the future (Chen, 2001). Furthermore, 20% of serodiscordant couples would practice unsafe sex in order to conceive (Klein, 2003).

This chapter will review issues related to contraception and pregnancy and will discuss guidelines for care during pregnancy to optimize the health of both the mother and the fetus and infant.

II. COUNSELING

The American College of Obstetricians and Gynecologists (ACOG) advocates reproductive counseling for all women of child bearing age as a part of primary care. For women known to be HIV-infected, education and counseling about pregnancy and HIV should be done early in the course of HIV care, not delayed until the woman is pregnant, so that decisions about contraception and if or when to get pregnant can be most informed and carefully considered. Discussions about pregnancy should be repeated at intervals throughout care, especially when personal circumstances change (e.g. new sexual partner, postpartum); when there is nonuse of effective contraception; where therapies are considered which may have adverse effects in pregnancy; or when the woman expresses a desire to become pregnant. Over one half of pregnancies in U.S. women are unplanned, and many of the risk factors for unintended pregnancy also place women at increased risk for HIV. These include:

- substance abuse (patient or partner)
- mental illness
- domestic violence

Adolescents are at an increased risk of unintended pregnancy and may also be at increased risk for HIV because of frequent unstable sexual relationships and unsafe sexual practices. Women with advanced HIV disease and HIV dementia may be at increased risk for unintended pregnancy if they are dependent on a contraceptive method (such as condom use or oral contraceptives) that requires negotiation with a sexual partner or other ongoing patient action (i.e., remembering to take pills). Issues to discuss when counseling about reproductive issues are listed in Table 7-1.

Table 7-1: HIV and Pregnancy Counseling Issues
• Impact of HIV on pregnancy course/outcome
• Impact of pregnancy on HIV progression
• Other reproductive issues based on maternal factors <ul style="list-style-type: none">- coexisting drug/alcohol use- advanced maternal age- hypertension, diabetes, etc.
• General preconception issues <ul style="list-style-type: none">- nutritional counseling (e.g. folic acid)- importance of early and intense prenatal care
• Long term health of mother and care for children (guardianship issues)
• Perinatal transmission
• Use of antiretrovirals and other medications in pregnancy
• Safe conception if partner HIV-negative

III. CONTRACEPTION

The majority of HIV-infected U.S. women use some form of contraception, most commonly condoms (Wilson, 1999; Watts, 1999). Women using no form of contraception do not necessarily intend to become pregnant but may lack significant power in their sexual relationship, be under pressure from partner or family to have children, may not have disclosed their HIV status to their partner, be unaware of their options concerning contraception or believe they cannot become pregnant, have a disorganized lifestyle that precludes consistent use of contraception, or simply have decided to take their chances. Unplanned also does not necessarily mean unwanted; several studies show low rates of elective pregnancy termination in HIV-positive women (Smits, 1999; Greco, 1999) and no significant difference in repeat pregnancy rates in HIV-positive compared with HIV-negative women from an inner-city population (Lindsay, 1995). Table 7-2 outlines currently available methods of contraception, their effectiveness, side effects and contraindications, and noncontraceptive benefits.

Table 7-2: Contraceptive Methods

Method	Failure Rates (% Pregnancies) in First Year of Typical and Perfect Use		Contraindications	Benefits	Potential Side Effects	Convenience	Disadvantages
	Typical	Perfect					
Hormonal							
Combined oral contraceptive pill (OC)	3	0.1	History of CVD, DVT, stroke; Hypertension; High LDL/HDL ratio; >35 and heavy smoker; Markedly impaired liver function; Hepatocellular adenoma; Headache with focal neurologic symptoms; Diabetes with nephropathy, retinopathy, neuropathy, or vascular disease; Breast cancer; Major surgery with immobilization	Decreased menstrual pain, PMS, and blood loss; May reduce acne; Decreased benign breast disease; Decreased functional ovarian cysts; Decreased ovarian and endometrial cancers; Decreased PID	Nausea; Headache; Weight gain; Dizziness; Breast tenderness; Vaginal spotting; Chloasma; Depression	Use independent from sexual intercourse	No STI protection; May increase susceptibility to some STIs; Must remember to take pill daily
Combined estrogen-progestin injection (Lunelle)	0.03-0.1	0.03-0.1	Same as for OCS	Same as for OCS	Similar to OCS; more spotting/irregular bleeding than with OCS	Use independent from sexual intercourse; Daily action not required	No STI protection; May increase susceptibility for some STIs; Must have IM injection monthly in medical office (5 day "grace" period)
Combined estrogen-progestin vaginal ring (Nuva Ring)	N/A	0.6	Same as for OCS	Same as for OCS	Similar to OCS; possible increased vaginal discharge	Use independent from sexual intercourse; Vaginal ring inserted for 3 wks out of every mo – precise placement not required	No STI protection; May increase susceptibility for some STIs

Table 7-2: Contraceptive Methods (continued)

Method	Failure Rates (% Pregnancies) in First Year of Typical and Perfect Use		Contraindications	Benefits	Potential Side Effects	Convenience	Disadvantages
	Typical	Perfect					
Hormonal (continued)							
Combined estrogen-progestin patch (Ortho Evra)	0.6-0.8 (may be higher with wt > 90kg)	0.6	Same as for OCs	Same as for OCs; improved user compliance	Similar to OCs; Skin irritation	Use independent from sexual intercourse; Patch applied weekly 3 of 4 weeks	No STI protection; May increase susceptibility for some STIs
Depo-medroxyprogesterone acetate (DMPA)	0.3	0.3	Unexplained vaginal bleeding; Breast cancer	Decreased risk of seizures; May have protective effects against PID, ovarian and endometrial cancer; Decreased blood loss; anemia Amenorrhea	Menstrual changes (spotting, irregular bleeding, amenorrhea); Weight gain Breast tenderness; Headache; Adverse effect on lipids; Depression	Often causes amenorrhea; Requires only 4 injections/yr; Requires no ongoing action by user; Use independent from sexual intercourse	No STI protection
Norplant	0.9	0.9	Same as above	Same as above	Tenderness or infection at site; Menstrual changes; Hair loss; Weight gain; Breast tenderness; Depression	Provides 5 yr of contraception; Requires no ongoing action by user; Use independent from sexual intercourse	No STI protection
Progestin-only pill	1.1-13.8	0.5	Same as above	Same as above	Menstrual changes (spotting, irregular bleeding, amenorrhea); Breast tenderness; Depression; Weight gain	Use independent from sexual intercourse	No STI protection; Ectopic pregnancy more likely among progestin-only pills; than other forms of hormonal contraception; Must remember to take pill daily

Barrier Methods									
12	3	Condom, male (latex, polyurethane, natural membrane)	Allergy to condom material	Protects against STIs, including HIV (except for natural membrane). Delays premature ejaculation	Allergy or sensitivity to condom material; Decreased sensitivity	Inexpensive and readily available; Does not require a prescription	Requires partner possible cooperation; Possible loss of spontaneity during sex		
21	5	Condom, female	Polyurethane allergy	Protects against STIs, including HIV	Allergy or sensitivity to polyurethane; Possible decreased sensitivity	Woman controlled; Less likelihood of breakage; Can be inserted up to 8 hr before intercourse; Does not require a prescription	May be awkward to use; Aesthetically unappealing to some		
	limited data								
36/18	26/9	Cervical cap — parous/nonparous	Latex allergy; Abnormal cervical/vaginal anatomy; History of TSS or recurrent UTIs; Known or suspected cervical/uterine malignancy; Abnormal Pap; Vaginal or cervical infection; Recent delivery or spontaneous/induced abortion	Limited STI protection	Pelvic pressure; Vaginal irritation; Allergy or sensitivity to latex; Vaginal or urinary tract infections	Woman controlled; Can be inserted ahead of time	Efficacy based on high motivation; Spermicide re-application required with each act of coitus; Should not be used during menses		
18	6	Diaphragm	Latex allergy; Abnormal vaginal anatomy; History of TSS or recurrent UTIs	Limited STI protection; Reduces risk of PID	Same as above	Woman controlled; Can be inserted up to 6 hr before intercourse	Same as above, except may be used during menses		
21	6	Spermicides	Allergy to nonoxynol-9	Protection against some STIs, significant against gonorrhea/chlamydia; In vitro activity against HIV	Vaginal irritation; Allergy; Vaginal and urinary tract infection	Woman controlled; Does not require a prescription; Easily available and inexpensive	Efficacy reduced when used without a barrier method; May increase susceptibility to HIV with frequent sexual activity; No protection against HIV		
0.8	0.6	IUD (Copper-Paragard)	Recent (within 3 mo) or recurrent pelvic infection; Postpartum, postabortion endometritis; Active STI; Women at increased risk for STIs; Severely distorted uterine cavity	None	Menstrual cramping; Increased bleeding; Risk of PID and uterine perforation following insertion; Anemia	Provides contraception for 10 yrs; Requires no ongoing user action	No STI protection; Increased risk of PID		

Table 7-2: Contraceptive Methods (continued)

Method	Failure Rates (% Pregnancies in First Year of Typical and Perfect Use)		Contraindications	Benefits	Potential Side Effects	Convenience	Disadvantages
	Typical	Perfect					
Levonorgestrel intrauterine system (Mirena)	0.1-0.3	0.1	Same as for Copper IUD	Overall reduction in menstrual blood loss (20% amenorrhea after 1 yr); Possible decreased rates of anemia, PID	Increased incidence of irregular bleeding in 1st 6 mo (compared to Copper IUD); Risk of PID and uterine perforation following insertion	Provides contraception for 5 yr; Requires no ongoing user action	No STI protection
Female surgical sterilization	0.4	0.4	Desire for future fertility; Active pelvic infection	Possible decreased risk of ovarian cancer; Decreased risk of salpingitis	Pain at surgical site; Subsequent regret; Increased risk of ectopic pregnancy if failure	Provides permanent contraception; Requires no ongoing user action	Permanent; No STI protection
Nonsurgical female sterilization (Essure)	0.2-0.4	0.2-0.4	Desire for future fertility; Active pelvic infection	Probably similar to surgical sterilization (experience limited)	Subsequent regret; Increased risk of ectopic pregnancy if failure; Cramping, nausea/vomiting with placement; Expulsion or uterine perforation (<3%)	Provides permanent contraception; Requires no ongoing user action; Lower cost, does not require surgery or general anesthesia as compared to surgical sterilization	Permanent; No STI protection; Requires office procedure for insertion, use of alternate contraception for 3 mo, and hysterosalpingographic confirmation of tubal occlusion
Male sterilization	0.15	0.10	Desire for future fertility	None	Pain at surgical site; Subsequent regret	Provides permanent sterilization for the man	Same as above, except sterility not immediate
Emergency contraception - Levonorgestrel 0.25mg/ Ethinylgestradol 50µg (Preven) - Levonorgestrel 0.75mg (Plan B)	Pregnancy Rate 3.2% (57% expected pregnancies prevented) 1.1% (85% expected pregnancies prevented)		Established pregnancy	None	Nausea and vomiting (less with Plan B); Changes in next menses (generally minor)	Can be used after unprotected intercourse or with other contraceptive "failure" (e.g. condom breakage)	Should be used within 72 hrs of intercourse; No STI protection; Failure rate higher if intercourse during fertile phase of cycle

CVD, cardiovascular disease; DVT, deep vein thrombosis; LDL, low-density lipoprotein; HDL, high-density lipoprotein; PID, pelvic inflammatory disease; PMS, premenstrual syndrome; IUD, intrauterine device; STI, sexually transmitted infection; TSS, toxic shock syndrome; UTI, urinary tract infection. Source: Hatcher, 1998; Johanson, 2004.

Hormonal methods of contraception, particularly combined estrogen-progestin oral contraceptives (OCs), can have significant drug interactions, resulting in either decreased contraceptive effectiveness or increased or decreased concentrations of the coadministered drug. Use of nelfinavir, ritonavir, lopinavir, and nevirapine are associated with decreases in ethinyl estradiol (estrogen component of OCs) with possible decrease in effectiveness (and possible increase in breakthrough bleeding); an alternative or additional method should be used. Indinavir, atazanavir and efavirenz are associated with increases in ethinyl estradiol and indinavir and atazanavir are associated with increases in norethindrone (progestin component in many OCs). Norethindrone levels are increased over 100% with atazanavir. The clinical significance of these increases in hormonal blood levels is unclear, but they raise concerns about potential increase in estrogen- or progestin-related side effects. Alternative methods of contraception should be considered; if OCs are used, lowest effective doses of affected hormonal components should be prescribed and an additional method is recommended. Amprenavir (and probably fos-amprenavir) not only increases blood levels of ethinyl estradiol and norethindrone, but OCs decrease amprenavir levels as well; these drugs should not be coadministered and an alternative contraceptive method should be used. Other medications known to interact with oral contraceptives (and in some cases with progestin-only contraceptives) include tetracyclines, penicillin, oral hypoglycemic agents, rifampin, tricyclic antidepressants, oral anticoagulants, β -blockers, methyldopa, vitamin C, benzodiazepines, and seizure medications. Clinicians treating women who are at risk for drug interactions should review the need for possible use of alternative methods of contraception or dose adjustment for the interacting agent. There is minimal information about drug interactions with use of newer hormonal contraceptive methods (patch, vaginal ring, estrogen-progestin injection).

Concerns have been raised about possible increased risk of HIV transmission or acquisition in hormonal contraceptive users. There is evidence that both combined oral contraceptives and progestin-only contraceptives may increase genital tract HIV shedding; furthermore, oral contraceptives have been associated with increased cervical ectopy, which has also been linked with genital tract HIV shedding. Similarly, ectopy or other epithelial changes secondary to hormonal contraception or associated effects on immune response may increase susceptibility to HIV, and animal studies have suggested a link between progesterone implants and vulnerability to simian immunodeficiency virus (Mostad, 1998; Plummer, 1998). Data from epidemiologic studies are conflicting and inconclusive regarding the relationship of these methods of contraception and HIV transmission (Martin, 1998; Stephenson, 1998; Kiddugavu, 2003; Wang, 1999; Kapiga, 1998). At the current time, given their effectiveness, overall safety, and ease of use, hormonal methods of contraception remain an appropriate option for HIV-infected or at-risk women. These women should be advised that these contraceptives do not protect against HIV transmission and consistent condom use should be emphasized.

Use of the intrauterine device (IUD) has been accompanied by concerns about a potential increased risk for HIV susceptibility. However, a recent large prospective cohort study of almost 2500 HIV-uninfected women found no association between IUD use and HIV transmission; there was also no increased risk associated with increasing duration of use (Kapiga, 1998). Furthermore, another study from Kenya found no increase in overall complications or infection-related complications in HIV-positive IUD users as compared to HIV-negative IUD users and complications did not differ by CD4 count (Morrison, 2001). Use of the IUD was not associated with increased rate of cervical HIV shedding 4 months after insertion over baseline pre-insertion shedding rates (Richardson, 1999). However, risk of pelvic inflammatory disease is increased in IUD users who are at increased risk for acquiring other sexually transmitted infections (STIs) and a recent study found an association between IUD use and bacterial vaginosis, also a risk factor for PID (Joesoef, 2001). Furthermore, copper IUDs are associated with increased menstrual flow and duration, possibly contributing to transmission risk and anemia in HIV-positive women. The IUD should be used cautiously in the setting of HIV infection.

Spermicides have in vitro activity against HIV; however, standard spermicidal doses of nonoxynol-9 (N-9) have been associated with an increase in irritation, colposcopic and histologic evidence of inflammation, and decreased numbers of vaginal lactobacilli in N-9 users, compared with placebo recipients (Stafford, 1998). In a randomized placebo-controlled clinical trial of N-9 conducted among commercial sex workers with high rates of sexual activity, N-9 did not protect against HIV infection, resulted in increased vaginal lesions, and possibly caused increased transmission (Richardson, 2002). Although these adverse effects might not occur with less frequent use, given current evidence, spermicides containing N-9 should not be recommended as an effective means of HIV prevention. A meta-analysis of randomized controlled trials using N-9 also found no evidence of protection against HIV acquisition (Wilkinson, 2002) and N-9 appears to offer no protection against sexually transmitted infections such as gonorrhea or chlamydia (WHO, 2002).

Condoms — used consistently — reduce HIV transmission risk by 80% and provide the best known protection against sexual transmission of HIV. They should be emphasized for all HIV-infected and at-risk women to decrease risk of HIV transmission/acquisition and transmission/acquisition of other STIs. Other barrier contraceptive methods provide limited STI protection and have not been shown to offer significant protection against HIV transmission.

Because male and female condoms are used for both prevention of infection and prevention of pregnancy, these two separate issues should be distinguished when counseling patients. There is some evidence that condom use is less likely in HIV-infected women using other methods of contraception. Condom use should be reinforced for HIV-positive or at-risk women when prevention of pregnancy is not a concern: postmenopausal

women, during pregnancy, despite infertility, and with the use of other methods of contraception. As with use of contraception in general, use of condoms for HIV prevention is related to education, relationship to sexual partner, and chaos in life. There is some indication that use of HAART and decrease in viral load may lead to drop-off in condom use.

IV. PREGNANCY TESTING

Indications for pregnancy testing in currently or recently sexually active women:

- missed menses (unless on Norplant or Depo-Provera)
- irregular bleeding (unless on Norplant or Depo-Provera)
- new onset of irregular bleeding after prolonged amenorrhea on Norplant/Depo-Provera
- new onset pelvic pain
- enlarged uterus or adnexal mass on exam
- consider before instituting new therapies

Pregnancy tests are performed on blood or urine and may be qualitative (positive/negative) or quantitative. Quantitative tests are useful in early pregnancy when ectopic pregnancy or abnormal intrauterine pregnancy (e.g., missed abortion) is suspected. Several qualitative urine pregnancy tests are available over the counter. Most pregnancy tests in current use are positive before the first missed menses with normal intrauterine pregnancy. Table 7-3 lists types of available pregnancy tests and their sensitivity.

	<i>Sensitivity</i>	<i>Comments</i>
Radioimmunoassay - blood	Positive within 7 days of fertilization	Quantitative or qualitative Used to follow women with possible ectopic pregnancy
Enzyme immunoassay - blood - urine	Positive approximately 10 days after fertilization	Available for home urine testing — positive results require confirmation
Antibody agglutination inhibition - urine	Positive approximately 18–21 days after fertilization	False positives may occur with hypothyroidism, renal failure, immunologic disorders, increased luteinizing hormone

V. HIV AND FERTILITY

Recent studies in Africa, as well as in developed countries, have suggested that HIV may have an adverse effect on fertility in both symptomatic and asymptomatic women (Desgrees, 1999; L.M. Lee, 2000; Zaba, 1998). A cross-sectional study from Uganda found likelihood of pregnancy lower in HIV-positive women compared with HIV-negative women and lowest

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in women who were symptomatic from HIV or were coinfecting with syphilis. A prospective study in the same population found that pregnancy rates were lower and pregnancy loss was more common in HIV-infected women (Gray, 1998). There are longer intervals between births for HIV-positive women compared to HIV-negative women (Glynn, 2000) and higher HIV viral loads have been associated with longer times to achieve pregnancy in women trying to conceive (Nguyen, 2003). In addition, both advanced disease stage and HIV-related therapies may be associated with abnormal sperm counts in HIV-infected men and menstrual dysfunction in HIV-infected women.

VI. EFFECTS OF PREGNANCY ON HIV INFECTION

A. CD4 COUNT AND HIV RNA LEVELS IN PREGNANCY

In both HIV-positive and HIV-negative women the response of CD4 cell counts to pregnancy is variable (Tuomala, 1997). Many studies have suggested that there is a decline in absolute CD4 cell counts in pregnancy, which return to baseline at the end of pregnancy or during the postpartum period. The decline in CD4 count is thought secondary to hemodilution; on the other hand, percentage of CD4 cells remains relatively stable. Therefore, percentage, rather than absolute number, may be a more accurate measure of immune function for HIV-infected pregnant women (Brettell, 1995; European Collaborative Study and the Swiss HIV Pregnancy Cohort, 1997; Miotti, 1992). When comparing changes in CD4 count/percentage over time, there is no difference between HIV-positive pregnant and nonpregnant women (O'Sullivan, 1995), suggesting that pregnancy does not accelerate decline in CD4 cells. HIV RNA levels (viral load) remain relatively stable throughout pregnancy in the absence of treatment (Burns, 1998). However, recent data suggest that HIV-RNA levels increase during the postpartum period regardless of ARV treatment (although use of HAART appears to blunt the effect), possibly due to immune activation associated with hormonal changes or to unmasking of a pregnancy-related viral load suppression. The implications for risk of transmission and treatment recommendations in the early postpartum period are unclear (Cao, 1997; Truong, 2003; Watts, 2003). The increase in viral load postpartum does not appear to reflect a long-lasting effect of pregnancy on viral load (Minkoff, 2003).

B. CLINICAL COURSE OF HIV IN PREGNANCY

Most studies to date examining the impact of pregnancy on HIV disease have been small but have not shown significant differences in HIV progression or survival between pregnant women and nonpregnant women with HIV infection. A recent meta-analysis of seven prospective cohort studies found no overall significant differences in death, HIV disease progression, progression to an AIDS-defining illness, or fall in CD4 count to below 200/mm³ between cases and controls (French,

1998). A subsequently reported prospective study of 331 women with known dates of seroconversion were followed for a median of 5.5 years; during this time 69 women were pregnant. There were no differences in progression between those who were and were not pregnant during follow-up (Alliegro, 1997). In addition, a long-term observational study showed no difference in viral load, CD4, or clinical disease progression in women with repeat pregnancy, compared to those with only one pregnancy (Minkoff, 2003).

VII. EFFECT OF HIV ON PREGNANCY COURSE AND OUTCOME

Adverse pregnancy outcomes may occur secondary to underlying disease processes (or their treatment), as well as for unknown reasons. Approximately 10% of U.S. pregnancies end prematurely, and preterm birth is the leading cause of perinatal morbidity and mortality. Data have accumulated that HIV, especially when more advanced, may result in increases in certain pregnancy complications. However, results of studies are conflicting. Some studies suggest that HIV-infected women have an increase in other risk factors for adverse pregnancy outcome (such as smoking, drug use, poor prenatal care) and if these risk factors are controlled for, there is no independent effect of HIV on adverse outcomes (Lambert, 2000). Furthermore, concerns have been raised that antiretroviral treatment itself may increase some adverse outcomes in pregnancy (see discussion under Antiretroviral Treatment). A recent study of 497 HIV-infected pregnant women enrolled in a perinatal clinical trial found that risk factors for adverse pregnancy outcomes (preterm birth, low birth weight, and intrauterine growth retardation) in antiretroviral-treated women are similar to those reported for uninfected women (Lambert, 2000). Table 7-4 summarizes the relationship between common pregnancy-related complications and HIV (Brocklehurst, 1998a; D'Ubaldo, 1998; van Bentham, 2000; Ngweshemi, 2003; Dreyfuss, 2003; Coley, 2001; Ladner, 1998).

Both HIV and pregnancy may affect the natural history, presentation, treatment, or significance of certain infections, and these, in turn, may be associated with pregnancy complications or perinatal infection.

A. VULVOVAGINAL CANDIDIASIS

Pregnancy is associated with both increased rates of colonization and an increase in symptomatic infections with species of *Candida*. HIV infection is also associated with an increase in colonization and possible increased infection rates, especially with declining immune function (Burns, 1997; Cu-Uvin, 1999; Duerr, 1997; Schuman, 1998; Spinillo, 1994). Therefore, pregnant women with HIV infection may be particularly susceptible to yeast infections. Only topical azole agents should be used during pregnancy and should be given for at least 7 days. Prophylactic topical therapy should be considered during courses of systemic, especially broad-spectrum, antibiotics.

<i>Adverse Pregnancy Outcome</i>	<i>Relationship to HIV Infection</i>
Spontaneous abortion	evidence of possible increased risk
Stillbirth	evidence of increased risk in developing countries
Perinatal/infant mortality	evidence of increased risk in developing countries
Intrauterine growth restriction	evidence of possible increased risk
Low birth weight (<2500 g)	evidence of possible increased risk, especially with more advanced disease
Preterm delivery	evidence of possible increased risk, especially with more advanced disease
Preeclampsia	no data
Gestational diabetes	no data
Placental abruption	no data
Placenta previa	no data
Chorioamnionitis	most recent studies do not suggest an increased risk in clinical or histologic chorioamnionitis; however, evidence of possible increased risk in developing countries
Oligohydramnios	no data
Group B strep infection	no data
Fetal malformation	no evidence of increased risk

B. BACTERIAL VAGINOSIS

Bacterial vaginosis (BV) has been associated with several adverse pregnancy outcomes, including preterm labor and birth, premature rupture of membranes, low-birth-weight infants, chorioamnionitis and amniotic fluid infection, postpartum and postabortal endometritis, and perinatal HIV transmission. HIV infection has been associated with increased prevalence and persistence of BV, and prevalence, persistence, and severity increase with lower CD4 cell counts (Jamieson, 2001). If BV is diagnosed during pregnancy, preferred therapies are metronidazole 250 mg po tid x 7 days or clindamycin 300 mg po bid x 7 days, since only oral agents have been shown to reduce preterm births in women with BV (Hauth, 1995; McGregor, 1995; Morales, 1994). Because BV is more common in the setting of HIV, and because both BV and HIV have been linked to increased risk of preterm birth, pregnant women with HIV should be regularly asked about signs or symptoms of vaginal infection and, if present, evaluated for possible BV. Infection should be treated if identified. Currently, there are insufficient data to suggest that screening for and treating BV during pregnancy in the general population reduces the overall rate of preterm birth (Berg, 2001). A recent meta-analysis (Caro-Paton, 1997) found no relationship between metronidazole exposure during the first trimester of pregnancy and birth defects.

C. GENITAL HERPES SIMPLEX

Primary herpes simplex virus (HSV) infection during pregnancy has been associated with spontaneous abortion and prematurity. Congenital or intrauterine infection is uncommon but maternal HSV shedding at delivery is associated with neonatal HSV infection, which is almost always symptomatic (including skin, eye, and central nervous system involvement, or disseminated infection involving multiple organ systems) and frequently lethal. The risk of neonatal herpes is greatest with primary HSV, especially when acquired close to delivery (30–50%), whereas only 0–3% of neonates become infected with recurrent maternal disease at delivery; however, because recurrent HSV is more common than primary disease, most neonatal infections are associated with recurrent HSV. Two thirds or more of mothers with infected infants are asymptomatic during pregnancy; only one third have a history of HSV in themselves or their sexual partner. Because most neonatal infection occurs during vaginal delivery, if genital lesions or prodromal symptoms are present at the time of labor or membrane rupture, cesarean section should be performed. Cesarean section is not indicated for recurrent HSV distant from the genital tract (e.g., thigh, buttocks) (ACOG, 1999b).

HIV infection, particularly with evolving immune compromise and higher plasma HIV viral load (Wright, 2003), is associated with increased HSV shedding and more frequent, severe, and prolonged episodes of genital or perianal herpes (Augenbraun, 1995). Higher doses and/or longer courses of antiviral agents may be required and suppressive therapy is often beneficial in nonpregnant individuals. Infection with HSV-2 is common among pregnant HIV-infected women and reactivation of herpes in labor occurs more frequently in the setting of HIV infection (Hitti, 1997).

Treatment of symptomatic HSV infections and suppressive therapy for frequent recurrences should be offered during pregnancy to HIV-infected women (USPHS/IDSA, 2003). The risk for herpes is high in infants of women who acquire genital HSV in late pregnancy and such women should be managed in consultation with an expert. The use of oral acyclovir prophylactically in late pregnancy has been shown to suppress genital HSV outbreaks and HSV shedding in HIV- women and may reduce the need for cesarean section for recurrent HSV (Brocklehurst, 1998a; Watts, 2001; Scott, 2001); however, this strategy has not been evaluated in HIV + women, who are more likely to have HSV-2 antibodies and to have both symptomatic and asymptomatic reactivation of genital HSV. Therefore, use of acyclovir for the purpose of reducing the need for cesarean section in all HIV + women is not recommended (USPHS/IDSA, 2003).

Acyclovir is the drug of choice for HSV therapy during pregnancy and there is no current evidence for increased risk for major birth defects or other adverse pregnancy outcomes (Reiff-Eldridge, 2000). While experience with valacyclovir is more limited, its safety profile is expected to be similar to acyclovir, since it is the prodrug of acyclovir. Experience with use of famciclovir in pregnancy is limited and exposures to this

drug should be reported to the Famciclovir Registry at 1-888-669-6682. Documented HSV infections during pregnancy which do not respond to these agents should be managed with expert consultation.

Prevention of neonatal herpes should also emphasize prevention of acquisition of herpes in susceptible women in pregnancy. If her sexual partner has a history of oral or genital HSV infection, serologic evidence of HSV infection, or infection status is unknown, the pregnant woman should be counseled to avoid unprotected genital and oral sexual contact during pregnancy. Type-specific HSV serology may be useful to identify the pregnant woman at risk for HSV and to guide counseling, especially if her sexual partner has HSV infection. At the onset of labor, all women should be questioned carefully about HSV symptoms, including prodromal symptoms, and all women should be examined carefully for herpetic lesions, in order to make judicious decisions about the use of cesarean section.

D. HUMAN PAPILLOMAVIRUS

Genital warts may be more frequently seen and often enlarge and become friable during pregnancy and in some cases may mechanically obstruct the vaginal canal in labor; perinatal exposure can result in laryngeal papillomatosis in infants and children, although a recent prospective study suggests that the risk of perinatal transmission of human papillomavirus (HPV) is low (Watts, 1998). Both HPV infection in general and genital warts are more common in HIV-infected individuals, correlated with level of immunosuppression. Imiquimod, podophyllin, and podofilox should not be used in pregnancy. In women with large volume or bulk of genital warts treatment in late pregnancy with laser, excision, or cavitronic ultrasonic aspiration may be considered. Cesarean section is not currently recommended to prevent neonatal exposure to HPV, although in rare instances cesarean section may be indicated when extensive lesions obstruct the vagina. Pregnant women with abnormal Pap smears should undergo colposcopy and cervical biopsy, if indicated; increased bleeding may occur with biopsy during pregnancy. Endocervical curettage should not be performed during pregnancy. Pap smear should be repeated with or without colposcopy at 34–36 weeks gestation in women with initial abnormal Pap smear to rule out progression of dysplasia. Women with preinvasive cervical lesions can deliver vaginally, if otherwise appropriate; women with suspected invasive cervical cancer should be referred to a gynecologic oncologist.

E. SYPHILIS

Syphilis is more prevalent in HIV-infected populations and HIV may affect clinical manifestations, serologic response, or response to treatment for syphilis. Pregnancy does not alter the clinical manifestations of syphilis but untreated primary or secondary syphilis during pregnancy affects essentially all fetuses, with 50% rate of prematurity, stillbirth, or neonatal death (Radolf, 1999). Even with later stages of syphilis, there

is a significant increase in adverse pregnancy outcomes, although the frequency and severity of fetal disease decrease with longer duration of untreated maternal infection. Manifestations of congenital syphilis in the newborn include mucocutaneous lesions, hepatosplenomegaly, osteochondritis/periostitis, jaundice, petechiae/purpura, and meningitis.

Congenital syphilis can generally be prevented by identification and appropriate treatment of syphilis during pregnancy. All pregnant women should have serologic testing for syphilis at the beginning of prenatal care and testing should be repeated at 28 wk gestation and at delivery, particularly in women who remain at risk for infection. Any woman with stillbirth after 20 wk gestation should be tested for syphilis. Development of neurologic symptoms mandates evaluation for possible neurosyphilis. Treatment of syphilis during pregnancy should be the penicillin regimen appropriate for the stage of syphilis, although a second injection one week after the first in cases of primary, secondary, or early latent syphilis should be considered, because of concerns about effectiveness of standard therapy in pregnant women and in the setting of HIV infection (USPHS/IDSA, 2003). HIV-positive women with late latent syphilis or syphilis of unknown duration should have cerebrospinal fluid examination before treatment. If there is concern for neurosyphilis, treatment should be with 7–10 days of IV penicillin (CDC, 2002).

Ultrasound evidence of hydrops or hepatosplenomegaly suggesting fetal syphilis increases risk for treatment failure and should be managed with expert consultation. Treatment in the second half of pregnancy is associated with the Jarisch-Herxheimer reaction in up to 40% of cases, with resulting premature labor and/or fetal distress (Myles, 1998); fetal and contraction monitoring for 24 hrs should be considered, especially in the setting of abnormal ultrasound findings, or, alternatively, patients should be advised to seek immediate attention after treatment if contractions or decrease in fetal movements occur (USPHS/IDSA, 2003). Pregnant women with a history of penicillin allergy should be skin tested and, if necessary, desensitized and treated with penicillin, because there are no proven effective alternatives to penicillin for treatment and prevention of congenital syphilis. Even with appropriate treatment of the pregnant woman with syphilis, fetal infection may still occur and neonates should be carefully evaluated for evidence of congenital infection.

Clinical and serologic follow-up should be performed in the third trimester and at delivery and at 3, 6, 9, 12, and 24 mo after treatment. Treatment failure should be managed with cerebrospinal fluid examination and retreatment. Some experts recommend monthly serologic testing after treatment after pregnancy with retreatment if there is a rise in titer.

F. CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is the most common cause of congenital viral infection in the United States: .2–2.2% of liveborn infants acquire this infection perinatally (ACOG, 1993a). Most maternal CMV infections are asymptomatic but may cause a mononucleosis-like illness. Transmission

can occur sexually or with injection drug use, because CMV has been recovered from virtually all body fluids. Transmission can also occur with oral contact with infected secretions (i.e. from children). Transmission of CMV from mother to infant may occur in utero (1–2% of infants born to women with CMV prior to pregnancy and up to 50% of infants born to women with primary infection during pregnancy), intrapartum (25–50% of exposed infants), and through breastfeeding (40–60% of exposed infants) (USPHS/IDSA, 2003). In general, it is in utero infection that results in significant neonatal/infant effects. Ninety percent of infected infants are asymptomatic at birth, but symptomatic infection is more likely with maternal infection acquired early in pregnancy. Even if asymptomatic, many infected infants subsequently develop deafness, mental retardation, or delayed psychomotor development. More severe clinical manifestations include symmetric growth restriction, hepatosplenomegaly, chorioretinitis, microphthalmia, hydrocephaly, microcephaly, and cerebral calcifications.

In the setting of HIV infection, in utero infection was detected in 4.5% of infants, compared to 1–2% transmission noted in previous studies of CMV-seropositive HIV-negative women. By six months of age, 40% of HIV-infected infants were CMV-seropositive compared to 15% of HIV-uninfected infants born to HIV-infected mothers (Kovacs, 1999). Because symptomatic infection in the newborn is usually associated with primary CMV infection of the mother during pregnancy, and because >90% of HIV-infected pregnant women are CMV seropositive in most studies, the risk of symptomatic infection in the newborn is low (Kovacs, 1999; Mussi-Pinhata, 1998; Quinn, 1987), and treatment of asymptomatic maternal CMV infection in order to prevent infant infection is not indicated (USPHS/IDSA, 2003). There have been some reports that cotransmission of HIV and CMV may be related to more rapid HIV progression (Kovacs, 1999; Mussi-Pinhata, 1998).

Testing for antibody to CMV should be considered in pregnancy, especially if the CD4 count is $<100/\text{mm}^3$ for reasons of maternal health evaluation; however, seropositivity is common and does not preclude viral shedding during pregnancy and perinatal transmission. Methods to reduce risk of exposure to CMV include safer sexual practices, careful handwashing, and transmission of only CMV antibody-negative blood products. Primary prophylaxis is not routinely recommended; however, after CMV disease (retinal or invasive CMV disease), chronic suppression is indicated in pregnancy and should be continued with expert consultation concerning choice of agents. (See Opportunistic Infection Prophylaxis below.)

G. TOXOPLASMOSIS

Approximately one third of U.S. women have toxoplasma antibodies, reflecting prior infection. Primary infection occurs in approximately .1–.5% of pregnancies and places the fetus at risk for congenital toxoplasmosis. Congenital infection is more common when infection in the mother occurs during the third trimester (59% in third trimester vs. 9% in first trimester)

but is generally more severe when occurring in the first trimester. Although the majority of infected infants are asymptomatic at birth, most will develop some sequelae of congenital toxoplasmosis; two thirds of infants infected after maternal first trimester infection have severe manifestations and 5% are stillborn or die in the perinatal period (ACOG, 1993a).

Congenital toxoplasmosis may affect all systems, but the most common findings are chorioretinitis, microcephaly, hydrocephaly, and cerebral calcifications.

Transmission of toxoplasmosis from a mother with antibody evidence of prior infection can occur in the setting of HIV infection (as opposed to in HIV-uninfected women), but does not seem to be common (0–3.7% in two studies), although there are limited data in more immunosuppressed mothers (European Collaborative Study and Research Network in Congenital Toxoplasmosis, 1996; Minkoff, 1997b).

Testing for IgG antibodies to toxoplasma is recommended for all HIV-infected individuals soon after the diagnosis of HIV is made and should be considered as part of prenatal testing in HIV-positive pregnant women. Primary prophylaxis and prophylaxis against recurrent disease in pregnancy are discussed below (See Opportunistic Infection Prophylaxis). Pregnant women with symptoms including fever, chills, malaise, lymphadenopathy, myalgias, and headache should be evaluated serologically for possible primary toxoplasmic infection. Evidence of primary infection or active toxoplasmosis should be evaluated and managed with expert consultation. Detailed ultrasound examination of the fetus should be performed in this situation to look for evidence of congenital toxoplasmosis. Infants born to women infected with HIV and seropositive for toxoplasma should also be evaluated for evidence of congenital toxoplasmosis if suspected by clinical presentation of the infant.

To prevent exposure to toxoplasmosis, pregnant women should be counseled to avoid raw or undercooked meat, wash hands after contact with raw meat or with soil, and wash fruits and vegetables well before eating them raw. Cats should preferably be kept inside and fed only canned or dried commercial food; litter boxes should be changed daily, preferably by someone who is not HIV-positive or pregnant.

H. HEPATITIS B

Approximately 300,000 new cases of hepatitis B virus (HBV) infection occur each year and more than 1 million Americans are chronic carriers. Most patients who become infected have complete resolution of infection and develop protective levels of antibody (anti-HBs). Chronic HBV infection develops in 1–6% of persons who are infected as adults; they are chronically HBsAg+ and are at risk of chronic liver disease, including cirrhosis and hepatocellular carcinoma (CDC, 1991). The presence of HBeAg indicates active viral replication and increased infectivity. HBV is transmitted parenterally, sexually, perinatally, and through household or institutional contact. Approximately one quarter of

regular sexual contacts of infected individuals will become seropositive and sexual transmission accounts for 30–60% of new infections. Perinatal transmission, usually with intrapartum contact with maternal blood and genital secretions, occurs in 10–20% of women who are HBsAg+, but increases to approximately 90% if the mother is also HBeAg+. Chronic HBV infection develops in about 90% of infected newborns, who are at high risk of chronic liver disease (ACOG, 1998).

All pregnant women should be screened for HBsAg. Symptomatic acute HBV infection should be treated supportively, with special attention to maintaining blood glucose levels and clotting function. Risk of preterm labor and birth may be increased with acute HBV infection in pregnancy. Treatment of chronic HBV infection is generally not indicated in pregnancy. Antiretroviral therapy containing lamivudine (3TC) may potentially decrease risk of perinatal HBV transmission in women with high HBV DNA levels, although this has not been examined in the setting of HIV infection.

Infants born to women who are HBsAg+ should receive hepatitis B immune globulin and initiate HBV vaccination within 12 hr after birth. HBV vaccine can be safely administered during pregnancy and should be considered in women who are high risk (injection drug use, STIs, multiple sexual partners, household or sexual contact of HBV carrier) and are anti-HBs- or anti-HBc-negative, indicating susceptibility. Some experts argue for more liberal use of vaccination in HIV-infected individuals, because HBV infection in the setting of HIV infection increases risk for chronic HBV infection. HIV can impair response to HBV vaccine; therefore, testing for hepatitis B surface antibody is recommended 1–2 mo after the third vaccine dose. Full revaccination should be considered for those who are nonresponders (ACOG, 1998; Bartlett, 1999).

I. HEPATITIS C

Hepatitis C virus (HCV) infection is primarily transmitted by injection drug use, but may also be transmitted sexually. Approximately 50% of those with acute HCV infection develop biochemical evidence of chronic liver disease, and 20% or more ultimately have chronic active hepatitis or cirrhosis and are at risk for hepatocellular carcinoma (CDC, 1998). Coinfection with HIV increases the risk and speeds the rate of development of progressive liver disease (Graham, 2001; Soto, 1997). Cofactors influencing disease progression include age, low CD4 cell count, and history of alcoholism. There is evidence that HCV infection may also hasten progression of HIV infection (Piroth, 2000).

Women newly diagnosed with HIV in pregnancy should have testing for antibody to HCV by enzyme immunoassay; positive results should be confirmed with HCV polymerase chain reaction (PCR) and liver function abnormalities should be documented. Negative serologic screening associated with history of risk factors for HCV transmission or unexplained liver function abnormalities is an indication for performance of HCV viral RNA testing, especially with low CD4 cell counts. Studies

have shown that serum transaminases tend to decrease during pregnancy in HCV-infected women, but may rise transiently postpartum, while HCV-RNA levels tend to increase during pregnancy (Gervais, 2000; Conte, 2000). Treatment of HCV infection aims to eradicate infection and prevent the long-term complications of progressive liver disease and generally includes combination therapy with interferon plus ribavirin. However, treatment is generally not recommended during pregnancy (USPHS/IDSA, 2003) and evaluation for treatment, including liver biopsy, can be delayed until three months or more after delivery to allow pregnancy-related changes in disease activity to resolve. Ribavirin is teratogenic at low doses in multiple animal species and both women and men of childbearing potential receiving ribavirin should be counseled regarding the need for effective contraception during and for six months after completion of therapy.

Women coinfecting with HIV and HCV should avoid alcohol, both during and after pregnancy, because alcohol use increases risk of cirrhosis. Vaccination against hepatitis A, if the woman is anti-HAV-negative, is recommended because the risk for fulminant hepatitis associated with hepatitis A is increased in HCV-infected individuals; this vaccination may be given safely during pregnancy (ACOG, 1998; Bartlett, 1999).

The risk of perinatal transmission of HCV is significantly higher among HIV-infected compared to HIV-uninfected women and has been reported to be approximately 22% or an increase in relative risk of 1.7–7.5-fold (European Paediatric Hepatitis C Virus Network, 2001). This may be related to higher HCV RNA levels seen in the setting of HIV infection, since perinatal transmission in both HIV-infected and –uninfected women is related to higher plasma HCV RNA levels (Yeung, 2001), although HCV transmission is highest with higher HCV RNA levels in the setting of HIV (Thomas, 1998). Furthermore, maternal coinfection with HIV and HCV may also increase risk for perinatal HIV transmission (Hershow, 1997). Scheduled cesarean section may reduce the risk of HCV transmission among HIV-coinfecting women; in one large study scheduled C-section was associated with a reduction in transmission of almost two-thirds compared to other modes of delivery, although concomitant mother-to-child transmission of HIV was not controlled for (European Paediatric Hepatitis C Virus Network, 2001). Perinatal HCV transmission may be more likely in HIV-infected infants born to dually infected mothers (Papaevangelou, 1998).

VIII. PERINATAL TRANSMISSION

The baseline rate of perinatal HIV transmission without prophylactic therapy is approximately 25%. The timing of transmission is a critical factor impacting on development of preventive interventions. There is evidence that transmission can occur during the course of pregnancy, around the time of labor and delivery, or postpartum through breast-feeding; however, two thirds to three quarters of transmission appears to occur during or close to the intrapartum period, particularly in non-breast-feeding populations (Mofenson, 1997).

POTENTIAL VARIABLES IN TRANSMISSION

A. HIV-RELATED FACTORS

- **Plasma HIV RNA level:** HIV RNA levels correlate with risk of transmission in both antiretroviral-treated and untreated women. The risk of perinatal transmission appears to be extremely low in women with undetectable plasma viral loads, but transmission has been reported at all levels of maternal HIV RNA. There is no upper limit of HIV RNA above which perinatal transmission always occurs (Garcia, 1999; Mofenson, 1999; Shaffer, 1999; Cooper, 2002).
- **Strain variation (genotype):** Each HIV-infected individual's viral pool is composed of a variety of HIV quasiespecies. One recent study found that in utero transmission was associated with transmission of major maternal viral variants, whereas intrapartum transmission was associated with transmission of minor maternal viral variants, suggesting that different selective pressures may be involved in determining the pattern of viral strain transmission depending on timing of transmission (Dickover, 2000). HIV in vaginal secretions can be derived from local expression and may have significant genotypic differences from plasma virus, with possible implications for perinatal transmission (Subbarao, 1998).
- **Biologic growth characteristics (phenotype):** Fetal blood mononuclear cells may be more susceptible to macrophage-tropic, non-syncytium-inducing HIV phenotypes and this may influence mother-to-infant HIV transmission (Palasanthiran, 1994; Reinhardt, 1995).
- **Genital tract viral load:** There is general correlation between plasma and genital tract viral load but discordance has been reported and may help explain some cases of transmission with undetectable plasma HIV RNA. In the Thai short-course zidovudine (ZDV) clinical trial, both plasma and cervicovaginal HIV RNA levels were suppressed by ZDV treatment and both were independently correlated with transmission (Chuachoowong, 2000). The female genital tract can also be a reservoir for virus with a different drug-resistance pattern than that observed in plasma (Fang, 1998). The use of HAART has been associated with undetectable HIV RNA levels in the genital tract and viral suppression in the genital tract may occur rapidly after initiating therapy (Cu-Uvin, 2000). It is possible that intra-cellular HIV in the genital tract can lead to transmission, even in the presence of antiretroviral treatment (Tuomala, 2003).
- **Antiretroviral resistance:** Special concerns have been raised about a possible increased risk for mother-to-child transmission associated with the potential development of antiretroviral resistance related to the use of single agents (i.e., ZDV or nevirapine) or dual nucleosides during pregnancy for perinatal prophylaxis. These regimens do not totally suppress viral replication, a common denominator in the development

of antiretroviral drug resistance, since the process of reverse transcription necessary for viral replication is mutation prone. In addition, the increasing prevalence of resistance in both ARV treatment-experienced and newly-infected and treatment-naïve individuals (implying transmission of resistant strains) makes the relationship between drug resistance and perinatal transmission even more critical to understand.

The presence of resistance mutations has been described in pregnant women and mother-to-child transmission of resistant virus has been reported, although it appears to be rare (Frenkel 1995; Johnson 2001). Studies to date of resistance mutations in the setting of ZDV monotherapy during pregnancy have shown increasing prevalence of ZDV mutations over time and an association with length of drug exposure and more advanced disease (Eastman, 1998; Welles, 2000; Sitnitskaya, 2001; Palumbo, 1999). Most studies, including PACTG 076, PACTG 185, Swiss cohort, or the PACTS, have not shown an increased risk of perinatal transmission associated with the detection of ZDV or other resistance mutations (Eastman, 1998; Kully, 1999; Palumbo 1999; Mofenson, 2002). However, in a recent Women and Infants Transmission Study (WITS) substudy, 25% of 142 maternal isolates from women receiving ZDV in pregnancy had at least one ZDV-associated resistance mutation and, on multivariate analysis, the presence of resistance mutations was independently associated with perinatal transmission (Welles, 2000). It has been pointed out that the characteristics of women in this cohort (mean CD4 count at delivery 315 cells/mL, usually did not receive ZDV in labor or for the neonate) and the factors associated with development of resistance (use of ZDV prior to pregnancy, higher HIV-RNA level, and lower CD4 count) illustrate the importance of current USPHS guidelines (discussed under Antiretroviral Therapy below) which advise the use of HAART in these circumstances, both for the woman's health and for prophylaxis against perinatal transmission. There is also some evidence that ARV-resistant virus may have decreased fitness for transmission; in the WITS substudy, when a transmitting mother had a mixed viral population of wild-type and low-level resistant virus, only the wild-type virus was found in the infant, suggesting that virus with low-level ZDV resistance may be less transmissible (Colgrove, 1998).

Selection of nevirapine-resistant virus has also been detected in women who received a single dose of nevirapine for prevention of perinatal transmission. In the HIVNET 012 clinical trial, ARV-naïve Ugandan women received one dose of nevirapine during labor and in 111 women who had detectable viral replication, 21 (19%) had genotypic mutations associated with nevirapine resistance at 6 weeks (Eshleman, 2001). However, maternal drug resistance was not associated with increased risk of perinatal transmission: rates of resistance were similar among mothers whose children were or were not infected.

- **CD4 cell count:** Lower CD4 count or decreased CD4:CD8 ratio have been consistently associated with increased risk of transmission.
- **Maternal immune response:** Studies have been inconsistent when evaluating the role of maternal antibodies, including anti-gp120, anti-gp41, anti-p24, and autologous neutralizing antibody titers. β -chemokine and cytokine responses may affect risk of transmission (Pitt, 2000; Rich, 1998).

B. MATERNAL/OBSTETRIC FACTORS

- **Clinical stage:** Maternal symptomatic disease or AIDS-defining illness are consistently associated with higher risk for transmission. Women with primary HIV infection in pregnancy, at which time plasma viremia is high, are also at increased risk for transmission (Nesheim, 1996).
- **STIs/other coinfections:** STIs have been shown to increase genital tract HIV shedding and also increase plasma viremia (Plummer, 1998), both of which may increase risk for perinatal transmission. STIs (Mandelbrot, 1996), syphilis (M.J. Lee, 1998), bacterial vaginosis (Taha, 1998), and placental malaria have been associated with increased risk for vertical transmission, as have increased levels of genital tract inflammatory cells (Panther, 2000; Chandramohan, 1998).
- **Vitamin A deficiency:** Vitamin A deficiency has been associated with increased risk of perinatal HIV transmission and increased genital tract HIV shedding (Nimmagadda, 1998). However, a recent randomized trial of vitamin A supplementation in South Africa found no overall reduction in mother-to-child transmission of HIV, although vitamin A recipients were less likely to have a preterm delivery, and in preterm deliveries, those infants assigned to the vitamin A group were less likely to be infected (Coutsoudis, 1999). A controlled clinical trial in Malawi of vitamin A supplementation combined with iron and folate vs iron and folate alone also found no effect on HIV perinatal transmission (Kumwenda 2002), although vitamin A did improve pregnancy outcome (increased birth weight and decreased infant anemia). In another randomized trial of vitamin A or multivitamins (B, C, E) from 20 weeks gestation through completion of lactation, vitamin A was actually associated with increased risk of HIV MTCT. Multivitamin supplementation was associated with reduced child mortality and MTCT through breastfeeding among women with immunologic or nutritional compromise (Fawzi, 2002)
- **Substance abuse:** Illicit drug use during pregnancy has been associated with increased risk for perinatal transmission (Landesman, 1996; Lyman, 1993; Rodriguez, 1996).

- **Cigarette smoking:** Cigarette smoking has been associated with an increased risk of perinatal transmission (Burns, 1994; Turner, 1997).
- **Antiretroviral therapy:** Monotherapy with ZDV or with nevirapine, as well as dual nucleoside agents, have demonstrated effectiveness in reducing perinatal transmission in randomized clinical trials (see page 284 Table 7-8). In the PACTG 076 study (ZDV given antepartum/intrapartum/neonatal), reduction in plasma viral load accounted for only 17% of ZDV's effectiveness, suggesting pre- and/or post-exposure prophylaxis as other possible mechanisms of action (Sperling, 1996). Although there are no completed clinical trials examining effectiveness of HAART regimens in reducing perinatal transmission, prospective cohort data from the WITS found that the protective effect of antiretroviral therapy increased with the complexity and duration of the regimen, and the use of HAART was associated with the lowest rates of transmission, 1.2% of 250 women (Cooper, 2002). Preliminary results from the PACTG 367 study, a combined retrospective and prospective chart analysis of over 2000 HIV-infected pregnant women at 67 U.S. clinical sites, found that in all subgroups of viral load, lowest transmission rates were seen with multiagent ARV therapy (Shapiro, 2004), both dual therapy and HAART.
- **Sexual behavior:** Unprotected sex with multiple partners has been associated with increased risk for perinatal transmission (Bulterys, 1997).
- **Preterm delivery:** Delivery at preterm gestational age has been associated with increased risk for perinatal transmission (Kuhn, 1997, 1999).
- **Duration of membrane rupture:** A recent metaanalysis from 15 prospective cohort studies, including almost 5000 deliveries, examined the role of duration of ruptured membranes in perinatal transmission (International Perinatal HIV Group, 2001). The likelihood of transmission increased linearly with increasing duration of ruptured membranes, with a 2% increase in risk for each hour increment. Women with clinical AIDS had the most pronounced increase in risk, with a 31% probability of vertical transmission after 24 hr of ruptured membranes. This study did not include women receiving HAART and did not control for viral load. The effect of duration of membrane rupture with very low viral loads is not clear.
- **Placental disruption-abruption, chorioamnionitis:** Clinical and histologic chorioamnionitis (Goldenberg, 1998; Mwanyumba, 2002) has been associated with increased risk of transmission. Placental abruption causing disruption of fetal-placental barrier and possible increased exposure of the fetus to maternal blood has also been suggested as a risk factor for transmission.

- **Invasive fetal monitoring:** Use of fetal scalp electrodes or fetal scalp sampling increases exposure of the fetus to maternal blood and genital secretions and may increase risk of vertical transmission (Maiques, 1999). Amnioscopy and amniocentesis increased risk in the French Perinatal Cohort (Mandelbrot, 1996).
- **Episiotomy, forceps:** Use of episiotomy or vacuum extraction or forceps may potentially increase risk of transmission by increasing exposure to maternal blood/genital secretions with trauma to maternal or neonatal tissue. On the other hand, judicious use of these techniques to shorten duration of labor or ruptured membranes with vaginal delivery may decrease likelihood of transmission.
- **Vaginal vs. cesarean delivery:** Several studies (done before routine use of viral load testing and use of combination antiretroviral therapy in pregnancy) indicate that cesarean delivery performed before the onset of labor and rupture of membranes significantly reduces the risk of perinatal HIV transmission by 55–80% (European Mode of Delivery Collaboration, 1999; International Perinatal HIV Group, 1999; Kind, 1998; Mandelbrot, 1998). Whether cesarean delivery offers any benefit when the mother is receiving HAART and/or if she has low or undetectable viral load is unknown, and cesarean section is not recommended in those circumstances (ACOG, 2000).

C. FETAL/NEONATAL FACTORS

Fetal/neonatal factors, including an immature immune system (particularly in the premature infant) and genetic susceptibility, as expressed by human lymphocyte antigen (HLA) genotype (Just, 1995) or CCR-5 receptor (a coreceptor for macrophage-tropic strains of HIV; a homozygous deletion in this gene confers a high degree of natural resistance to HIV sexual transmission) mutations may play a role in perinatal transmission (Kostrikis, 1999; Mangano, 2000; Philpott, 1999). A recent study from South Africa (Kuhn, 2000) found that early acquired cellular immune responses to HIV, presumably from in utero exposure, were present in over one third of 86 uninfected infants born to HIV-infected mothers. These detectable immune responses appeared to provide complete protection against subsequent HIV transmission at delivery and through breast-feeding.

D. BREAST-FEEDING

Overall breastfeeding appears to increase the risk of perinatal transmission by 5–20% (DeCock, 2000). In 1998 breastfeeding is estimated to have accounted for up to 50% of newly infected children globally (Fowler, 1999). Factors that have been associated with an increased risk of breast milk transmission include the following:

- Maternal factors:
 - acute HIV infection or recent seroconversion (Dunn, 1992), most likely related to high HIV viral loads
 - advanced HIV infection clinically or with low CD4 counts
 - high plasma or breast milk viral load
 - inflammatory breast conditions, such as mastitis or breast abscess
 - cracked nipples
 - vitamin A deficiency
 - colostrum
- Newborn factors:
 - Oral thrush
 - Other mucosal lesions due to trauma or infection
 - Preterm birth or low birthweight
 - Nutritional deficiencies
- Breastfeeding characteristics:
 - Timing –highest in first months, increases with longer duration of breastfeeding (Miotti, 1999)
 - Pattern of breastfeeding-mixed feeding (addition of other solids or liquids to breastmilk) associated with increased risk over exclusive breastfeeding (Coutsoudis, 2000)

A recent randomized clinical trial of breastfeeding vs. formula feeding in Kenya (Nduati, 2000) found that formula feeding prevented 44% of infant infections and was associated with a significantly improved survival.

STRATEGIES FOR PREVENTION OF PERINATAL TRANSMISSION

Based on the potential factors impacting perinatal HIV transmission discussed above, several basic approaches to prevention have been suggested. These include:

- Identification and treatment of modifiable risk factors
- Decreasing viral load
- Decreasing viral exposure
- Stimulation of the immune system (passive or active immunization)

Currently, most major efforts at prevention are aimed at decreasing viral load.

IX. GUIDELINES FOR CARE

A. ANTEPARTUM

HISTORY/PHYSICAL EXAMINATION

(See also Chapter IV on Primary Medical Care.)

- **HIV history:** date of diagnosis; history of HIV-related symptoms or opportunistic infections or malignancies; lowest CD4 cell count; highest and current viral load; complete antiretroviral history, including specific drugs, side effects or toxicity, length of treatment, adherence, results of resistance testing (if performed), and response to treatment
- **Pregnancy history:** previous pregnancies and outcomes, complications, mode of delivery, use of antiretroviral prophylaxis, and HIV status of other children
- **Signs or symptoms of HIV/AIDS:** (initial and follow-up evaluations) assess signs or symptoms that suggest symptomatic HIV infection or AIDS (e.g., generalized lymphadenopathy, thrush, constitutional symptoms such as fever [38.5°C] or diarrhea >1 mo, herpes zoster involving two episodes or >1 dermatome, peripheral neuropathy, wasting, dysphagia, shortness of breath, persistent mucocutaneous herpetic ulcerations, cognitive dysfunction, etc.).
- **Signs or symptoms of pregnancy-related complications:** (the initial and follow-up evaluations) elevated blood pressure, significant edema, severe headache, vaginal bleeding or leakage of fluid, intractable nausea and vomiting, dysuria, abnormal vaginal discharge, persistent abdominal or back pain or cramping, decrease in fetal movement, etc. Gingival disease has recently been identified as a risk factor for preterm labor (Hill, 1998).
- **Signs or symptoms of ARV toxicity:** (initial and follow-up evaluations) nausea/vomiting, abdominal pain, jaundice, extreme fatigue, skin rash.

Certain symptoms of HIV disease, antiretroviral toxicity, and normal or abnormal pregnancy may overlap, resulting in possible delay in appropriate diagnosis and management.

- **Relevant family history of possible heritable diseases.**

LABORATORY EXAMINATION BY TRIMESTER SEE TABLE 7-5.

Table 7-5: Laboratory Evaluation in the HIV-Infected Pregnant Woman

<i>Test</i>	<i>Comment</i>
Entry into Prenatal Care and Ongoing	
HIV serology	Unconfirmed HIV infection; + test with other techniques; always repeat in the case of a new diagnosis to rule out false+
CD4 cell count/% HIV RNA	Repeat every 3–4 mo or as indicated to monitor changes with ARV therapy; at milestones for therapeutic decisions, re: ARV therapy/OI prophylaxis
Viral resistance testing (genotyping)	Acute HIV infection, virologic failure, sub-optimal viral suppression after initiation of ARV therapy, or high likelihood of exposure to resistant virus based on community prevalence or source characteristics
CBC	Repeat at minimum of every trimester in women on stable ARV therapy; for changes in regimen, repeat q 2–4 wk until stable; in general, consider more frequent testing if low or receiving marrow-toxic drugs (e.g., ZDV)
Serum chemistry panel (liver enzymes, electrolytes, +/- amylase)	Repeat at minimum of every trimester in women on stable ARV therapy; for changes in regimen, repeat q 2–4 wk until stable. Repeat as indicated with abnormal results or use of hepatotoxic/nephrotoxic drugs
Syphilis serology	
Hepatitis serology: HBsAg, anti-HCV, anti-HAV	Order anti-HBs or anti-HBc and anti-HAV to screen for hepatitis B and A vaccine candidates. If anti-HCV+, order HCV-RNA
Rubella, Blood type and Rh, Antibody screen, Urine culture, GC/chlamydia testing, Pap smear	Cytobrush can be used
PPD	+ skin test = ≥ 5 mm induration; anergy testing not indicated; obtain CXR if at high risk for TB exposure
Hemoglobin electrophoresis, red blood cell indices	Perform in women at increased risk for hemoglobinopathies
G6PD	Optional — may consider screening black women or those receiving oxidant drugs (e.g., dapsone, sulfonamides)

Table 7-5: Laboratory Evaluation in the HIV-Infected Pregnant Woman (continued)	
<i>Test</i>	<i>Comment</i>
CMV IgG	Consider especially with CD4 <100 mm ³ or in patients at low risk for CMV (non-IDU)*
Toxoplasmosis IgG	Screen all patients with initial HIV diagnosis; repeat with CD4 <100/mm ³ and not on TMP-SMZ, or with symptoms suggestive of toxoplasmic encephalitis
Urine toxicology screen	As indicated
Serum screening for Tay-Sachs disease	Consider screening both partners if at increased risk (Ashkenazi Jews, French-Canadian, or Cajun descent)
Bacterial vaginosis screening	Consider in women at high risk for preterm labor (previous preterm birth); women with signs/symptoms of vaginitis
16–20 wk	
Ultrasound	Gestational dating, anomaly screen; repeat as indicated to monitor fetal growth
Maternal serum α -fetoprotein**	Voluntary; requires counseling; screening test for neural tube and abdominal wall defects; abnormal result (usually >2.5 multiple of the median) requires further evaluation
Triple screen (HCG, unconjugated estriol, α -fetoprotein)**	Voluntary; requires counseling; noninvasive test to determine risk of neural tube & abdominal wall defects, Down syndrome, and trisomy 18
24–28 wk	
CBC, Syphilis serology, Antibody screen	
Diabetes screen	Glucose 1 hr after 50 g glucola — 3 hr oral GTT if abnormal; may need additional glucose monitoring in women on protease inhibitors (consider 20 wk screening and repeat at 24–28 wk if on PIs)
32–36 WK	
GC/chlamydia testing	
Group B streptococcus culture (35–37 wk) (vaginal and rectal)	Recommend intrapartum chemoprophylaxis with IV PCN G (2.5 million units q 4 hr) if positive (or if GBS bacteriuria during current pregnancy or with previous infant with invasive GBS disease; if unknown GBS status, IP prophylaxis with delivery <37 wk gestation, membrane rupture \geq 18 hr or IP temperature \geq 100.4°F/38.0°C (Schrag, 2002).

Table 7-5: Laboratory Evaluation in the HIV-Infected Pregnant Woman (continued)	
Test	Comment
CD4, HIV-RNA	Results may influence decisions about mode of delivery
Syphilis serology	Consider in high-risk patients or populations
Other Considerations	
Test	Indication
Liver enzymes, electrolytes	Assess more frequently in third trimester in setting of NRTI therapy, nevirapine, recent changes in ARV therapy
Serum lactate, electrolytes, liver enzymes; consider anion gap, CPK, amylase, lipase	Signs or symptoms suggest possible lactic acidosis in setting of NRTI therapy, especially if long-term
Fasting lipid profile	Consider at baseline and at 3–6 mo after starting PI- or NNRTI-based therapy; subsequent measurements based on initial results and risks
Liver enzymes (ALT, AST) every 2 wks in the first 6 wks of treatment, then every mo for first 12 wks; then every 1-3 mo.; more frequently in patients with pre-existing liver disease	Initiation of nevirapine therapy (does not apply to single dose prophylactic therapy in labor)
* Seroprevalence CMV IgG in US adults is 50–60%; IDU patients ≥90%	
** Accurate gestational age is essential for interpretation of both tests.	
** Though not yet considered standard of care, 1st trimester screening for genetic abnormalities can be done with nuchal lucency assessment on ultrasound and with biochemical markers.	
ARV, antiretroviral; OI, opportunistic infections; CBC, complete blood count; PPD, purified protein derivative; G6PD, glucose 6-phosphate dehydrogenase; CMV, cytomegalovirus; TMP-SMZ, trimethoprim-sulfamethoxazole; HCG, human chorionic gonadotropin; GTT glucose tolerance test; PCN G, penicillin G; IDU injection drug use. PI, protease inhibitor; CXR, chest x-ray; R/O, rule out; GBS, Group B streptococci; IP, intrapartum CPK, creatine phosphokinase; NRTI, nucleoside reverse transcriptase inhibitor; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor	

VII

ANTEPARTUM FETAL SURVEILLANCE/TESTING

The general purpose of antepartum fetal testing and surveillance is to identify fetal abnormalities or compromise so that appropriate interventions can be undertaken to optimize fetal health and prevent fetal damage or death; or, in some instances, to aid in decisions regarding continuation of pregnancy (ACOG, 1999).

- **Fetal surveillance:** Indications include:
 - maternal conditions in which risk of fetal death is increased. This includes (but is not limited to) hemoglobinopathies, chronic renal disease, systemic lupus erythematosus, hypertension, and diabetes.
 - pregnancy-related conditions in which risk of fetal death is increased. This includes pregnancy-induced hypertension, decreased fetal

movement, oligohydramnios, polyhydramnios, intrauterine growth retardation, postterm pregnancy, mild to moderate isoimmunization, previous fetal death, and multiple gestation.

- HIV considerations: There are no data specifically on the need for and use of fetal surveillance techniques in the HIV-infected woman during pregnancy, and HIV per se is not an indication for fetal testing. However, HIV-infected women who have coexisting medical conditions placing the fetus at increased risk should have fetal surveillance; furthermore, HIV infection, especially when more advanced or associated with substance abuse, may be associated with increased risk for poor fetal growth, which places the fetus at increased risk. May consider in pregnant women on HAART particularly when containing newer agents with little experience of use in pregnancy. Need for fetal surveillance in the HIV-positive pregnancy should be determined on an individual basis.

Fetal surveillance techniques include:

- Fetal movement assessment: "kick-counts" – perception of 10 distinct movements in a period of up to 2 hr is reassuring.
- Nonstress test (NST): reactive or reassuring test is defined as two or more fetal heart rate accelerations (at least 15 beats/min above baseline and lasting at least 15 sec on fetal monitor) within a 20-min period.
- Contraction stress test (CST): negative or reassuring test is absence of late or significant variable fetal heart rate decelerations with at least three contractions (lasting at least 40 sec) within 10 min.
- Biophysical profile: consists of an NST combined with observations of fetal breathing, fetal movements, fetal tone, and amniotic fluid volume by real-time ultrasonography. Each component is given a score of 2 (normal or present) or 0 (abnormal or absent); a composite score of 8 or 10 is normal.
- Modified biophysical profile: combines NST and amniotic fluid index (AFI), which is the sum of measurements of the deepest amniotic fluid pocket in each abdominal quadrant; normal AFI is >5 cm. This test combines a short-term indicator of fetal acid-base status (NST) and an indicator of long-term placental function (AFI); placental dysfunction often leads to poor fetal growth and oligohydramnios.
- Umbilical artery Doppler velocimetry: evaluation of flow velocity wave forms in the umbilical artery; in the normally growing fetus, characterized by high-velocity diastolic flow; of benefit only in pregnancies complicated by intrauterine growth restriction.

Although there is no data from randomized clinical trials, antepartum fetal surveillance has been consistently associated with lower rates of fetal death than in untested pregnancies from the same institution or than historic controls with similar complicating factors. Testing should be initiated at 32–34 wk gestation, but may be started as early as 26–28 wk in pregnancies at very high risk. When the condition prompting testing persists, testing should be repeated periodically (weekly or, in some cases, biweekly) until delivery. Fetal reevaluation should also be repeated with significant deterioration in maternal medical condition or acute decrease in fetal movement, regardless of the time elapsed since the previous test.

NST, CST, biophysical profile, and modified biophysical profile are the most commonly used forms of testing and have a negative predictive value >99%. However, they are not predictive of acute events, such as placental abruption or umbilical cord accidents. On the other hand, the positive predictive value of an abnormal test can be quite low and the response to an abnormal result should be dictated by the individual clinical situation. Any abnormal test result requires further evaluation or action. Maternal perception of decreased fetal movements should be evaluated by NST, CST, biophysical profile, or modified biophysical profile. If normal, the mother can be reassured that the fetus is in no immediate danger. A nonreactive NST or abnormal modified biophysical profile is usually followed by additional testing with a CST or full biophysical profile. Management will be based on results of these tests, gestational age, degree of oligohydramnios (if assessed), and maternal condition. Oligohydramnios should prompt evaluation for membrane rupture. Depending on the degree of oligohydramnios, the gestational age, and the maternal medical condition, oligohydramnios warrants either delivery or close maternal/fetal surveillance.

- **Ultrasound.** Indications for obstetric ultrasound are many. Some of the more common include (ACOG, 1993b):
 - pregnancy dating
 - evaluation of fetal growth
 - evaluation of vaginal bleeding during pregnancy
 - determination of fetal presentation
 - suspected multiple gestation
 - significant uterine size/clinical dates discrepancy
 - pelvic mass
 - suspected ectopic pregnancy
 - document fetal viability/rule out fetal death
 - biophysical profile for antepartum fetal surveillance
 - suspected polyhydramnios/oligohydramnios
 - placental localization
 - abnormal serum β -fetoprotein or triple screen
 - evaluation for fetal anomalies
 - evaluation of fetal condition in late registrants for prenatal care

With transvaginal ultrasound, an intrauterine gestational sac can be seen by 5 wk after the last menstrual period and fetal heart activity can be detected by 6 wk. First-trimester bleeding is the most common indication for early ultrasound, when the major differential diagnoses are threatened abortion (miscarriage) and ectopic pregnancy. Accurate pregnancy dating is best accomplished in the late first and second trimesters.

In the setting of HIV infection, an ultrasound should be considered in the second trimester for accurate dating, which is important later in gestation if scheduled cesarean section is planned to avoid premature delivery (see below). This will also allow survey of fetal anatomy and screening for anomalies. A third trimester (or other follow-up) ultrasound(s) should be considered, particularly in women with more advanced disease, those on HAART, and/or with other maternal pregnancy-related factors possibly impacting on fetal growth, in order to monitor growth.

- **Amniocentesis/chorionic villus sampling/percutaneous umbilical blood sampling:** Because of concerns about increasing risk of perinatal transmission with these invasive techniques, they should be performed only for obstetric indications, with careful counseling; attempts to minimize viral load prior to the procedure should be considered.

ANTIRETROVIRAL TREATMENT

(See Table 7-6.) Although there are special considerations in using antiretroviral drugs during pregnancy, the basic principle is that therapies of known or possible benefit to the woman should not be withheld during pregnancy unless there are known adverse effects for mother, fetus, or infant that outweigh the potential benefits (Minkoff, 1997a). The goals in the use of antiretroviral drugs during pregnancy are two-fold: (1) treatment of maternal infection and (2) reduction in the risk of perinatal transmission. Pregnant women meeting the criteria outlined for other adults and adolescents should be offered standard combination antiretroviral therapy, generally including two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (excluding efavirenz). (See Chapter IV on Primary Medical Care.) If such criteria are not met, ARV therapy appropriate for prevention of perinatal transmission, including combination treatment, should be offered.

Table 7-6 Preclinical and Clinical Data Relevant to the Use of Antiretrovirals During Pregnancy

(See Safety and Toxicity of Individual Antiretroviral Drugs in pregnancy for more detail on drugs)

Antiretroviral drug	FDA pregnancy category†	Placental passage [newborn: mother drug ratio]	Long-term animal carcinogenicity studies	Animal teratogen studies
Nucleoside and nucleotide analogue reverse transcriptase inhibitors				
Abacavir (Ziagen, ABC)	C	Yes (rats)	Positive (malignant and non-malignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats)	Positive (rodent anasarca and skeletal malformations at 1000 mg/kg (35x human exposure) during organogenesis; not seen in rabbits)
Didanosine (Videx, ddI)	B	Yes (human) [0.5]	Negative (no tumors, lifetime rodent study)	Negative
Emtricitabine (Emtriva, FTC)	B	Unknown	Not completed	Negative
Lamivudine (EpiVir, 3TC)	C	Yes (human) [~ 1.0]	Negative (no tumors, lifetime rodent study)	Negative
Stavudine (Zerit, d4T)	C	Yes (rhesus monkey) [0.76]	Positive (mice and rats, at very high dose exposure, liver and bladder tumors)	Negative (but sternal bone calcium decreases in rodents)
Tenofovir DF (Viread)	B	Yes (rat and monkey)	Not completed	Negative (osteomalacia when given to juvenile animals at high doses)
Zalcitabine (HIVID, ddC)	C	Yes (rhesus monkey) [0.30–0.50]	Positive (rodent, thymic lymphomas)	Positive (rodent hydrocephalus at high dose)
Zidovudine (Retrovir, AZT, ZDV)	C	Yes (human) [0.85]	Positive (rodent, noninvasive vaginal epithelial tumors)	Positive (rodent near-lethal dose)

Table 7-6 Preclinical and Clinical Data Relevant to the Use of Antiretrovirals During Pregnancy (continued)				
Antiretroviral drug	FDA pregnancy category [†]	Placental passage [neuborn: mother drug ratio]	Long-term animal carcinogenicity studies	Animal teratogen studies
Non-nucleoside reverse transcriptase inhibitors				
Delavirdine (Rescriptor)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male and female mice but not rats, bladder tumors in male mice)	Positive (rodentventricular septal defect)
Efavirenz (Sustiva)	D	Yes (cynomologus monkey, rat, rabbit) [~1.0]	Positive (increased hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas in female but not male mice)	Positive (cynomologus monkeyencephaly, anophthalmia, micro-ophthalmia)
Nevirapine (Viramune)	C	Yes (human) [~1.0]	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative
Protease inhibitors				
Amprenavir (Agenerase)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male mice and rats)	Negative (but deficient ossification and thymic elongation in rats and rabbits)
Atazanavir	B	Unknown	Not completed	Negative
Fosamprenavir (Lexiva)	C	Unknown	Positive (increased benign and malignant liver tumors in male rodents)	Negative (deficient ossification with amprenavir but not fosamprenavir)
Indinavir (Crixivan)	C	Minimal (humans)	Positive (thyroid adenomas in male rats at highest dose)	Negative (but extra ribs in rodents)
Lopinavir/Ritonavir (Kaletra)	C	Unknown	Not completed	Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)

Nelfinavir (Viracept)	B	Minimal (humans)	Positive (thyroid follicular adenomas and carcinomas in rats)	Negative
Ritonavir (Norvir)	B	Minimal (humans)	Positive (rodent, liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rodents)
Saquinavir (Fortovase)	B	Minimal (humans)	Not completed	Negative
Fusion inhibitors				
Enfuvirtide (Fuzeon)	B	Unknown	Not done	Negative

† Food and Drug Administration Pregnancy Categories:
 A - Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters).
 B - Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.
 C - Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
 D - Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
 X - Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.
 Source: Perinatal HIV Guidelines Working Group, 2005.

Nevertheless, there are additional issues to consider with treatment in pregnancy:

- **Pharmacokinetics:** (See Table 7-7.) There are potential changes in dosing secondary to the physiologic changes during pregnancy; at the current time, pharmacokinetic information on existing antiretroviral agents during pregnancy is limited, and has not been correlated with clinical efficacy. PK data on the NRTI and NNRTI drugs studied are similar to that in nonpregnant adults and these drugs cross the placenta to a variable extent. In general protease inhibitors have different PK levels during pregnancy and do not cross the placenta. Adequate drug levels are achieved in pregnant women with nelfinavir 1250 mg bid (Bryson, 2002), but levels were low and more variable with dosing 750 mg tid. Small PK studies conducted with non-boosted indinavir and saquinavir, as well as lopinavir/ritonavir, found inadequate drug concentrations in pregnancy using standard dosing; adequate drug levels were achieved with saquinavir 800 mg/ritonavir 100 mg (Acosta, 2004) and a boosted indinavir PK study is underway, as well as a trial of altered dosing of lopinavir/ritonavir. PK parameters of nevirapine are not significantly altered in pregnancy (Aweeka, 2004), but several recent studies show prolonged postnatal drug levels for over 3 weeks in a significant proportion of women after a single-dose of nevirapine given in labor (Jourdain, 2004).
- **Perinatal transmission:** The effect of different drugs and drug combinations on vertical transmission. Current information from clinical trials on the use of antiretroviral agents during the antepartum period and perinatal transmission are summarized in Table 7-8.

Although there are no clinical trial data regarding effectiveness of HAART in reducing perinatal transmission, there is prospective cohort data which suggests that the lowest rates of transmission occur with effective combination ARV therapy and with reductions in viral load to undetectable levels. Both choice of ARV therapy and suppression of viral load to <1000 copies/mL are important and probably additive. An analysis of the WITS (Cooper, 2002) cohort found the transmission rate was 1.2% in women receiving HAART and was 1% when HIV-RNA levels were suppressed below 400 c/mL. Preliminary results of a retrospective/prospective combined analysis (PACTG 367) of over 4000 women found that in all subgroups of viral load, multiagent ARV—both dual nucleoside and HAART—was associated with the lowest rates of perinatal transmission and when viral load was <1000 c/mL in these women, transmission rate was <1% (Shapiro, 2004).

Table 7-7: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy			
<i>Antiretroviral drug</i>	<i>Pharmacokinetics in Pregnancy</i>	<i>Concerns in Pregnancy</i>	<i>Rationale for Recommended Use in Pregnancy</i>
NRTI/NRTIs		See text for discussion of potential maternal and infant mitochondrial toxicity.	NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection (AZT alone may be considered for prophylaxis of perinatal transmission in pregnant women with HIV RNA <1,000 copies/mL)
Recommended agents (NRTI/NRTIs)			
Zidovudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant	Preferred NRTI for use in combination antiretroviral regimens in pregnancy based on efficacy studies and extensive experience; should be included in regimen unless significant toxicity or stavudine use.
Lamivudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant	Because of extensive experience with lamivudine in pregnancy in combination with zidovudine, lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.

Table 7-7: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (continued)			
Antiretroviral drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Alternate agents (NRTI/NtRTIs)			
Didanosine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.
Emtricitabine	No studies in human pregnancy	No studies in human pregnancy	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated	No evidence of human teratogenicity. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together	Alternate NRTI for dual nucleoside backbone of combination regimens. Stavudine should be used with didanosine only if no other alternatives are available. Do not use with zidovudine due to potential for antagonism.
Abacavir*	Phase III study in progress.	Hypersensitivity reactions occur in ~ 5–8% of nonpregnant persons, a much smaller percentage are fatal and usually associated with rechallenge; rate in pregnancy unknown. Patient should be educated regarding symptoms of hypersensitivity reaction	Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen. #
Insufficient data to recommend use (NRTI/NtRTIs)			
Tenofovir	No studies in human pregnancy. Phase I study in late pregnancy in progress.	Studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within two months of starting maternal therapy. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown.	Because of lack of data on use in human pregnancy and concern regarding potential fetal bone effects, tenofovir should be used as a component of a maternal combination regimen only after careful consideration of alternatives.

Not recommended (NRTI/NtRTIs)			
Zalcitabine	No studies in human pregnancy	Rodent studies indicate potential for teratogenicity and developmental toxicity	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives not available
NNRTIs			
Recommended agents (NNRTIs)			
Nevirapine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated	No evidence human teratogenicity. Increased risk of symptomatic, often rash-associated and potentially fatal, liver toxicity among women with CD4+ lymphocyte counts > 250/mm ³ when first initiating therapy, unclear if pregnancy increases risk.	Nevirapine should be initiated in pregnant women with CD4+ lymphocyte counts > 250/mm ³ only if benefit outweighs risk; if used, monitor closely for liver toxicity in first 18 weeks of therapy. Women who enter pregnancy on nevirapine regimens and are tolerating well may continue therapy, regardless of CD4+ lymphocyte count.
Not recommended (NNRTIs)			
Efavirenz	No studies in human pregnancy	Significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving efavirenz during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure; there are three case reports of neural tube defects in humans after first trimester exposure; relative risk unclear.	Use of efavirenz should be avoided in the first trimester, and women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Alternative effective regimens should be considered, if available. Use after the second trimester of pregnancy can be considered if other alternatives not available and if adequate contraception can be assured postpartum.

Table 7-7: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (continued)			
<i>Antiretroviral drug</i>	<i>Pharmacokinetics in Pregnancy</i>	<i>Concerns in Pregnancy</i>	<i>Rationale for Recommended Use in Pregnancy</i>
Delavirdine	No studies in human pregnancy	Rodent studies indicated potential for carcinogenicity and teratogenicity	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives not available
Protease Inhibitors		Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs	
Recommended agents (Protease Inhibitors)			
Nelfinavir	Adequate drug levels are achieved in pregnant women with nelfinavir, 1250 mg, given twice daily	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant. Nelfinavir dosing at 750 mg three times daily produced variable and generally low levels in pregnant women	Given pharmacokinetics data and extensive experience with use in pregnancy compared to other PIs, preferred PI for combination regimens in pregnant women, particularly if HAART is being given solely for perinatal prophylaxis. In clinical trials of initial therapy in non-pregnant adults, nelfinavir-based regimens had a lower rate of viral response compared to lopinavir/ritonavir or efavirenz-based regimens, but similar viral response compared with atazanavir or nevirapine-based regimens.

<p>Saquinavir-soft gel capsule [SGC] (Fortavase)/ritonavir</p>	<p>Adequate drug levels are achieved in pregnant women with saquinavir-SGC 800 mg boosted with ritonavir 100 mg given twice daily.</p> <p>Recommended adult dosing of saquinavir-SGC 1000 mg plus ritonavir 100 mg may be used.</p> <p>No pharmacokinetic data on saquinavir-hard gel capsule [HGC]/ritonavir in pregnancy, but better GI tolerance in non-pregnant adults.</p>	<p>Well-tolerated, short-term safety demonstrated for mother and infant. Inadequate drug levels observed in pregnant women when saquinavir-SGC given alone at 1200 mg three times daily.</p>	<p>Given pharmacokinetics data and extensive experience with use in pregnancy, ritonavir-boosted saquinavir-SGC can be considered a preferred PI for combination regimens in pregnant women.</p>
<p>Alternative agents (Protease Inhibitors)</p>			
<p>Indinavir</p>	<p>Study underway to evaluate pharmacokinetics of indinavir 800 mg with ritonavir 100 mg, given twice daily</p>	<p>Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Two studies including six women receiving indinavir 800 mg three times daily showed marked lower levels during pregnancy compared to postpartum, although suppression of HIV RNA was seen</p>	<p>Alternate PI to consider if unable to use nelfinavir or saquinavir-SGC/ritonavir. Use of unboosted indinavir during pregnancy is not recommended. Optimal dosing for the combination of ritonavir/indinavir in pregnancy unknown.</p>

Table 7-7: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (continued)			
<i>Antiretroviral drug</i>	<i>Pharmacokinetics in Pregnancy</i>	<i>Concerns in Pregnancy</i>	<i>Rationale for Recommended Use in Pregnancy</i>
Lopinavir/ritonavir	Phase III safety and pharmacokinetic study in progress using twice daily lopinavir 400 mg and ritonavir 100 mg	Limited experience in human pregnancy	Preliminary studies suggest increased dose may be required during pregnancy, though specific dosing recommendations not established. If used during pregnancy, monitor response to therapy closely. If expected virologic result not observed, consider increasing dose in consultation with a specialist with expertise in HIV in pregnancy.
Ritonavir	Phase III study in pregnancy showed lower levels during pregnancy compared to postpartum	Minimal experience in human pregnancy	Given low levels in pregnant women when used alone, recommended for use in combination with second PI as low dose ritonavir "boost" to increase levels of second PI
Insufficient data to recommend use (Protease Inhibitors)			
Amprenavir	No studies in human pregnancy	Oral solution contraindicated in pregnant women because of high levels of propylene glycol, which may not be adequately metabolized during pregnancy.	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use of capsules during pregnancy. Oral solution contraindicated
Fos-amprenavir	No studies in human pregnancy	No experience in human pregnancy	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy.
Atazanavir	No studies in human pregnancy	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental passage of other PIs has been low	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy.

Fusion Inhibitors			
Insufficient data to recommend use (Fusion Inhibitors)			
Enfuvirtide	No studies in human pregnancy	No experience in human pregnancy	Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy.
<p><i>NRTI</i>=nucleoside reverse transcriptase inhibitor; <i>NRTI</i>=nucleoside reverse transcriptase inhibitor; <i>NNRTI</i>=non-nucleoside reverse transcriptase inhibitor; <i>PI</i>= Protease inhibitor; <i>SGC</i>=soft gel capsule; <i>HGC</i>=hard gel capsule</p> <p>* Zidovudine and lamivudine are included as a fixed-dose combination in <i>Combivir</i>[®], and zidovudine, lamivudine, and abacavir are included as fixed-dose combination in <i>Trizivir</i>[®].</p> <p># Triple <i>NRTI</i> regimens including abacavir have been less potent virologically compared to <i>PI</i>-based HAART regimens. These regimens should be used only when an <i>NNRTI</i> or <i>PI</i>-based HAART regimen cannot be used (eg, due to significant drug interactions). A study evaluating use of zidovudine/lamivudine/abacavir among pregnant women with HIV RNA < 55,000 copies/mL as a class-sparing regimen is in development.</p> <p>Source: Perinatal HIV Guidelines Working Group, 2005.</p>			

Table 7-8: Overview of Antiretroviral Intervention Trials to Prevent Mother-to-child Transmission of HIV

<i>Site/sponsor</i>	<i>Antepartum</i>	<i>Intrapartum</i>	<i>Post-partum Mother</i>	<i>Post-partum Infant</i>	<i>Results</i>
US (PACTG 076) • Randomized, placebo-controlled • Formula feeding • N=477	Starting at 14-34 wks Arm 1: ZDV 100 mg 5x/d Arm 2: Placebo	Arm 1: ZDV intravenous infusion Arm 2: Placebo	No ARV	Arm 1: ZDV 2 mg/kg qid x 6 wk Arm 2: Placebo	• At 18 mo, tx 7.6% ZDV vs 22.6% placebo, 68% efficacy (Connor, 1994)
THAILAND (CDC) • Randomized, placebo-controlled • Formula feeding • N=392	Starting at 36 wks Arm 1: ZDV 300 mg bid Arm 2: Placebo	Arm 1: ZDV 300 mg q 3 hr Arm 2: Placebo	No ARV	No ARV	• At 6 mos, tx 9.4% ZDV vs 18.9% placebo, 50% efficacy (Shaffer, 1999)
IVORY COAST (CDC) • Randomized, placebo-controlled • Breastfeeding • N=280	Starting at 36 wks Arm 1: ZDV 300 mg bid Arm 2: Placebo (stopped 2/98)	Arm 1: ZDV 300 mg q 3 hr Arm 2: Placebo (stopped 2/98)	No ARV	No ARV	• At 3 mos, tx 16.5% ZDV vs 26.1% placebo, 37% efficacy (Wiktor, 1999)

<p>IVORY COAST/BURKINA FASO (DITRAME; ANRS 049a)</p> <ul style="list-style-type: none"> • Randomized, placebo-controlled • After trial completion, continued to enroll into an open-label ZDV regimen cohort • Breastfeeding • N=400 	<p>Starting at 36-38 wks</p> <p>Arm 1: ZDV 300 mg bid</p> <p>Arm 2: Placebo (stopped 2/98)</p>	<p>Arm 1: ZDV 600 mg x1</p> <p>Arm 2: Placebo (stopped 2/98)</p>	<p>Arm 1: ZDV 300 mg bid x 1 wk</p> <p>Arm 2: Placebo (stopped 2/28)</p>	<p>No ARV</p>	<ul style="list-style-type: none"> • At 6 mos, tx 18.0% ZDV vs 27.5% placebo, 38% efficacy • At 15 mos, tx 21.5% ZDV vs 30.6% placebo, 30% efficacy • At 24 mos (pooled analysis with CDC), tx 22.5% ZDV vs 30.2% placebo, 26% efficacy • 18 mo mortality: 17.6% ZDV vs 22.1% placebo • Open-label ZDV cohort (N=209), 15 mo tx with ZDV regimen, 19.6% <p>(Dabis, 1999; DITRAME-ANRS 049 Study Group, 1999; Leroy, 2002)</p>
<p>THAILAND/PHPT (Hanard)</p> <ul style="list-style-type: none"> • Randomized, comparative, factorial • No placebo (076-like control) • Formula feeding • N=1,437 	<p>ZDV 300 mg bid</p> <p>Arm 1 (Long-Long, LL): 28 wks</p> <p>Arm 2 (Long-Short, LS): 28 wks</p> <p>Arm 3 (Short-Long, SL): 36 wks</p> <p>Arm 4 (Short-short, SS): 36 wks</p>	<p>ZDV 300 mg q 3 hr</p> <p>Arm 1: Oral</p> <p>Arm 2: Oral</p> <p>Arm 3: Oral</p> <p>Arm 4: Oral</p>	<p>No ARV</p>	<p>ZDV 2 mg/kg qid</p> <p>Arm 1: 6 wks</p> <p>Arm 2: 3 d</p> <p>Arm 3: 6 wks</p> <p>Arm 4: 3 d</p>	<ul style="list-style-type: none"> • Interim analysis 3/99 (N=449 enrolled), stopped SS arm due to sig higher tx than LL, — At 6 mos, tx 10.5% SS vs 4.1% LL • Final analysis 7/00, no sig differences, — At 6 mos, tx 6.5% LL vs 4.7% LS vs 8.6% SL • In utero tx sig different: — 1.6% [LL+LS] vs 5.1% [SL+SS] <p>(Lallemant, 2000)</p>

Table 7-8: Overview of Antiretroviral Intervention Trials to Prevent Mother-to-child Transmission of HIV (continued)

Site/sponsor	Antepartum	Intrapartum	Post-partum Mother	Post-partum Infant	Results
SOUTH AFRICA, UGANDA, TANZANIA (PETRA) • Randomized, placebo-controlled • Breastfeeding • N=1,797	Starting at 36 wks Arm 1: ZDV 300 mg bid plus 3TC 150 mg bid Arm 2: Placebo Arm 3: Placebo Arm 4: Placebo (stopped 2/98)	Arm 1: ZDV 300 mg q 3 hr plus 3TC 150 mg q 12 hr Arm 2: ZDV 300 mg q 3 hr plus 3TC 150 mg q 12 hr Arm 3: ZDV 300 mg q 3 hr plus 3TC 150 mg q 12 hr Arm 4: Placebo (stopped 2/98)	Arm 1: ZDV 300 mg bid plus 3TC 150 mg bid x 7 d Arm 2: ZDV 300 mg bid plus 3TC 150 mg bid x 7 d Arm 3: Placebo Arm 4: Placebo (stopped 2/98)	Arm 1: ZDV 4 mg/kg bid plus 3TC 2 mg/kg bid x 7 d Arm 2: ZDV 4 mg/kg bid plus 3TC 2 mg/kg bid x 7 d Arm 3: Placebo Arm 4: Placebo (stopped 2/98) Petra Study Team	• At 6 wks, tx: — 5.7% AP/IP/PP (63% efficacy) — 8.9% IP/PP (42% efficacy) — 14.2% IP — 15.3% placebo • At 18 mos, tx: — 14.9% AP/IP/PP — 18.1% IP/PP — 20.0% IP — 22.2% placebo (Petra Study Team, 2002)
FRANCE (ANRS 075) • Non-randomized, open-label • Formula feeding • N=445	Standard ZDV after 14 wks 3TC 150 mg bid added at 32 wks	Standard intravenous ZDV	Non-study ARV	Standard ZDV x 6 wks 3TC 2 mg/kg bid x 6 wks	• Tx 1.6% ZDV/3TC vs 6.8% 1994-97 historical, ZDV-alone control (Mandelbrot, 2001)
THAILAND (Ministry of University Affairs, Bangkok) • Non-randomized, open-label • Formula feeding • N=106	Starting at 34 wks ZDV 300 mg bid plus 3TC 150 mg bid	ZDV 300 mg q 3 hr plus 3TC 150 mg q 3 hr	No ARV	ZDV 2 mg/kg qid x 4 wks	• At 18 mos, tx 2.8% vs 11.7% historical, ZDV-alone control (N=60: 36 wk start, oral IP, 4 wk infant) (Chaisiwattana, 2002)

<p>UGANDA (HIVNET 012)</p> <ul style="list-style-type: none"> • Randomized; originally had 3rd placebo arm, stopped 2/98 • Breastfeeding • N=626 	<p>Arm 1: No ARV</p> <p>Arm 2: No ARV</p> <p>Arm 3: No ARV</p>	<p>Arm 1: NVP 200 mg x1</p> <p>Arm 2: ZDV 300 mg q 3 hr</p> <p>Arm 3: Placebo (stopped 2/98)</p>	<p>No ARV</p>	<p>Arm 1: NVP 2 mg/kg x 1 at 48-72 hr</p> <p>Arm 2: ZDV 4 mg/kg bid x 7 d</p> <p>Arm 3: Placebo (stopped 2/98)</p>	<ul style="list-style-type: none"> • At 14-16 wks, tx 13.1% NVP vs 25.1% ZDV, 47% efficacy • At 18 mos, tx 15.7% NVP vs 25.8% ZDV, 41% efficacy <p>(Guay, 1999)</p>
<p>US/EUROPE/BRAZIL/BAHAMAS (PACTG 316)</p> <ul style="list-style-type: none"> • Randomized, [NVP] placebo-control • Women and infants received non-study standard ARV • Formula feeding • N=1,248 	<p>Non-study ARV (23% ZDV alone, 36% combo without PI, 41% combo with PI)</p>	<p>Standard intravenous ZDV</p> <p>Arm 1: NVP 200 mg x 1</p> <p>Arm 2: Placebo</p>	<p>Non-study ARV</p>	<p>Standard ZDV (with or without other ARV) x 6 wks</p> <p>Arm 1: NVP 2 mg/kg x 1 at 48-72 hr</p> <p>Arm 2: Placebo</p>	<ul style="list-style-type: none"> • Stopped early due to low 1.5% overall tx (53% in utero) • At 6 mos, tx 1.4% NVP vs 1.6% placebo <p>(Dorenbaum, 2002)</p>
<p>SOUTH AFRICA (SAINT)</p> <ul style="list-style-type: none"> • Randomized, comparative • Breastfeeding (42%) and formula feeding • N=1,331 	<p>Arm 1: No ARV</p> <p>Arm 2: No ARV</p>	<p>Arm 1: NVP 200 mg x1</p> <p>Arm 2: ZDV 600 mg then 300 mg q 3 hr plus 3TC 150 mg q 12 hr</p>	<p>Arm 1: NVP 200 mg x 1 at 24-48 hr</p> <p>Arm 2: ZDV 300 mg bid plus 3TC 150 mg bid x 7 d</p>	<p>Arm 1: NVP 6 mg x 1 at 24-48 hr (>2kg)</p> <p>Arm 2: ZDV 12 mg bid plus 3TC 6 mg bid x 7 d (>2 kg)</p>	<ul style="list-style-type: none"> • At 8 wks, tx 12.3% NVP vs 9.3% ZDV/3TC (p=0.11) <p>(Woodley, 2003)</p>
<p>THAILAND (CDC)</p> <ul style="list-style-type: none"> • Non-randomized, open-label • Formula feeding • N=195 	<p>Starting at 34-36 wks</p> <p>ZDV 300 mg bid</p>	<p>ZDV 300 mg q3 hrs plus NVP 200 mg x1</p>	<p>No ARV</p>	<p>ZDV 2 mg/kg qid x 4 wks plus NVP 6 mg x 1 at 48-72 hr</p>	<ul style="list-style-type: none"> • Tx 4.6% <p>(Chalermschokecharoenkit, 2004)</p>

Table 7-8: Overview of Antiretroviral Intervention Trials to Prevent Mother-to-child Transmission of HIV (continued)

Site/sponsor	Antepartum	Intrapartum	Post-partum Mother	Post-partum Infant	Results
THAILAND/PHPT (Harvard) <ul style="list-style-type: none"> • Randomized, comparative • All women/infant get short-course ZDV • Formula feeding • N=1,844 	Starting at 28 wks Arm 1: ZDV 300 mg bid Arm 2: ZDV 300 mg bid	Arm 1: ZDV 300 mg q 3 hr Arm 2: ZDV 300 mg q 3 hr plus NVP 200 mg x 1 Arm 3: ZDV 300 mg q 3 hr plus NVP 200 mg x 1	No ARV	Arm 1: ZDV 2 mg/kg qid x 7 d Arm 2: ZDV 2 mg/kg qid x 7 d Arm 3: ZDV 2 mg/kg qid x 7 d plus NVP 6 mg x 1 at 48-72 hr	<ul style="list-style-type: none"> • Interim analysis 6/02: --ZDV alone Arm 1 stopped due to higher tx than in ZDV/ NVP Arm 3 • Analysis through 3/03: --ZDV alone 6.3% --Arms 2 & 3 combined 1.7% --NVP/placebo 2.8% --NVP/NVP 1.9% (Lallemant, 2004)
MALAWI (Fogarty) <ul style="list-style-type: none"> • Randomized, comparative • Designed for infants of women 1st identified as HIV+ in labor/PP • Breastfeeding • N=1,119 	No ARV	No ARV	No ARV	Arm 1: NVP 2 mg/kg x 1 at 48-72 hr Arm 2: NVP 2 mg/kg x 1 at 48-72 hr plus ZDV 4 mg/kg bid x 7 d	At 6-8 wks, tx rate: NVP 20.9% NVP/ZDV 15.3% (26.8% efficacy), when limited to infants uninfected at birth: NVP 12. % vs NVP/ZDV 7.7% (36.4% efficacy) (Taha, 2003)
MALAWI (Fogarty) <ul style="list-style-type: none"> • Randomized, open label • Breastfeeding • N=894 	No ARV	NVP 200 mg x 1	No ARV	Arm 1: NVP 2 mg/kg x 1 at 48-72 hr Arm 2: NVP 2 mg/kg x 1 at 48-72 hr plus ZDV 4 mg/kg bid x 7 d	At 6-8 wks, tx rate: NVP 14.1% NVP/ZDV 16.3% (p=.36) When limited to infants uninfected at birth: NVP 6.5% vs NVP/ZDV 6.9% (p=.88) (Taha, 2004)

Courtesy: Lyme Mofenson, M.D.

- **Fetal/infant adverse effects:** Potential teratogenicity, carcinogenicity, mutagenicity, or fetal/neonatal side effects/toxicity from transplacentally transferred drugs. The potential for adverse effects may be related to several factors: the drug itself, dose, gestational age at exposure, duration of exposure, interactions with other drugs or agents to which the fetus is exposed, and the genetic make-up of mother and fetus. Potential toxicity of antiretroviral drugs with perinatal exposure applies both to the infected and uninfected fetus and/or infant.

Information about the safety of drugs in pregnancy comes from animal toxicity studies, anecdotal experience, cohort studies, registry data, and clinical trials. Preclinical data do not necessarily correlate with adverse effects in humans. There are approximately 1200 known animal teratogens, but only about 30 are known human teratogens. Of currently available drugs, ZDV is the agent for which there is the most information, and information about other antiretrovirals agents, particularly when used in combination, is more limited. Issues related to specific drugs and their possible impact on fetal safety are addressed below; all antiretroviral drugs are discussed in more detail in Chapter XIV on Pharmacology and the U.S. Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant Women Infected with HIV-1 for Maternal Health and for Reducing Perinatal HIV-1 Transmission in the United States, which is updated regularly online at <http://www.aidsinfo.nih.gov>.

- **Zidovudine (ZDV):** In the PACTG 076 study the only side effect significantly different between ZDV and placebo recipients was the presence of anemia in ZDV-exposed infants; however, the anemia was mild and resolved spontaneously without need for transfusion (Connor, 1994). There has been no evidence of increase in congenital abnormalities in infants exposed to ZDV in utero, compared with the general population. Uninfected children who were participants in the PACTG 076 study have now been followed for nearly 6 years with no evidence of impact of ZDV on growth, neurodevelopment, or immunologic status (Culnane, 1999).

Two transplacental carcinogenicity studies in mice showed different results: in one study (Olivero, 1997), two very high doses (approximately 25x and 50x daily human therapeutic exposure) were associated with an increase in lung, liver, and female genital tract tumors; in the second study (Ayers, 1997), a much lower dose (approximately 3x human therapeutic exposure) was not associated with an increase in tumors. A consensus conference reviewed all available information and concluded that the known benefits of zidovudine far outweighed the theoretical risks, but recommended long-term follow-up of infants exposed in utero to zidovudine or other antiretrovirals. In a follow-up of over 700 infants with in utero exposure to ZDV, no malignancies were observed in up to 6 yr of age (Hanson, 1999).

- **Efavirenz:** In primate studies efavirenz was associated with anencephaly, anophthalmia, microphthalmia, and cleft palate at doses comparable to human exposure. There have been four reports of central nervous system defects in human infants with early in utero exposure. Efavirenz should be avoided during pregnancy, particularly early

pregnancy, and in women at risk for pregnancy (trying to get pregnant or unsafe sexual practices). Pregnant women who have conceived while on efavirenz should be counseled about possible fetal risks and ultrasound screening should be considered to look for fetal anomalies.

- **Amprenavir:** Amprenavir oral solution contains high levels of propylene glycol (the capsule form does not contain propylene glycol). Pregnant women and infants and children under the age of 4 are unable to adequately metabolize and eliminate propylene glycol, leading to accumulation and potential serious adverse events, including hyperosmolarity, lactic acidosis, seizures, and respiratory depression. Amprenavir oral solution is contraindicated in pregnancy and in children under the age of 4 yr.
- **Indinavir:** Indinavir has been associated with indirect hyperbilirubinemia and increased risk for renal stones. There are theoretical concerns from in utero exposure to indinavir about risk for renal stones in neonates who cannot voluntarily hydrate themselves adequately and possible complications associated with exacerbation of physiologic hyperbilirubinemia (especially in premature infants, who are at greater risk for neonatal jaundice and kernicterus); however, placental passage of indinavir in humans appears to be minimal, which should minimize risk. Third trimester in utero exposure to indinavir in Rhesus monkeys found fetal plasma drug levels only 1–2% of maternal drug levels and no exacerbation of physiologic hyperbilirubinemia in neonates. Nevertheless, neonates exposed to indinavir late in gestation should be closely monitored. Because of its short half-life, these concerns probably do not apply to use of indinavir earlier in pregnancy.
- **Atazanavir:** The most common laboratory abnormality observed with use of atazanavir is hyperbilirubinemia, with 15–24% of subjects receiving atazanavir developing jaundice or scleral icterus. This abnormality was reversible with drug discontinuation and did not appear to be associated with increased risk of liver injury. The degree of placental passage and the potential risk of exacerbation of physiologic hyperbilirubinemia in neonates is unknown.
- **Tenofovir:** Recent studies in animal models suggest potential risks for bone abnormalities with infant (and possibly fetal) exposure to relatively low doses of tenofovir (Castillo, 2002; Tarantal, 2002). No human studies in pregnancy are available.
- **Hydroxyurea:** Although hydroxyurea is not a true antiretroviral drug, it has been used in some antiretroviral regimens in the past; this agent is no longer recommended as part of any antiretroviral regimen. Hydroxyurea has been referred to as a “universal teratogen” with evidence of teratogenicity in every animal species studied and defects involving multiple organ systems. This agent should be avoided during pregnancy and in women at risk for pregnancy.
- **Mitochondrial toxicity:** A large prospective cohort of almost 4400 HIV uninfected or HIV-indeterminant children (2644 with perinatal antiretroviral exposure) born to women with HIV identified 12 cases of mitochondrial dysfunction over 18 months of follow-up (0.26%), all with antiretroviral exposure (Barret, 2003); risk was higher with exposure to combination ARV therapy (primarily ZDV/3TC) than to ZDV alone. All children presented with neurologic symptoms, often with abnormal magnetic resonance imaging and/or hyperlactatemia, and all had deficit in one of the mitochondrial respiratory chain complexes and/or abnormal muscle biopsy. The same group has reported an increase in febrile seizures during the first 18 months

of life among uninfected infants with antiretroviral exposure (French Perinatal Cohort Study Group, 2002). Other studies have found associations between antiretroviral exposure and markers of mitochondrial dysfunction, including lower mitochondrial DNA quantity (Poirier, 2003) and transient hyperlactatemia (Giaquinto, 2001).

However, a retrospective review of deaths occurring among over 16,000 HIV-exposed but uninfected children (with and without antiretroviral exposure) followed 1986-1999 in five large prospective US cohorts found no deaths felt consistent with mitochondrial dysfunction. In this study most ARV exposure was to ZDV alone (Perinatal Safety Review Working Group, 2000). Neurologic adverse events were reviewed in 1,798 infants exposed to ZDV/3TC or placebo in the PETRA study, an African perinatal prophylaxis trial; no increased risk of neurologic events was observed among children treated with ZDV/3TC compared with placebo, regardless of intensity of treatment (Petra Study Team, 2002). In a review of clinical symptoms in 2414 uninfected children, 1008 with perinatal antiretroviral exposure, and with median follow-up of over 2 years, there was no association between antiretroviral exposure and clinical manifestations (European Collaborative Study, 2003). Mitochondrial toxicity can also manifest as cardiomyopathy and in a study of 382 uninfected infants, serial echocardiograms for the first 5 years of life found no significant differences in ventricular function stratified by ZDV exposure (Lipshultz, 2000).

Although there is conflicting data regarding ARV exposure and mitochondrial dysfunction, the likelihood of severe or fatal manifestations appears to be extremely small. However, mitochondrial dysfunction should be considered in ARV-exposed but uninfected children who present with severe clinical findings of unknown etiology, particularly neurologic findings. Appropriate monitoring should be considered for all exposed infants.

Given the limited and relatively short-term experience with all antiretroviral agents in pregnancy, long-term follow-up of infants exposed to these medications in utero is important.

- **Adverse pregnancy outcomes:** Concerns about possible increased risk for preterm delivery were raised by a small retrospective series of pregnant women receiving combination antiretroviral therapy (Lorenzi, 1998). Subsequently a large European cohort of almost 4000 mother-child pairs (only 323 on combination therapy) found a 2.6-fold (95% CI 1.4-4.8) increase in preterm delivery associated with exposure to combination therapy with or without protease inhibitors compared with no treatment, after adjusting for CD4 count and injection drug use; risk was doubled in women who were on therapy before pregnancy as compared with those initiating therapy in the third trimester (The European Collaborative Study and the Swiss Mother + Child HIV Cohort Study, 2000).

In contrast, a preliminary report from an observational study of pregnant HIV-infected US women found no association between combination ARV therapy and preterm birth in over 3000 women, 82% of whom received combination therapy (Read, 2003). The highest rates of preterm delivery was among women on no ARV therapy. A large meta-analysis of 7 clinical studies including 2,123 pregnant women receiving antenatal ARV therapy and 1,143 women on no therapy found no increased rates of preterm labor,

low birth weight, low Apgar scores, or still birth with exposure to multiple ARV drugs as compared to one drug alone or to no therapy (Tuomala, 2002).

Given this conflicting data, no changes in antiretroviral management are indicated in pregnancy. Several studies have found increased preterm birth rates in women on no ARV therapy, especially with more advanced disease (Brocklehurst, 1998b; Leroy, 1998; Martin, 1997)

- **Maternal adverse effects:**

- **Hepatotoxicity/Skin rash:** Women, particularly those with CD4 counts $>250/\text{mm}^3$, have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity (Stern, 2002) and deaths from hepatic failure have been reported in pregnant women receiving HAART regimens including nevirapine (Lyons, 2003; Langlet, 2000). It is not known whether pregnancy increases risk for hepatotoxicity in women receiving nevirapine; however, because some of the early symptoms of hepatotoxicity are relatively nonspecific and can be confused with common symptoms during pregnancy, health care providers for pregnant women receiving nevirapine should be aware of this potential complication and should regularly and frequently monitor clinical symptoms and hepatic transaminases (i.e., ALT and AST), particularly during the first 18 weeks of therapy, when this toxicity is most likely. When suggestive clinical symptoms develop, accompanied by elevation in ALT and/or AST, or when transaminases are significantly elevated in the absence of symptoms, nevirapine should be stopped and should not be restarted in the future. (USPHS Guidelines). **When antiretroviral therapy is being started in pregnancy and CD4 counts are greater than $250/\text{mm}^3$, nevirapine should be used as part of the regimen only if benefit clearly outweighs the risk.** These toxicities have not been reported in women receiving single dose nevirapine for prevention of perinatal transmission.

- Lactic acidosis/steatosis:** Lactic acidosis and hepatic steatosis, clinical disorders linked to mitochondrial toxicity in long-term nucleoside analogue users, may have a female preponderance, and a possible genetic susceptibility has been suggested. Bristol-Myers Squibb has reported several maternal deaths due to lactic acidosis/hepatic steatosis, all in women receiving a combination of d4T/ddI as part of their antiretroviral regimen at the time of conception and for the duration of pregnancy, and other non-fatal cases of lactic acidosis have been reported in pregnant women receiving this combination (Mandelbrot, 2003). All nucleoside analogue drugs can induce mitochondrial dysfunction, but use of ddI and/or d4T carries greater risk than use of ZDV, 3TC, abacavir, or tenofovir because of their greater potential for interfering with mitochondrial replication. Typical initial symptoms are relatively nonspecific and include nausea, vomiting, abdominal pain, dyspnea, and weakness. Metabolic acidosis with elevated serum lactate and liver enzymes is common. It is not known if pregnancy increases the incidence of this syndrome; however, pregnancy itself can mimic some of the early symptoms of lactic acidosis/hepatic steatosis and is also associated with some rare but life-threatening disorders of liver metabolism (acute fatty liver of pregnancy; hemolysis, elevated liver enzymes and low platelets—the HELLP syndrome). Therefore, pregnant women receiving nucleoside analogue drugs should have liver enzymes and electrolytes evaluated

more frequently during the last trimester of pregnancy and any new symptoms should be evaluated promptly and thoroughly. Signs and symptoms of lactic acidosis/hepatic steatosis tend to improve with drug discontinuation; therefore, if this condition is suspected drugs should be stopped promptly. Because of the maternal deaths noted above, **clinicians should prescribe the combination of d4T/ddI during pregnancy with caution and generally only when other nucleoside analogue combinations have failed or been associated with unacceptable toxicity or side effects.**

**- Interaction of drugs with pregnancy-related side effects/
physiologic changes:**

- Drugs that cause gastrointestinal upset may not be well tolerated in early pregnancy when morning sickness is common and may increase risk for nonadherence or inadequate blood levels from vomiting. In this situation, all ARVs should be discontinued and restarted when the nausea and vomiting is gone or has been effectively treated.
- Protease inhibitors and hyperglycemia: Protease inhibitors (PIs) have been associated with the development or worsening of existing hyperglycemia or diabetes and pregnancy also increases risk for glucose intolerance. It is unknown whether the use of PIs in pregnancy will exacerbate risk for development of gestational diabetes. Women receiving PIs in pregnancy should have their glucose levels monitored closely and be questioned regularly about symptoms of hyperglycemia.
- **Anemia:** Several antiretroviral agents, in particular ZDV, may cause bone marrow suppression and result in anemia. Pregnant women are at increased risk for anemia because of increased demands on nutritional stores, including iron and folic acid, and the addition of ARV regimens including ZDV may exacerbate anemia. Iron and folate supplementation should generally be given, as well as nutritional counseling to maintain adequate intake of other nutrients. Administration of ZDV is usually associated with macrocytosis; this should be kept in mind when evaluating anemia and should not exclude consideration of causes of microcytic or normocytic anemia, nor should it result in an assumption of causes of macrocytic anemia, such as folate or B12 deficiency. Treatment of anemia, including use of erythropoietin, may be considered in such women, as opposed to discontinuation of drug.

ANTIRETROVIRAL DRUG RESISTANCE ISSUES

The development of antiretroviral drug resistance is one of the major factors leading to therapy failure in HIV-infected individuals and there are concerns that resistance may also limit the effectiveness of antiretroviral drugs in providing prophylaxis against perinatal transmission (see IX A above). Resistance emerges under selective pressure, especially when viral replication is not completely suppressed. Women who have been treated in the past with incompletely suppressive regimens (e.g., single or dual nucleosides); have documented clinical, immunologic, or virologic failure with previous regimens (with or without a history of resistance on genotypic or phenotypic testing); or have a history of nonadherence or problems with intolerance are at increased risk for having resistance to one or more antiretroviral agents. These factors should be considered in decisions about choice of ARV regimen during pregnancy.

There is also an increasing prevalence of antiretroviral drug resistance in newly infected and treatment naïve individuals, implying transmission of drug-resistant strains. The prevalence of antiretroviral drug resistance in surveys of U.S. and European newly infected individuals who had never been exposed to therapy has been >10% for primary resistance mutations in the reverse transcriptase gene in the majority of studies and ranged as high as 23%; primary resistance mutations in the protease gene ranged from 1–16% (Wainbert, 1998; Weinstock, 2000; Little, 1999; Boden, 1999). Drug resistance testing is recommended if a woman has acute HIV infection during pregnancy and should be considered in pregnant women who are ARV naïve but have significant probability of having been infected with drug-resistant virus (Perinatal HIV Guidelines Working Group, 2004).

GENERAL PRINCIPLES FOR ANTIRETROVIRAL TREATMENT IN PREGNANCY

(Perinatal HIV Guidelines Working Group, 2004)

- Decisions regarding choice of antiretroviral regimens for maternal treatment should be the same in pregnant and nonpregnant women, with the additional considerations outlined above.
- Monitor CD4 count/viral load according to guidelines for nonpregnant adults: in pregnancy, this should be done approximately each trimester, but may be needed more frequently with failing or altered therapy. CD4 percentage may be a more accurate reflection of immune status during pregnancy than absolute CD4 cell count, because of possible variation in absolute CD4 count secondary to dilutional effects associated with hemodynamic changes in pregnancy.
- The three-part ZDV chemoprophylaxis regimen (Table 7-9) should be recommended as a minimum for all HIV-infected pregnant women to reduce the risk of perinatal HIV transmission. Current clinical trial and epidemiologic data confirm the effectiveness of this regimen; no other regimen studied to date in randomized clinical trials has shown superior results. However, cohort studies have suggested additional benefit to decreasing perinatal transmission with use of combination ARV regimens.

In women already receiving antiretroviral therapy when they become pregnant and this regimen does not include zidovudine, ZDV should be included as part of the regimen after 14 wk gestation, if feasible. There is evidence that duration of prior ZDV therapy in women with more advanced disease may not reduce effectiveness of ZDV in decreasing perinatal transmission (Stiehlm, 1999). However, ZDV should not be substituted for another antiretroviral agent when this is likely to reduce the efficacy of this regimen in treatment of maternal disease, i.e., with previous clinical failure of ZDV or history of documented ZDV resistance. The decision to add ZDV to an effective regimen must take into account the possible effect on adherence.

Table 7-9: Zidovudine Perinatal Transmission Prophylaxis Regimen

Antepartum	Initiation at 14–34 wk gestation and continued throughout pregnancy A. PACTG 076 Regimen: ZDV 100 mg 5 times daily B. Acceptable Alternative Regimen: • ZDV 200 mg 3 times daily or • ZDV 300 mg 2 times daily
Intrapartum	During labor, ZDV 2 mg/kg intravenously over 1 hr, followed by a continuous infusion of 1 mg/kg/hr intravenously until delivery.
Postpartum	Oral administration of ZDV to the newborn (ZDV syrup, 2 mg/kg every 6 hr) for the first 6 wk of life, beginning at 8–12 hr after birth.

In some circumstances ZDV cannot be used during the antepartum period (e.g., intolerance to ZDV). Stavudine (d4T) and ZDV are pharmacologically antagonistic and should not be used together; therefore, women on d4T-containing regimens with prior ZDV failure should be continued on the most effective regimen for their disease and ZDV should be excluded if d4T is maintained.

ZDV administration is recommended during the intrapartum period and for the newborn regardless of the antepartum antiretroviral regimen.

- Effective combination antiretroviral therapy is recommended (including ZDV if feasible) for women with clinical, immunologic, or virologic indications for treatment and for maximum prevention of perinatal transmission (regardless of clinical or immunologic status).

Women who present in labor with no prior antepartum antiretroviral therapy should be treated with one of several effective regimens, described below (Intrapartum) and in Table 7-10.

- Women with high CD4 counts and low or undetectable HIV-RNA levels, for whom initiation of antiretroviral therapy for the treatment of maternal infection would be considered optional, should be counseled about the potential benefits and risks of combination therapy and offered this therapy, along with the three-part ZDV perinatal prophylaxis regimen. Combination therapy should be selected based on efficacy data (in studies generally conducted among non-pregnant individuals); safety data for both mother and fetus/infant; and general experience with use in pregnancy. When several potential effective regimens are available and no specific safety concerns have been identified, in general drugs with wider experience in pregnancy should be selected.

Using ZDV alone is an option in this situation (with current USPHS guidelines when viral load < 1000 copies/mL). This has the advantage of limiting exposure to other drugs during pregnancy but there are concerns about potential selection of ZDV-resistant viral variants and limitation of future maternal therapeutic options, as well

Table 7-10: Comparison of Intrapartum/Postpartum Regimens for HIV-1-infected Women in Labor Who Have Had No Prior Antiretroviral Therapy (Scenario #3)						
Drug Regimen	Source of Evidence	Maternal Intrapartum	Infant Postpartum	Data on Transmission	Advantages	Disadvantages
ZDV	Epidemiologic data, U.S.; compared to no ZDV treatment	2 mg/kg intravenous bolus, followed by continuous infusion of 1 mg/kg/hr until delivery	2 mg/kg orally every six hours for six weeks*	Transmission 10% with ZDV compared to 27% with no ZDV treatment, a 62% reduction (95% CI, 19–82%)	Has been standard recommendation	Requires intravenous administration and availability of ZDV intravenous formulation Adherence to six week infant regimen Reversible, mild anemia with 6 week infant ZDV regimen
ZDV/3TC	Clinical trial, Africa; compared to placebo	ZDV 600 mg orally at onset of labor, followed by 300 mg orally every three hours until delivery AND 3TC 150 mg orally at onset of labor, followed by 150 mg orally every 12 hours until delivery	ZDV 4 mg/kg orally every 12 hours AND 3TC 2 mg/kg orally every 12 hours for seven days	Transmission at six weeks 9% with ZDV-3TC vs. 15% with placebo, a 42% reduction	Oral regimen Adherence easier than six weeks of ZDV	Requires administration of two drugs

<p>Nevirapine</p>	<p>Clinical trial, Africa; compared to oral ZDV given intrapartum and for one week to the infant</p>	<p>Single 200 mg oral dose at onset of labor</p>	<p>Single 2 mg/kg oral dose at age 48-72 hours**</p>	<p>Transmission at six weeks 12% with nevirapine compared to 21% with ZDV, a 47% reduction (95% CI*, 20- 64%)</p>	<p>Inexpensive Oral regimen Simple, easy to administer Can give directly observed treatment</p>	<p>Unknown efficacy if mother has nevirapine-resistant virus Transient nevirapine resistance mutations detected at 6 weeks postpartum in 19% of women receiving single-dose intrapartum nevirapine, and 46% of infants who became infected despite receiving nevirapine</p>
<p>ZDV- Nevirapine</p>	<p>Theoretical</p>	<p>ZDV 2 mg/kg intravenous bolus, followed by continuous infusion of 1 mg/kg/hr until delivery AND Nevirapine single 200 mg oral dose at onset of labor</p>	<p>ZDV 2 mg/kg orally every six hours for six weeks AND Nevirapine single 2 mg/kg oral dose at age 48-72 hours**</p>	<p>No data</p>	<p>Potential benefit if maternal virus is resistant to either nevirapine or ZDV Synergistic inhibition of HIV replication with combination in vitro</p>	<p>Requires intravenous administration and availability of ZDV intravenous formulation Adherence to six week infant ZDV regimen Unknown if additive efficacy with combination Transient nevirapine resistance mutations detected at 6 weeks postpartum in 15% of women receiving single-dose intrapartum nevirapine with ZDV or other antiretroviral drugs</p>
<p>ZDV, zidovudine; CI, confidence interval; 3TC, lamivudine * ZDV dosing for infants <35 weeks gestation at birth is 1.5 mg/kg/dose intravenously, or 2.0 mg/kg/dose orally, every 12 hours, advancing to every 8 hours at 2 weeks of age if >30 weeks gestation at birth or at 4 weeks of age if <30 weeks gestation at birth [121]. **if the mother received nevirapine less than one hour prior to delivery, the infant should be given 2 mg/kg oral nevirapine as soon as possible after birth and again at 48-72 hours.</p>						

as possibly increasing the risk for transmission. The development of resistance should be minimized by the relatively short duration of therapy and the more limited viral replication present in individuals with low HIV RNA level and high CD4 count. Follow-up of women enrolled in the PACTG 076 study has shown no significant differences in immunologic status or progression of disease (median follow-up 4.2 yr) in women who received ZDV compared with placebo recipients. (Bardeguez, 1998). However, recent data from PACTG 367 suggests that there is increased efficacy for prevention of perinatal transmission with combination ARV therapy, even when HIV-RNA is <1000 copies/mL (Shapiro, 2004).

- In antiretroviral-naïve patients clinicians may consider delaying initiation of ARV therapy until after 10–12 wk of gestation, based on considerations of the woman's health status, the potential (but generally low) risk of delaying therapy for several weeks, and the potential benefits of avoiding first trimester drug exposure for the fetus and the primary time period of nausea and vomiting in pregnancy.
- In antiretroviral-experienced patients, who become pregnant or are referred into prenatal care while receiving ARV therapy, therapy should be continued or modified, subject to the considerations outlined above. If pregnancy is recognized in the first trimester, some women and their clinicians may consider temporary discontinuation of therapy until after completion of the first trimester because of concerns about potential teratogenicity, or because of significant nausea and vomiting in early pregnancy leading to concerns about inadequate absorption of medications.

Current data are insufficient to either support or refute fetal risk with early exposure to antiretroviral agents with the exception of efavirenz. Discontinuation of therapy may lead to viral rebound, which could theoretically increase risk of intrauterine HIV transmission or have an adverse effect on maternal disease. The woman's clinical, immunologic, and virologic status should also be considered in decisions regarding continuation of therapy in the first trimester.

If the decision is made to stop therapy temporarily, all agents should be stopped simultaneously and restarted simultaneously in the second trimester to avoid development of drug resistance.

- Decisions regarding use of ARV therapy during pregnancy should be made by the woman after detailed discussion of benefits and potential risks of therapy. This includes discussion of:
 - treatment recommendations for health of the HIV-infected woman,
 - current information regarding effectiveness of antiretroviral therapy in reducing perinatal transmission,
 - known or potential effects of antiretroviral drug exposure on the pregnant woman,
 - known or potential effects of antiretroviral drug exposure on the fetus/newborn, and
 - the importance of adherence to any prescribed antiretroviral regimen.

There continue to be missed opportunities in prevention of transmission of HIV from mother to child. HIV has to first be identified in the woman; situations where counseling and testing have not been available or not utilized because of lack of perception of risk on the part of the woman or her health care provider have been associated with perinatal transmission in some cases. Women who become infected or seroconvert during pregnancy may be missed unless HIV testing is repeated later in pregnancy. Lack of prenatal care and active substance abuse, which frequently coexist, have also been linked to potentially avoidable increased risk for transmission (Bardeguez, 2000).

ANTIRETROVIRAL PREGNANCY REGISTRY

The Antiretroviral Pregnancy Registry is a collaborative effort between pharmaceutical companies, the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and obstetric and pediatric practitioners to collect observational information on antiretroviral exposure during pregnancy in order to assess potential fetal/infant anomalies after exposure to these agents. Patient names are not used and information is confidential. Health care providers who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to antiretroviral drugs to the Registry: 1011 Ashes Drive, Wilmington, NC 28405; telephone (800) 258-4263; fax (800) 800-1052, Internet access www.APREgistry.com.

OPPORTUNISTIC INFECTIONS

Prophylaxis indications and recommendations for primary prophylaxis of opportunistic infections in pregnancy are noted in Table 7-11. Once an individual has had the following infections, prophylaxis to prevent recurrence is recommended as standard of care. (See Chapter IV on Primary Medical Care.) First-choice regimens are outlined.

- ***Pneumocystis carinii* pneumonia:** same regimen as for primary prophylaxis. Criteria for discontinuation: CD4 > 200/mm³ for ≥ 3 mo.
- **Toxoplasmic encephalitis:** sulfadiazine 500–1000 mg po qid **plus** pyrimethamine 25–50 mg po qd **plus** leucovorin 10–25 mg po qd; counsel regarding concerns about potential teratogenicity of pyrimethamine. Criteria for discontinuation: CD4 > 200/mm³ for ≥ 6 mo and completed initial therapy and asymptomatic for toxoplasmosis.
- **Disseminated *Mycobacterium avium* complex:** azithromycin 500 mg po qd **plus** ethambutol 15 mg/kg po qd. Criteria for discontinuation: CD4 > 100/mm³ for ≥ 6 mo and completed 12 mo of MAC therapy and asymptomatic for MAC.
- **CMV:** choice of agents should be individualized in pregnancy after consultation with experts. Criteria for discontinuation: CD4 > 100–150/mm³ for ≥ 6 mo and no evidence of active disease and regular ophthalmic examinations.

Table 7-11: Opportunistic Infections and Primary Prophylaxis in Pregnant Women

Strongly Recommended				
Pathogen	Indication	Regimen	Alternatives	Comments
<i>Pneumocystis carinii</i>	CD4 < 200/mm ³ or oral thrush	TMP-SMZ DS 1 po qd TMP-SMZ SS 1 po qd	Dapsone 50 mg po bid Dapsone 100 mg po qd Aerosolized pentamidine (AP) 300 mg q mo (via Respigard II nebulizer) TMP-SMZ DS 1 po tiw	Some providers may prefer to use AP in first trimester because of lack of concerns about fetal exposure, secondary to theoretical concerns about possible teratogenicity with systemic medications. Criteria for stopping primary prophylaxis: CD4 > 200/mm ³ for ≥ 3 mo.
<i>Mycobacterium tuberculosis</i>	TST reaction ≥ 5mm or prior positive TST without treatment or contact with active TB	INH 300 mg po qd plus pyridoxine 50 mg po qd x 9 mo INH 900 mg po biw plus pyridoxine 100 mg po biw x 9 mo Rifampin 600mg po qd x 4 mo.	Rifampin 600 mg po qd x 4 mo	Some providers may choose to initiate prophylaxis after the first trimester, because of concerns about possible teratogenicity. Anecdotal experience with rifampin has not been associated with adverse pregnancy outcomes. Pyrazinamide should generally be avoided, particularly in the first trimester, because of lack of information concerning fetal effects. INH use during pregnancy has been associated with elevated risk for hepatotoxicity and LFTs should be monitored. Choice of drugs requires consultation with obstetric experts and public health authorities. Consult with obstetric experts and public health authorities if alternative regimen required
INH-resistant multidrug (INH and rifampin) resistant	Same; high probability of exposure to INH-resistant <i>M. tuberculosis</i>			
<i>Toxoplasma gondii</i>	IgG antibody to <i>Toxoplasma</i> and CD4 < 100/mm ³	TMP-SMZ DS 1 po qd	TMP-SMZ SS 1 po qd	If patient cannot tolerate TMP-SMZ, the recommended alternative is dapsone-pyrimethamine-leucovorin; however, because of the low incidence of TE during pregnancy and possible fetal risk with pyrimethamine, chemoprophylaxis may reasonably be deferred until after pregnancy Criteria for stopping primary prophylaxis: CD4 > 200/mm ³ for ≥ 3 mo.
<i>Mycobacterium avium</i> complex	CD4 < 50 mm ³	Azithromycin 1200 mg po qw	Rifabutin 300 mg po qd	Some providers may prefer to defer prophylaxis until after the first trimester, because of general concerns about administering drugs in early pregnancy. Experience with rifabutin in pregnancy is limited. Criteria for stopping primary prophylaxis: CD4 > 100/mm ³ for ≥ 3 mo.

TMP-SMZ, trimethoprim-sulfamethoxazole; INH, isoniazid; TST, tuberculin skin test; TE, toxoplasmic encephalitis; LFT, liver function tests.
 Source: Adapted from USPHS/IDSA, 2001.

- **Histoplasmosis:** amphotericin B 1.0 mg/kg iv qw; may be preferred, particularly during the first trimester, because of embryotoxicity and teratogenicity in animals exposed to itraconazole.
- **Cryptococcosis:** amphotericin B 0.6–1.0 mg/kg iv qw-tiw; may be preferred, particularly during the first trimester, because of craniofacial and skeletal abnormalities in infants after prolonged in utero exposure to fluconazole. Criteria for discontinuation: CD4 > 100–200/mm³ for ≥ 6 mo and completed initial therapy and asymptomatic for cryptococcosis.
- **Coccidiomycosis:** amphotericin B 1.0 mg/kg iv qw; may be preferred, particularly during the first trimester, because of craniofacial and skeletal abnormalities in infants after prolonged in utero exposure to fluconazole.

IMMUNIZATIONS (ACOG, 1991; CDC, 1993; USPHS/IDSA, 2001)

Immunization should be considered in pregnancy when the risk for exposure is high, risk of infection for mother or fetus is high, and the vaccine is thought unlikely to cause harm. HIV-infected individuals with immune suppression should avoid live virus or live bacteria vaccines. HIV-positive persons who are symptomatic or have low CD4 cell counts may have suboptimal responses to vaccination. Some, but not all, studies have shown a transient (< 4 wk) increase in viral load after immunization. This is of some theoretical concern, given the association between viral load and perinatal transmission. This increase in viremia may be prevented with appropriate antiretroviral therapy (Bartlett, 2003). For this reason, clinicians may consider deferring routine vaccination until after the patient is on an effective antiretroviral regimen and avoiding administration late in pregnancy, close to delivery, when most transmission is thought to occur.

Current immunization recommendations for HIV-positive pregnant women are:

- **pneumococcal vaccine** – “generally recommended” if not received during previous 5 years; consider revaccination if initially immunized with CD4 < 200/mm³ with increase to CD4 > 200/mm³ in response to ARV treatment.
- **influenza vaccine** – “generally recommended”; administer before flu season annually.
- **tetanus-diphtheria (Td) vaccine** – booster dose every 10 yr after completion of primary series.
- **hepatitis B vaccine** – “generally recommended” for all susceptible (anti-HBc-negative) patients; three doses at 0, 1, 6 mo.

- **hepatitis A vaccine** — “generally recommended” for all susceptible (anti-HAV-negative) patients with chronic hepatitis C or hepatitis B; also indicated before travel to endemic areas, in injection drug users, and with community outbreaks; two doses at 0, 6 mo.
- **enhanced potency inactivated polio vaccine** — use if not previously immunized and traveling to areas where risk for exposure is high; oral polio vaccine is a live virus vaccine and is contraindicated in HIV-positive persons.
- **immune globulins**
 - immune globulin recommended for measles exposure in symptomatic HIV-positive persons and hepatitis A with exposure to HAV in close contact/sex partner or travel to underdeveloped country (especially in patients with advanced HIV, who may have poor antibody response to vaccine)
 - hyperimmune globulins recommended:
 - varicella-zoster virus (VZV) immune globulin-susceptible adult (undetectable antibodies to VZV or no history of either chickenpox or shingles) after significant exposure (household, hospital room, close indoor contact > 1 hr, prolonged face-to-face contact) to chickenpox or VZV; give within 96 hr of exposure.
 - hepatitis B immune globulin (HBIG)-needlestick or sexual contact with HBsAg+ person in susceptible individual (anti-HBc-negative); HBIG should be given and HBV vaccine series should be started within 14 days of exposure.

REDUCTION OF SECONDARY RISK FACTORS

Treatment of STIs or other coinfections; encouragement of safer sexual practices during pregnancy; discouragement of smoking and drug use; and substance abuse treatment should be employed as measures that may decrease risk of perinatal transmission.

FREQUENCY OF VISITS

Determined on an individual basis, based on gestational age, health of the mother, presence of pregnancy-related complications, antiretroviral regimen and response, and psychosocial needs. In uncomplicated pregnancies visits generally are scheduled monthly in early pregnancy and every 1–2 wk from 28–30 wk of gestation until delivery. Coordinate with other health care visits when possible.

CONSULTATIONS TO CONSIDER DURING PREGNANCY

Certain consultations may be needed during pregnancy in the HIV-infected woman. Ideally, many of these can be handled within the same clinic or center where the patient is seen for obstetrical care or for primary medical care. When possible, referral of the pregnant woman with HIV to an obstetrician with HIV expertise and experience is advised. In this case many of the HIV-specific treatment issues may also be managed by this individual. In general, possible consultative needs include:

- **Perinatology:** to address special obstetrical concerns, including use of HIV-related or other medications in pregnancy, discussions about fetal monitoring/evaluation, other appropriate antepartum/intrapartum evaluation and management. When indicated, consultation should ideally be with a perinatologist who has HIV experience/expertise
- **Infectious disease/HIV specialist (particularly important if newly diagnosed in pregnancy):** to address HIV-related treatment issues, including choice of ARV regimen, need for OI prophylaxis or treatment
- **Pediatrics:** to address care of the infant after birth, including testing for HIV, use of zidovudine and PCP prophylaxis in exposed infants
- **Nutrition:** to address proper diet, need for nutritional or vitamin/mineral supplementation; food safety issues, when needed
- **Substance abuse management:** when indicated
- **Psychiatry/psychology:** to address signs/symptoms of depression, other psychiatric disorders and their management, if needed
- **Social services:** to address needs related to housing, transportation, domestic violence, access to medications and to medical care, etc.

COUNSELING AND SUPPORT

- **Support systems:** At the initial visit the health care provider should assess the patient's support system — who knows her HIV status, problems encountered with disclosure, family and/or friends to whom she turns for ongoing support, barriers to disclosure to sexual or needle-sharing partners. These issues should be readdressed at intervals throughout pregnancy as needed. The use of peer counselors may be especially helpful.
- **Contraception use postpartum:** Discussion about postpartum contraceptive plans should be initiated in early to midpregnancy to allow comprehensive education and counseling about available options and adequate time for informed decision making.
- **Condom use during pregnancy:** Sexual activity should be reviewed at each visit and condom use reinforced.
- **Drug use/treatment:** History of and/or ongoing substance abuse, including tobacco and alcohol, as well as illicit drugs, should be assessed at the initial visit and at intervals during prenatal care, if indicated. Type of substance(s), amount of use, route of administration, and prior drug or alcohol treatment should be documented. The patient should be counseled about specific risks associated with substance abuse in pregnancy (see Chapter X on Substance Abuse) and drug or alcohol treatment during pregnancy should be encouraged and facilitated for active problems.

- **Adherence:** Each patient should be educated and counseled about the importance of adherence to prescribed medications, particularly antiretroviral drugs, before they are initiated and medication adherence should be assessed and reinforced at each visit. (See Chapter V on Adherence.)
- **Clinical trials:** Pregnant HIV-positive women should be informed about the availability of and offered participation in clinical trials for which they are eligible.
- **Advance directives:** The issue of advance directives for care in the event of sudden deterioration in the woman's health, as well as guardianship plans for children in the event of the mother's incapacitation or death, should be discussed; legal assistance should be facilitated, if needed.

X. INTRAPARTUM

The goals of intrapartum management are to further reduce the risk of perinatal transmission and to minimize the risk of maternal and neonatal complications.

A. UNIVERSAL PRECAUTIONS

Gowns, gloves, and eye protection should be used in all deliveries and in examinations or procedures likely to generate splashing blood or amniotic fluid. (See Chapter XIII on Occupational Exposure.) When used, this should provide adequate protection for healthcare workers. Medical care should not be altered due to considerations of potential occupational exposure.

B. FETAL/MATERNAL MONITORING

External fetal monitoring should be employed but avoid use of fetal scalp electrodes or fetal scalp sampling unless necessary to ensure fetal well-being. Avoid artificial rupture of membranes unless obstetrically indicated.

C. MODE OF DELIVERY

Cesarean section, when performed before the onset of labor and/or membrane rupture (scheduled or elective), has been associated with decreases in mother-to-child transmission ranging from 55–80% in the absence of ARV prophylaxis and with ZDV alone (International Perinatal HIV Group, 1999; European Mode of Delivery Collaboration, 1999). Studies included a meta-analysis of 15 prospective cohort studies including over 7800 mother-infant pairs and an international randomized mode of delivery clinical trial. Both studies were done before viral load testing and use of optimal combination ARV regimens became standard of care in the US. Neither study found a benefit with cesarean section performed after onset of labor or membrane rupture. Recent data from PACTG 367

(Shapiro, 2004) in almost 2900 pregnancies found that in all subgroups of viral load, combination ARV therapy was associated with the lowest rates of transmission and with viral load <1000 c/mL, MTCT rates were significantly lower with multiagent vs single-agent ARV therapy (0.6% vs 2.2%, adjusted OR 0.2, 95% CI 0.04, 0.8) but did not differ by mode of delivery. Recent observational data from over 4500 women in the European Collaborative Study found that among women with undetectable viral load and after adjusting for ARV therapy during pregnancy, scheduled cesarean section was not associated with additional benefit in reduction of transmission (Thorne, 2004).

When making decisions about mode of delivery, potential maternal risks with cesarean section should be considered. Maternal morbidity and mortality are increased with cesarean section over vaginal delivery (Hebert, 1999). Although this risk is most marked with urgent or emergency cesarean section or after labor or membrane rupture, complications after scheduled cesarean section still exceed those seen with vaginal delivery (Roman, 1998; Gregory, 1998; Van Ham, 1997; McMahon, 1996). Most complications relate to postpartum infections (e.g., endometritis, wound infection, urinary tract infection, pneumonia) but also include complications related to hemorrhage, since blood loss is generally greater with cesarean section. Factors which increase the risk of complications include low socioeconomic status, genital infections, malnutrition, and smoking, and prolonged labor or membrane rupture, some of which may be more common in the setting of HIV infection.

Current data suggest that cesarean section is associated with a slightly increased risk of complications among HIV-infected women than among uninfected women, with the greatest differences seen among women with more advanced disease (European Mode of Delivery Collaboration, 1999; Watts, 2000; Read, 2001; Marcollet, 2002; Semprini, 1995; Grubert, 1999; Maiques-Montesinos, 1999; Vimercati, 2000; Grubert, 2002; Rodriguez, 2001; Urbani, 2001; European HIV in Obstetrics Group, 2004). However, complication rates in most studies of HIV-infected women were generally within the range reported among HIV-uninfected women and were not of sufficient frequency or severity to outweigh the potential benefit in selected cases where scheduled cesarean section may further decrease risk of MTCT (Perinatal HIV Guidelines Working Group, 2004). HIV-infected women, particularly when more immunosuppressed, may be at increased risk of postpartum endometritis, even with vaginal delivery (Temmerman, 1994).

Current recommendations (Perinatal HIV Guidelines Working Group, 2004; ACOG, 2000):

- Counsel all HIV-infected pregnant women about the possible benefit vs risk of scheduled cesarean section, as well as the limitations of current data. The woman's autonomy to make an informed decision regarding route of delivery should be respected and honored.

- Scheduled cesarean section should be recommended in the following situations:
 - HIV-RNA >1000 c/mL (regardless of ARV therapy).
 - Women with unknown HIV-RNA level, not on ARV therapy or receiving ZDV alone.
- Cesarean section is unlikely to add additional benefit in reduction of MTCT with HIV-RNA <1000 c/mL in ARV-treated mothers.
- The most recently determined HIV-RNA level should be used when counseling about mode of delivery.
- Scheduled cesarean section should be performed at 38 weeks gestation, based on clinical and ultrasonographic estimates of gestational age, to minimize risk of labor or membrane rupture prior to procedure. This is associated with a small increased risk of iatrogenic preterm delivery and infant respiratory distress syndrome, as compared to standard recommendations for scheduled cesarean section at 39 weeks when indicated in HIV-uninfected women.
- When scheduled cesarean section is performed, ZDV infusion should begin three hours before surgery to achieve adequate blood levels.
- Other ARV medications taken during pregnancy should be given on schedule.
- Prophylactic antibiotics are generally recommended at the time of scheduled cesarean section, although no controlled studies have evaluated their efficacy in this situation.
- Women who have planned scheduled cesarean section but present in early labor or shortly after membrane rupture should be counseled and managed on an individual basis, based on most recent HIV-RNA level, ARV therapy, and projected length of labor (based on cervical dilatation at admission, rate of cervical change, and status of membranes/length of rupture). Cesarean section after 4 or more hours of membrane rupture is less likely to reduce MTCT and risks of perioperative infection after cesarean section are increased with increasing duration of membrane rupture.

D. INTRAPARTUM ARV MANAGEMENT

ARV medications taken during pregnancy should be continued on schedule during the intrapartum period, regardless of route of delivery. If one or more ARV agents are not tolerated during labor because of nausea or vomiting, the entire regimen should be stopped simultaneously and restarted simultaneously after delivery. Women who are taking combination ARV regimens for the purpose of reducing risk of MTCT and who do not yet meet criteria for starting ARV therapy for treatment of maternal disease may discontinue treatment after delivery. Recent pharmacokinetics data has shown prolonged levels of nevirapine postnatally with levels persisting for over 3 weeks in a

significant proportion of women who received a single-dose of NVP in labor (Muro, 2004; Jourdain, 2004); this has raised concerns that stopping all drugs in an NVP-containing regimen at the same time will result in a variable period of time during which the woman is exposed to functional monotherapy and may be at increased risk for developing resistance. The role of staggered stopping of components of an ARV regimen in this situation is unclear and the duration of continued therapy needed with a "tail" is unknown. A recent report of women receiving NVP/ZDV/3TC during pregnancy found that stopping the NVP at delivery and continuing ZDV/3TC for 5–7 additional days made no difference in development of resistance (Lyons, 2005).

Regardless of ARV regimen used during pregnancy, women with HIV infection should receive ZDV in labor: 2 mg/kg ZDV in a 1 hr IV loading dose, followed by 1 mg/kg/hr by IV infusion. In women on a d4T-containing regimen during pregnancy, intrapartum ARV management should involve IV ZDV OR continuation of the oral combination ARV regimen, but not both, because of the pharmacologic antagonism between ZDV and d4T. As noted above, if scheduled cesarean section is planned, ZDV infusion should begin 3 hr preoperatively.

For women who present in labor with no prior antiretroviral therapy, several effective regimens are available. (Guay, 1999; Perinatal HIV Guidelines Working Group, 2004; Wade, 1998) These are outlined in Table 7-10.

There has been increasing concern with use of single-dose NVP either alone or in addition to other antiretrovirals because of data showing rates of NVP resistance after delivery ranging from 15%–40% (Eshleman, 2001; Cunningham, 2002; Jourdain, 2004; Martinson, 2004) in women with detectable viremia. Variables associated with development of maternal NVP resistance include longer half-life of nevirapine in individual women (Jackson, 2000), high baseline HIV-RNA level or low baseline CD4 count (Eshleman, 2001), viral subtype (subtype D.A) (Eshleman, 2004), body compartment (breast milk vs plasma) (Lee, 2003), and timing of sampling post NVP administration (Martinson, 2004; Eshleman, 2001). In the SAINT trial in South Africa, in which women received both an intrapartum and a postpartum NVP dose, NVP resistance was detected in 67% of women and 53% of infected infants, with no further benefit in terms of reducing transmission (Sullivan, 2002). The potential implications for future maternal treatment options from resistance to one dose of nevirapine are unclear. However, in a recent report of women who were started on NVP-containing HAART regimens after delivery, exposure to single-dose NVP in labor was associated with inferior virologic response (HIV-RNA < 50 c/mL) after 6 months of treatment; those with documented NVP-resistance were least likely to have optimal viral suppression (Jourdain, 2004).

NVP-resistance has also been detected in 17%–46% of infected infants after exposure to single-dose NVP (Eshleman, 2001) or single-dose NVP in addition to short-course ZDV (Chaix, 2004). Specific resistance mutations differed between mother and infant (Eshleman, 2001) and there was no evidence that the development of NVP-resistance increased risk of MTCT (Eshleman, 2001; Chaix, 2004).

Women of unknown HIV status who present in labor with no prenatal care may be offered rapid HIV testing, after careful counseling and with informed consent. Positive results should be confirmed by standard serologic testing but enable the initiation of an appropriate antiretroviral regimen to reduce the risk of perinatal transmission.

E. VAGINAL CLEANSING

A promising potential intervention to reduce transmission at the time of vaginal delivery is vaginal cleansing to decrease neonatal exposure to maternal blood and genital secretions. A clinical trial of 0.25% chlorhexidine manual vaginal cleansing on admission and every 4 hr until delivery in over 3300 women compared to some 3600 controls found no significant impact on HIV transmission, except when membranes had been ruptured for more than 4 hr before delivery (Biggar, 1996). However, this intervention reduced early neonatal and maternal postpartum infectious morbidity and neonatal mortality (Taha, 1997). A prospective trial of vaginal lavage using 0.2% or 0.4% chlorhexidine or no intervention also found no overall reduction in transmission with lavage, although data suggested that lavage before membrane rupture with chlorhexidine 0.4% may reduce MTCT (Gaillard, 2001). A more recent small (n = 107) vaginal cleansing study using benzalkonium chloride found no effect on perinatal HIV transmission or perinatal/infant mortality (Mandelbrot, 2002). Currently, vaginal cleansing cannot be recommended for prevention of mother-to-child transmission.

XI. POSTPARTUM

A. INFANT FEEDING

When replacement feeding is acceptable, feasible, affordable, sustainable, and safe, breastfeeding should be discouraged in women known to be HIV-infected, because of the well-documented increased risk for MTCT of HIV with breastfeeding. In low-resource settings, where there may be no good alternatives to breastfeeding, HIV-infected women should be counseled and assisted to exclusively breastfeed (breastmilk only without any additional solids or liquids) for up to 6 months, followed by rapid weaning (WHO, 2001). Breastfeeding mothers should be taught proper breastfeeding technique, including prevention, recognition, and prompt management of breast problems (e.g., mastitis, abscess, cracked nipples) or oral thrush or other oral lesions in the infant.

B. ASSESS HEALING

Assess healing of wound sites, uterine involution, and appropriate cessation of postpartum bleeding. Because of the potential for an increase in post-cesarean section wound infection, assessment of wound healing should be done between the time of hospital discharge and the routine postpartum visit.

C. CARE FOR MOTHER AND INFANT

HIV-infected mothers may neglect their own care while trying to provide appropriate care for their infant and other children or family members. It is essential that she be linked with comprehensive medical and supportive care services, including HIV specialty care; primary medical and gynecologic care; family planning; mental health or substance abuse treatment services; and assistance with food, housing, transportation, and legal/advocacy services, if needed. Although there are few data available, HIV-infected women may be at increased risk for postpartum depression.

Women who have received ZDV monotherapy during pregnancy should be reevaluated in the postpartum period with clinical assessment, CD4 count, and HIV RNA level to determine need for ongoing antiretroviral therapy. It is essential that access to and continuity of antiretroviral treatment as needed for maternal health be ensured.

Because of the physical recovery from giving birth, the stresses and demands of caring for a new baby, and possible postpartum depression, the new mother may be particularly vulnerable to problems with adherence to ARV treatment. Additional support and attention to this issue is warranted.

Similarly, the HIV-exposed infant should be linked into ongoing pediatric care, with HIV diagnostic tests as described below and appropriate HIV specialty care if HIV-infected.

D. CONTRACEPTION/CONDOM USE

Discussions about contraception and condom use should be continuous throughout pregnancy and reviewed and reinforced at the time of the postpartum visit.

E. LONG-TERM FOLLOW-UP OF MOTHER AND INFANT

All HIV-positive mothers and infants exposed to ZDV and/or other antiretroviral drugs or combinations during pregnancy should have long-term follow-up to assess possible late effects of these therapies on HIV progression in the mother or neoplasia or organ-system toxicity in exposed children.

XII. CARE OF THE HIV-EXPOSED INFANT (Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 2004)

A. DIAGNOSIS OF HIV

The standard for diagnosis of HIV infection in exposed infants is the use of viral assays (HIV DNA PCR (preferred), HIV RNA PCR, or viral culture) obtained within 48 hr of birth, at 1–2 mo, and 3–6 mo. HIV can be excluded in non-breastfed infants with two or more negative tests performed at age \geq 1 mo, with one of these performed at age \geq 4 mo. HIV IgG antibody tests will generally be positive in exposed infants for up to 18 mo of age because of transplacental passage; two negative tests performed at $>$ 6 mo and at least 1 mo apart will also exclude infection in infants without clinical evidence of infection. P24 antigen testing is less sensitive than other virologic tests and has a high frequency of false-positive results in infants $<$ 1 mo of age.

HIV DNA PCR is the preferred virologic assay for diagnosis with 93% (90% CI=76–97%) sensitivity by age 14 days (Dunn, 1995). Data on use of HIV RNA PCR are more limited but sensitivity appears to be comparable to HIV-DNA PCR for early diagnosis of HIV infants. HIV culture is sensitive for early diagnosis but is more complex and expensive, and has a longer turnaround time for results. Using these tests approximately 40% of infected infants can be identified by age 48 hr and are considered to have early or intrauterine infection; infants with initial negative testing during the first week after birth and subsequent positive tests are considered to have intrapartum infection. Almost all infected infants can now be diagnosed by the age of 4–6 mo. ZDV monotherapy for perinatal prophylaxis has not been shown to delay detection of HIV or decrease sensitivity or predictive value of virologic assays (Connor, 1994; Kovacs, 1995), although performance of these tests when the mother has received more intensive combination antiretroviral therapies has not been studied.

B. ARV TREATMENT

All HIV-exposed infants should receive ZDV prophylaxis (2 mg/kg every 6 hr) for the first 6 wk of life as part of the three-part zidovudine regimen to prevent perinatal HIV transmission. If the mother has received no antepartum or intrapartum ZDV, the newborn regimen should be started as soon as possible after delivery, preferably with 6–12 hr of birth. For preterm infants ($<$ 35 wks), ZDV 1.5 mg/kg IV or 2.0 mg/kg po q 12 hr, then increased to q 8 hr at 2 wk (if $>$ 30 wks at birth) or 4 wk (if $<$ 30 wks at birth) is recommended (Capparelli, 2003). Initiation of ZDV prophylaxis for the neonate within 48 hr (most infants initiated

ZDV within 24 hr) of birth resulted in an approximately 50% decrease in infection compared with no therapy (Wade, 1998). A recent clinical trial of infant post-exposure prophylaxis (no maternal antepartum or intrapartum ARV exposure) in breastfeeding infants in Malawi found that single-dose infant nevirapine plus one week of ZDV had 36.4% efficacy as compared to single-dose infant nevirapine alone when evaluation was limited to infants uninfected at birth (Taha, 2003). This study does not address whether this regimen is superior to 6 wks of ZDV alone, which remains the standard recommendation from the USPHS. The use of single-dose nevirapine in mothers and newborns has been associated with the development of nevirapine resistance in a certain proportion of infants infected despite prophylaxis, as noted above. The implications of this resistance for progression of infection or response to future NNRTI-containing ARV regimens is unknown. The efficacy of other ARV agents or combinations in HIV-exposed infants, particularly in cases where the mother is known or suspected to have ZDV or NVP resistance, is unknown and appropriate dosing regimens in neonates are not well-defined for many drugs.

Once infection is documented, more intensive combination antiretroviral therapy is recommended with clinical symptoms of HIV infection or evidence of immunosuppression (immune categories 2 or 3 – Table 7-12) regardless of age or viral load. Some experts recommend initiating potent ART as soon as the diagnosis is confirmed, regardless of clinical or immunologic status or viral load, because HIV-infected infants under the age of 12 mo are considered to be at high risk for disease progression and the prognostic value of standard virologic or immunologic parameters is less than that for older children. Once HIV infection is confirmed, decisions about antiretroviral therapy should be made in consultation with a specialist in the treatment of pediatric HIV infection.

Table 7-12: 1994 Revised Human Immunodeficiency Virus Pediatric Classification System

Immune Category	< 12 Mo		5 Yr		6-12 Yr	
	CD4/mm ³	%	CD4/mm ³	%	CD4/mm ³	%
Category 1: no suppression	≥ 1500	≥ 25%	≥ 1000	≥ 25%	≥ 500	≥ 25%
Category 2: moderate suppression	750-1499	15%-24%	500-999	15%-24%	200-499	15%-24%
Category 3: severe suppression	<750	<15%	<500	<15%	<200	<15%
<i>Clinical Category</i>	Children < 13 Yr					
Category N: not symptomatic	Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.					
Category A: mildly symptomatic	Children with 2 or more of the following conditions but none of the conditions listed in categories B and C: <ul style="list-style-type: none"> • Lymphadenopathy (≥0.5 cm at more than two sites; bilateral = one site) • Hepatomegaly • Splenomegaly 					
Category B: moderately symptomatic	Children who have symptomatic conditions, other than those listed for category A or category C, that are attributed to HIV infection. Examples of conditions in clinical category B include, but are not limited to, the following: <ul style="list-style-type: none"> • Anemia (<8 gm/dL), neutropenia (<1,000/mm³), or thrombocytopenia (<100,000/mm³) persisting for ≥ 30 days • Bacterial meningitis, pneumonia, or sepsis (single episode) • Candidiasis, oropharyngeal (ie, thrush) persisting for > 2 months in children aged > 6 months • Cardiomyopathy • Cytomegalovirus infection with onset before age 1 month • Diarrhea, recurrent or chronic • Hepatitis • Herpes simplex virus (HSV) stomatitis, recurrent (ie, more than two episodes within 1 year) • HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month 					
Category C: severely symptomatic	Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome, with the exception of LIP (which is a category B condition) <ul style="list-style-type: none"> • Dermalitis • Parotitis • Recurrent or persistent upper respiratory infection, sinusitis, or otitis media 					

Source: Adapted from CDC, 1994.

C. *PNEUMOCYSTIS CARINII* PNEUMONIA PROPHYLAXIS

All HIV-exposed infants should receive *P. carinii* pneumonia prophylaxis with trimethoprim-sulfamethoxazole (150/750 mg/m²/day in two divided doses po tid on consecutive days) beginning at 4–6 wk and extending for the first year of life or until HIV infection is excluded. Dapsone or atovaquone are alternatives.

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VIII. ADDRESSING CULTURAL ISSUES TO IMPROVE QUALITY OF CARE

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I. INTRODUCTION

Over the past five years, medical and public health researchers and policy makers have noted the growing role of behavioral, social, and cultural matters in outcomes in health and disease. A consistent theme among the recommendations and findings in their reports is the interdependent role of cultural issues in health care and quality of care. Cultural issues in health care were identified as important in medical education (Cuff, 2004), in the health care work force (Smedley, 2004; Gebbie, 2003), in health care disparities (Smedley, 2003), and in health communications (Nielsen-Bohlman, 2004). These inquiries suggest the need for core competencies, as reflected in curricular changes as well as new directions in research and policy. Women and the cultural factors related to gender are among the issues emphasized by policy makers, researchers, and clinicians alike

Culture is defined as learned and shared behaviors, beliefs, and values that provide meaning to an individual's life and that serve as a lens and guiding framework through which individuals, families, and communities understand and respond to their experiences (Hahn, 1995). Culture is affected by home, religion, ethnic group, language, neighborhood, school, and age-group (Cruickshank, 1989; Helman, 2000). Culture, social and economic status, and gender roles significantly influence the decisions women make when seeking health care and can be both a positive and a negative factor in facilitating use of health services. Providers who can effectively identify and address cultural factors associated with illness and its management are in a better position to improve diagnosis, treatment strategy, and patient outcomes.

This chapter will discuss the cultural and social considerations, including gender roles, for women living with HIV infection and help identify the benefit that provider-based assessment tools can offer in improving women's access to and utilization of HIV primary health care.

II. ECONOMIC ISSUES

Poverty remains a basic underlying context for most women living with HIV infection. In the US women with HIV are often poor and un- or under-insured. Their ability to improve their economic status is often impaired by lack of education or work skills and their role as mothers or caretakers for other family members, who may also have HIV infection. They may depend on the economic support (including insurance benefits)

of their husband or boyfriend, making them particularly vulnerable if abandoned. Women also generally have lower-paying jobs and often earn less for comparable work than men. Ultimately food, housing, and, when substance abuse is present, the need for drugs or alcohol may take priority over health care. Lack of insurance, transportation, or flexible working hours can also affect access to appropriate care (Bunting, 1999).

The economic situation is most extreme in sub-Saharan Africa, where national economies and social institutions in the hardest-hit countries have been devastated because so many individuals in their most-productive years have become sick or have died from HIV/AIDS. Husbands, who are often the primary wage earners, may leave their wives when they learn the woman is HIV-infected. Besides caring for themselves, the women left behind become the sole supporters and care givers for their children and other family members. Lack of food, housing, and employment as well as lack of clean water, electricity, and other basic resources may be deficient or lacking and impact the health care professional's ability to provide basic primary care in addition to antiretroviral treatment (ART).

Many women with HIV have had to rely on the government public health and social service system for help and health care and may have experienced difficult moments in asking for help or have suffered humiliation on behalf of their families in trying to get what they need (Sowell, 1999). Because of stigma and poverty, women are vulnerable to a decreased ability to meet their needs, including housing, food, and work, as well as decreased access to health care services and/or delayed health-care seeking for themselves (Amaro, 1995; Mays, 1987). Women with dependent children and those who are pregnant may be even more reluctant to seek care, partly because they fear having their children taken from them, particularly when issues of substance abuse are involved (Pivnick, 1991).

III. GENDER ROLES AND SOCIAL EXPECTATIONS

While women have central responsibilities within their families, gender roles often constrain their authority and influence their ability to make decisions about their own health and medical care. Women's social responsibilities clearly affect their health seeking behaviors, potentially delaying their own treatment and resulting in the placement of others' priorities above their own (Anderson, 1993). Women often defer their needs to those of their children and significant others. In a study of inner-city HIV-positive women and their infants, most women studied secured medical care for their infants, but only 46% reported ever seeking HIV-related health care for themselves (Butz, 1993). Women may experience more stigma and discrimination related to HIV than men because of its connotations with promiscuity and prostitution and sexuality in general. Because of past experiences of stigma and discrimination, many minority women tend not to trust the entire health and human service infrastructure. These factors combine to make health care less accessible

and less of a priority in the lives of many HIV-infected women. Women who are at risk fear getting tested for HIV based on the stigma of testing positive (Gupta, 2002). Therefore, they may delay seeking care until they are quite ill.

Along with the stigma and discrimination of an HIV diagnosis, women living with HIV experience alterations in their personal relationships. The core of many women's identity is mediated through their relationships to their children and significant others, and to their roles in the family structure. A diagnosis of HIV may result in abandonment or violence by partners. When multiple family members are also infected with HIV, the woman is generally the caretaker when they are ill, resulting in significant social, psychological, and economic burdens (Gupta, 2002). The well-being and the return of normalcy for a family depend on the care-seeking ability of the woman and the sensitivity of health care providers in facilitating the process of seeking care (Anderson, 1999). Each of the woman's relationships—including her relationships with members of the health care team—may affect the others and each can have a profound impact on how the woman makes choices about her HIV infection and comorbidities.

The social position and imbalances of gender/power in many societies contribute to low self-esteem and difficulties negotiating safe sexual practices with their partners. The implementation of an empowerment program for Latina immigrant women demonstrated that targeting broader sociocultural issues may increase the skills necessary for these women to avoid transmission of HIV infection by their sexual partners (Gomez, 1999). The women in this study showed significant increases in comfort with sexual communication, were less likely to maintain traditional sexual gender norms, and reported changes in decision making power.

Providers need to understand the choices that women have made and the social support structures that best serve them, based on their roles and cultural beliefs. Significant relationships may include informal relationships and non-family members who can help the woman throughout her HIV disease course. These important non-family relationships may replace a family system that has not provided the support needed since the woman was diagnosed with HIV. Within the African American population, one can find various arrangements that constitute a family and that provide great support for women in times of crisis (Asante, 1995). Many Hispanic women have *madrinas* (godmothers) and *comadres* (friends related by marriage or baptism) who are great sources of support for them during times of crisis. Providers need to understand the family dynamics in order to facilitate trust, understanding, and empowerment of these women so that they can choose the options that fit their culture and their life's reality. Before giving the initial HIV test results and discussing disclosure issues, it is essential to have an understanding of the communication dynamics in the family, especially with the significant other of the woman.

IV. PSYCHOLOGICAL ISSUES

Women face an array of psychological issues, related not only to possible coexisting substance abuse, mental illness, domestic violence, and poverty, but also to the stresses of living with HIV disease and often being the primary care provider for the family. Most HIV/AIDS-infected minority women are stigmatized even before becoming HIV infected because of drug use, race, or poverty (Wofsy, 1987). Many of these women are single heads of households with young, dependent children, and, in general, lack a community of support such as that seen among gay men (Weiner, 1991). This situation affects the actual and perceived availability of supportive resources over the course of HIV disease. Limited emotional resources affect HIV-infected women's access to both psychological and medical services. Low self-esteem is the rule rather than the exception and plays a major role in ability to access and adhere to care.

Women experience a variety of emotions related to their HIV infection. They may feel anger at a partner who infected them sexually or guilt with a partner to whom they have been unable to disclose their status or guilt if they have transmitted HIV to any of their children.

At the initial visit with the health care provider the woman may feel overwhelmed and experience shock, disbelief, guilt, anger, sadness, and even suicidal ideation. At intermediate visits, many of the same emotions are still present, although some may be more attenuated while others may have greater prominence. Emotional assessments should be continued in order to provide appropriate interventions and help establish trust. Crisis visits may occur frequently until the woman and her family stabilize their lives, as well as the medical conditions of all infected family members. Reasons for crisis may range from HIV issues to domestic violence to medical deterioration of one or more family members. These scenarios call for all team members to work together and devise a plan or procedure that will address the issues and problems that arise. A debriefing session by the care coordinator/social worker with the woman after the crisis has been resolved is important to prevent potential future crises.

Despite this complex picture and against all odds, many of these women have strong coping abilities and profound survival instincts. Some studies have suggested that interventions to support use of active coping strategies as physical symptoms increase may be effective in promoting positive adaptation to HIV disease (Moneyham, 1998).

V. PROVIDER-PATIENT COMMUNICATION

The recent Institute of Medicine study *Unequal Treatment* called particular attention to the role of culture in undermining effective communication between members of racial/ethnic minorities and their providers (Smedley, 2003). Clinical decision making (Eisenberg, 1979), patient satisfaction, adherence to treatment, and poor health outcomes are related to the communication between patients and their providers. While the IOM study focused on US racial and ethnic minorities, many of the issues are relevant internationally.

Providers working with HIV-infected women face the challenges of understanding how culture influences the access and use of health services, the place of HIV in the priorities of women's everyday lives and the constraints of social and cultural traditions on women's decision making around health and disease. When providers don't understand the cultural beliefs of their patients, they increase the likelihood that these beliefs will be barriers to providing care. Providers should assess their own cultural beliefs and consider how they affect their behavior towards patients.

Most of us understand some of the basic differences in culture, such as food, dress, music and language. But it is more difficult to understand that people may view the world from different perspectives. When we are aware of differences, we may change our behavior out of respect for restrictions between males and females or customs about greetings or otherwise adjust our behavior. Even when we are not fluent in another culture's traditions, making accommodations may be easier with people we know and with groups we frequently interact with. Cross-cultural misunderstandings and confusion are more likely to arise when both provider and patient lack experience with each other's culture.

Because of the cultural diversity of communication styles and the potential for missed communication and misunderstanding between patients and providers, it is vital that health care professionals understand that different cultures communicate differently. Factors impacting cross-cultural communication include the meaning of specific words, the pacing of language, the volume and tone of the spoken words, and whether or not gestures are utilized as part of the communication process.

Effective communication makes use of context, as well as words, gestures, and symbols.

"Individuals from low-context cultures prefer a direct, literal style of interaction, and people are expected to say more or less exactly what they mean. Examples of low-context cultures are: United States, Canada, Europe, Israel, and Australia. Low-context cultures value self-expression skills such as clarity, fluency, and brevity. Speakers often seek to convince and persuade their listeners."

"The Orient, the Arab world, and much of Africa are examples of high-context cultures. The preferred style of interaction is an indirect one in which meaning is carried less by the literal meaning of the words and more by contextual clues such as the place, time, and situation and the relationships between speakers. High-context cultures value harmony, subtlety, sensitivity, and tact more than clarity. Speakers often seek to connect with their listeners." (McKay, 1995)

Understanding the differences between low-context and high-context cultures can enhance the interaction between the client and the provider. Culture is not the enemy or adversary of clinicians. Like any other information in the clinical encounter, culture is information that a provider can understand and learn to manage.

The questions in Table 8-1 can be used as a tool that providers can apply to understanding clients from a different culture. This approach creates an atmosphere in which patients can become partners in the provision of their care (Weeks, 1979).

Table 8-1: Questions to Enhance Provider Understanding of Clients from a Different Culture
<i>Assumptions- Provider's and Patient's</i>
• What are the patient's assumptions? What are my assumptions?
• What assumptions about health do I bring to the interaction?
• What assumptions about illness do I bring to the interaction?
• Do I assume the patient knows why she is there?
• Do I assume that I know what she wants to get out of the interaction or the visit? Am I clear about what I want to get out of the interaction?
• Do I assume the patient wants to get better? Get better in what regard?
• Am I assuming that she wants what I would want if our roles were reversed? Did I ask to assure that this in fact the case?
• Am I assuming that she will tell me if she cannot adhere to the treatment plan? Did I confirm that she could tell me if she would not be able?
<i>Health Literacy and Complementary Therapies</i>
• Is what I am saying understandable by the patient? Can she read?
• Is the patient clear that this is a partnership and that we are engaging in joint care planning?
• Am I presenting the information in a non-judgmental and non-coercive way?
• Are there others from whom the patient has sought care? What did they tell her?
• Is there someone else the patient would like to include in her care?
• Has the patient used any other therapies, medications, herbs, elixirs, ointments, teas to help her with this problem?
<i>Patient Priorities</i>
• What questions can I ask to initiate a dialog and partnership for joint care planning? What is important to her?
• Does she want to get better? What does "better" mean to her?
• What does she need to get better?
• What can we do to help her get better? Address non-medical and medical issues.
• What can we do first? Look for tasks/ activities that will be a small start and yield early successes.
<i>Holistic Approach</i>
• How have I attended to the non-medical health, wellness, and quality of life needs?
• There are things that we may not be able to help with. Are there others we can find to help with these issues?

Additional considerations
Provider Level:
• Therapeutic alliance is important. Partnering in care will improve health outcomes.
• Don't have to do it all at once. Small successes are great motivators for next steps.
• Need for on going assessment since situations change constantly.
• Need to ask questions in a simple and non judgmental way.
• Need to demonstrate respect for the patient and her differences.
• Understand that we as health care providers bring both positive and negative issues to the therapeutic relationship. Strive to increase the positive and decrease the negative.
• Improved insights into patient motivations and what they are ready to tackle and when are critical.
• Understand that we have the power to improve as we assume our patients do.
• Improved quality of life and clinical outcomes matter.
System Level Interventions
<i>Senior leadership should make these expectations clear and model them for staff</i>
• Communication styles and strategies that demonstrate respect for diversity – diversity of signs, posters, pamphlets (also sensitive to limited English proficiency) are important.
• Consents, legal documents and releases should be written in easy-to-understand English. Translations should also be in plain language.
• Physical environment should be warm and welcoming.
• Team effort and team approach are key.

VI. CULTURAL ISSUES

Because most women living with HIV infection in the United States come from two primary groups, African and Hispanic Americans, this section will focus on cultural beliefs associated with these two groups. A comprehensive care program that broadly addresses the sociocultural aspects of a woman's life in a collaborative and multidisciplinary fashion will facilitate the treatment and care of women from diverse cultural backgrounds. These examples will illustrate strategies and approaches that local providers can adapt to their patients and the local circumstances in which women struggle to negotiate their care.

A. HISPANIC CULTURE

In Hispanic populations, one complex facet of cultural sensitivity and competency lies in the diversity of the subgroups that make up this population in the United States. The subgroups and their representation are: Mexican American, 58.5%; Central and South American, 10.8%; Puerto Rican, 9.6%; Cuban, 3.5%; all other Hispanic (including Spaniards),

17.8% (U.S. Census Bureau, 2001). Each of these subgroups has its distinct culture, as well as various levels of assimilation into the general population. Providers need to address these distinctions in developing intervention and prevention programs for HIV/AIDS and other health issues.

Amidst the diversity among Hispanic Americans, social scientists have identified cultural values that most Hispanics share regardless of their country of origin. The identified core values are (Marin, 1989):

- *Familismo* - the importance of the family to the individual
- *Colectivismo* - the importance of friends and extended family members, such as godmothers (*madrinas*) and godfathers (*padrinos*)
- *Simpatia* - the act of being polite; respectful not confrontational
- *Personalismo* - the preference to be with other persons of the same ethnic group
- *Respeto* - the act of upholding one's own integrity without damaging another person

For Hispanics, HIV/AIDS is not an individual issue, but one that affects the family structure and the unity within the community. In many Hispanic families the husband makes the decisions for all members of the family, including his wife. The extended family in the Hispanic culture may also play a major role in making decisions. Clinicians need to assess the role of the woman within her family and her culture and her adherence to strict cultural beliefs.

CASE STUDY: HISPANIC

NAME: DE

AGE: 35 YEARS

ETHNICITY: MEXICAN AMERICAN

DE came into our program on 11/4/93. Her first visit with the physician was the day she learned of her HIV status, when she was 27 weeks pregnant with her second child. She had a 14-month-old daughter who was followed for urological problems. Her HIV risk factors included two heterosexual partners and history of a blood transfusion after her first pregnancy in 1992 because of hemorrhage. She stated she was tested because of the blood transfusion. We performed HIV testing on her daughter, and explained the risk to her unborn child; the plan of care for the child after birth was reviewed.

At the time of diagnosis DE had a CD4 count of 178. She maintained her health during her pregnancy, continued to care for her daughter, and began getting care for her HIV disease. With psychological evaluation, she tested in the lower ranges for verbal intelligence and conceptual processing.

DE's support system included her mother (who initially did not know DE's status), and her common-law husband, who was not the father of her oldest child, but was the father of the child she was carrying. The HIV test results for her daughter and husband were negative. DE experienced a variety of emotions, including fear, anxiety, and depression, and needed much support from the entire staff to assist her not only in understanding what HIV was and how it affected her and her family, but also in obtaining financial support. As with most new clients, DE was

Case Study: Hispanic (continued)

distrustful of staff initially, but with care, concern, and perseverance, our entire team (physicians, nurses, social workers, psychologist, foster granny volunteers, etc.) developed a trusting relationship with her.

Her second child was a boy, and within 1-2 months of life it was obvious he was infected and he had a very low CD4 count. DE never missed a clinical appointment for him and, in fact, was always there even before clinic began. She provided excellent care to her son, learned to give him his medications, and had good relationships with the medical staff.

By 1996 her own health had deteriorated significantly and her care was transferred to another physician, but she continued to bring her son to our program for care. She was linked with hospice services and almost died several times, but each time improved to the point where she was ultimately taken off the hospice list. Her determination to personally care for her son was a strong motivating factor in her ability not only to stay alive, but to actually improve her health status.

DE was able to make the choice as to how and where her son would spend his last days, and was at his bedside when his short life ended. She let balloons loose into the sky at his burial to signify that her son had gone to heaven.

DE continues to live, and both she and her husband have dropped in to the clinic occasionally to visit and to show us photos of the family trip to Disney World, pictures of her son in his last hours, etc. DE has also become involved with the Pediatric AIDS quilt project, started by one of our program nurses.

B. AFRICAN AMERICAN CULTURE

As with other minorities, African Americans experience high rates of unemployment and overall poverty. Any discussion of core values must be evaluated in the context of these concerns. Even though family conflict is reported in all races and socioeconomic groups, minorities have a higher rate of conflict because they are more vulnerable to arrest by the police and referral to public agencies (Gibbs, 1990). These problems may be more appropriately viewed as community problems rather than problems of the black family (Gilbert, 2002). Amidst the complexity of life for African American individuals and their families, they are sustained by their core values, which have historical roots in Africa.

The core values that most African Americans embrace have been described by Sudarkasa (1996). The seven core values are respect, responsibility, reciprocity, restraint, reverence, reason, and reconciliation. They are defined as follows:

- Respect - the respect for others, from parents and relatives to elders or leaders in the community.
- Responsibility - being accountable for self and for those less fortunate in one's own extended family and in one's community.
- Reciprocity - giving back to family and community in return for what has been given (mutual assistance).

- Restraint - giving due consideration to the family or community/group when making decisions.
- Reverence - deep awe and respect towards God, towards the ancestors and towards many things in nature.
- Reason - taking a reasoned approach to settling disputes within the family or the community.
- Reconciliation - the art of settling differences; that is, putting a matter to rest between two parties.

Respect and responsibility were major guiding principles for behaviors within families in Africa that have been carried over to African American families today. Restraint is related to the notion of "sacrifice." Parents exercise restraint over their own destinies in order to provide for their children, who in turn repay the "sacrifice" by, in many instances, putting their parent's needs before their own (Sudarkasa, 1988).

Spirituality is a strong cultural value among both African American and Hispanic American women. Historically, the church in the African American community has been the single most important organization advocating for public policies to influence improvements in health, education, and financial quality of life (Poole, 1990). From this perspective there is a continuum between religion and one's quality of life. As the guiding center for the extended family, reinforcing the sense of self and self-esteem within the culture, the church offers opportunities for the whole family's development (Butler, 1992).

Churches in the African American community have created and mobilized leaders and increased hope (Neeleman, 1998; USDHHS, 1998). In order to provide comprehensive health care to African American and Hispanic women, programs should include the spiritual dimension in all aspects of care.

Many African Americans share a distrust of the health care system related to historical experiences such as the Tuskegee experiment. Airhihenbuwa (1990) suggests that African Americans operate in a society where rules and social systems appear to be adversarial. The degree to which they perceive the odds against them as manageable or overwhelming will depend to a significant degree on the transactional competency and success of their parents, the competence of the role models in their primary community, and the availability and accessibility of resources and support to help them in their coping efforts (Myers, 1983).

CASE STUDY: AFRICAN AMERICAN

NAME: BA

AGE: 43 YEARS

ETHNICITY: AFRICAN AMERICAN

BA was referred to the program after delivering a baby boy 7½ weeks prematurely; he was born withdrawing from drugs and was subsequently found to be HIV infected. After the referral was made at 5 p.m. on a Friday, two nurse case managers went to the hospital to meet with BA and to initiate the process of caring for her child. While there, local law enforcement officers came into the patient's room and informed her that they were removing her newborn son from her custody because of her drug use during pregnancy.

BA was 43 years old and had a history of injection drug use since the age of 15 when she ran away from home. She was homeless at the time of delivery and was attempting to reunite with her family. She had had no prenatal care.

On initial assessment she was happy but nervous and apprehensive about the possibility that her child could be infected with HIV. Doctors had told her that her uterus was so badly scarred from sexually transmitted diseases that she was unlikely to get pregnant. This pregnancy was a pleasant surprise for her and she saw this baby as a gift, a miracle from God.

She was admitted to an outpatient drug rehabilitation program and her baby was placed in foster care. With the help of her caseworker she reunited with her mother and sisters after revealing her HIV status. She also met with her spiritual counselor on a regular basis to discuss life and death issues.

BA completed her 6-month drug rehabilitation program successfully and was able to petition the courts and get her son back. She tended not to keep her own medical appointments and deferred most of her energy to her child's care. She was in the hospital when her son became very ill and was also hospitalized. She was able to talk with the pediatrician and sign advance directives for her child. He died in his mother's arms during that hospitalization. When the nurses and caseworker came to be with her at the hospital, she shared the following: "I have done a lot of things wrong in my life and I didn't think I had a chance to get in the pearly gates. But you know I have loved my son and he knew that. I tried to be the best mother I could be for the short time I had him. So when I die and I go up and see St. Peter at the pearly gates he is just going to nod his head no. As I am just about to leave I hear someone running and I turn around to hear a little boy screaming "St. Peter, that's my mom and she loved me and I love her. You have to let her in!"

BA remained clean for the entire year that her infant was alive, but relapsed back into drug dependence upon his death. She lived two years, during which time she was back and forth between drug rehabilitation programs and hospitalizations for her HIV infection. A key factor in her care was the assignment of a case manager and the coordination with her drug rehabilitation team. She had constant contact with her spiritual counselor, with whom she had had a long-lasting relationship since childhood. BA died surrounded by her family, the staff, and her spiritual counselor.

C. COMMUNITY

In addition to the major core values of a culture, other considerations include the “vital signs” of the community in which the woman lives. These vital signs include, but are not limited to, prevailing cultural beliefs, pressing issues for the community, employment rate, the level of poverty, the definition of health espoused by most people in the community, access to health care, characteristics of the community leaders and their followers, support structures, and the level of trust in the health care system. These factors can be described as a community’s ecological system (Meyer, 1988).

Health care providers should be encouraged to view the people of the community in the context of their social environment. The interrelatedness of individuals to their environment leads one to view people not as solitary subjects, but as integral parts of a whole. With both Hispanics and African Americans the community is vital to a good and healthy life. However, both of these populations experience a disproportionate level of displacement due to the requirements for economic survival. Health and human service providers who want to serve these populations with sensitivity and quality must understand the complexity of living with HIV disease in the midst of poverty. According to Fullilove (1996), psychological well-being depends on strong, nurturing places.

VII. INTERVENTIONS

The following interventions are suggested to help health care providers give more effective and culturally-appropriate care:

- Strategies that utilize a holistic approach towards women’s care should include the social, economic, and psychological well-being of the individual.
- Assign a case manager/case coordinator to help the woman negotiate multiple parts of the health care/social services system; help decrease anxiety and establish trust; and serve as a broker and advocate for her and her family’s needs.
- Teach the woman about the structure of the health and human services system in her community.
- Establish peer interventions so that women are able to talk with other infected women about negotiating day-to-day responsibilities and dealing with stigma/discrimination issues.
- The initial visit is often filled with many different emotions and reactions. Take time to deal with these reactions, begin the process of developing trust, assess possible suicidal thoughts, and give information in small bites over several closely spaced visits.
- Give simple straightforward explanations.
- Identify the woman’s ethnic subgroup of origin, when appropriate.

- Include a bilingual provider on the health care team (do not use the children or the custodian to translate; this demonstrates a lack of respect and may result in miscommunication or misunderstanding).
- Diagram the family structure and discuss the role of each member; review the role of women within the family; family dynamics need to be understood before recommending disclosure actions.
- Develop or link with empowerment programs targeting sexual communication, negotiation, and self-esteem.
- Recognize extended family members as key supports for the patient.
- Explore the cultural values and beliefs of the woman, both at the initial assessment and over time.
- Show respect for spiritual beliefs and how they affect advance directives and other decisions women make
- Initial assessment by the case manager or peer outreach worker in the home may give additional insights into the family structure and the roles the woman fulfills within her family.
- Understand each woman's priorities and develop strategies to meet those needs she considers most important.
- During intermediate visits, work on establishing trust between the woman and her provider/health care team. Trust is an essential continuous, dynamic process requiring open and ongoing communication between women and their health care providers/team.
- During regular visits, inquire about the health status of all members of the family, especially the children; continue to assess the emotional status of the woman.
- Identify and have a working knowledge of the core values of the community you are serving.
- Develop an alliance with key community based organizations.
- Teach staff about the effect of community and culture on the woman's decision-making and belief/value system.
- Identify women who have to leave their community for long periods of time for employment (e.g., migrant workers), and assist them in making connections for health care while away and in ensuring access to needed medications.

VIII. SUMMARY

Women living with HIV infection are living with a multitude of medical and social problems. They live not in isolation but as integral members of their communities and primary caregivers for their families. Although HIV infection is often not their primary concern, this does not mean they

do not want help. To understand and assist women living with HIV, it is important to take a systems approach, to look at the whole to understand the parts, to think in loops rather than in straight lines (O'Connor, 1997). High quality care for women living with HIV disease is best given by addressing not only her medical needs, but also her economic needs, her relationships, her emotional responses, her culture, and her community: all of the faces of a multi-faceted life.

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IX. PSYCHIATRIC ISSUES

Joyce Seiko Kobayashi, MD

I. INTRODUCTION

While healthcare providers for women living with HIV focus primarily on the physical manifestations related to HIV, understanding the emotional experience of the woman and the potential psychiatric problems associated with HIV is important to optimize care.

The health care provider can provide significant comfort during normal adjustment phases and common emotional transitions through skilled emotional support, assessment of coping skills, patient education, and empathy. When normal adjustment issues give way to formal psychiatric or neuropsychiatric disorders, accurate diagnosis and appropriate treatment are required.

Further care may require referral for substance abuse treatment or psychiatric evaluation, or referral to programs of social support, housing, case management, and other services, depending on the needs of the individual. Care providers who develop a comprehensive treatment plan for the HIV-positive woman that includes emotional support and psychiatric treatment for comorbid psychiatric conditions help her to feel that the entirety of her pain and suffering is being addressed.

For a more detailed discussion of the neurological manifestations of HIV, see chapter IV; and for more discussion about substance abuse and treatment, see chapter X.

This chapter will address a range of psychiatric issues relating to HIV disease in women, from normal adjustment issues to psychiatric disorders, and will make specific recommendations for provider and program response, evaluation, and management.

II. PERSPECTIVES ON BEING A WOMAN WITH HIV

Three different perspectives are important to develop a more comprehensive view of the woman experiencing HIV: 1) the individual perspective as the woman journeys through the common emotional milestones of HIV; 2) the perspective of women as a group, because women, in contrast to men, tend to cope with HIV within the context of their most important relationships; and 3) the contemporary context of the majority of HIV-infected U.S. women who are members of racial or ethnic minorities, living in poverty, affected directly or indirectly by substance abuse, and often with personal experiences of adult victimization and/or childhood abuse. The experience of the woman infected with HIV at any given time may be more influenced by one or another of these dimensions.

For example, the initial shock of an HIV diagnosis may be experienced with personal fears of stigma and suffering; or with common concerns about rejection and abandonment by a partner; or simply experienced as further victimization in the context of a traumatic history and daily struggles to survive. The way women face the challenges of HIV personally, as women, and in the context of their past histories is a strong predictor of psychiatric co-morbidity (Sherbourne, 2003). The goal of skilled support is to facilitate positive transformation of this experience.

A. EMOTIONAL MILESTONES: THE EXPERIENCE OF THE INDIVIDUAL HIV-POSITIVE WOMAN

The emotional adjustment after learning that one is HIV-positive, including coping as an individual on a daily basis with the demands of having HIV and becoming an HIV patient, commonly follows a natural course of progression through stages (See Table 9-1). For every “shock” – a new diagnosis, a new symptom, the need to take more pills, more intrusions on daily routines – there is often the “aftershock” of anger and avoidance, fear and denial. While emotional adjustment may vary by culture, race, and ethnicity, by level of social support and caretaking responsibilities, and by age and severity of physical and psychiatric symptoms, these emotional milestones are broadly applicable. With knowledgeable support and timely clinical intervention, these reactions can be transformed into acceptance, with important opportunities for prevention of HIV transmission to others and safer behaviors for oneself.

B. COPING WITH HIV: THE EXPERIENCE OF HIV-POSITIVE WOMEN IN THE CONTEXT OF RELATIONSHIPS

Women experience HIV infection within the context of their various relationships. When examining HIV-infected adults in medical care in the U.S., over one-quarter have children; women are more than three times as likely to have children compared to men and are more than twice as likely to live with their children (Schuster, 2000). In a prospective observational cohort of 871 HIV-positive women, 35% had a family member with HIV infection, including one-half of Latina women, one-third of black women, and one-fifth of white women; in 38% this was a sibling, 24% a husband, and 27% had more than one family member with HIV (Fiore, 2001). In a clinic-based sample in Connecticut (N = 68), nearly three out of four of the HIV-positive women knew at least one person who had died of AIDS (Ickovics, 1998).

Table 9-1: Providing HIV Care at Emotional Milestones

<i>Patient Milestones</i>	<i>Health Care Provider Skills Required</i>		
	<i>Be Able To</i>	<i>Educate Patient About</i>	<i>Show Empathy For</i>
HIV prevention	Discuss high-risk behaviors with ease Discuss prevention measures (e.g. condoms, safe sex, clean needles) with ease	HIV, HIV disease HIV transmission Negotiating safe behaviors	Denial Lack of interest High-risk behaviors
Deciding to get tested for HIV	Discuss details of sexual histories with ease Identify high-risk behaviors Help patient prepare for results Help patient anticipate emotional impact	HIV antibody testing	Denial Ambivalence Fear
Accepting, understanding HIV-positive serostatus	Tell bad news with empathy Anticipate common concerns Encourage discussion Assess emotional impact	HIV antibody testing HIV disease, prognosis HIV transmission behaviors CD4, viral load	Denial, anger Fears of rejection, stigma Fears of death Continuing high-risk behaviors
Disclosure of HIV serostatus	Discuss decisions about whom to tell Discuss decisions about when to tell	Anticipating reactions Negotiating safe sex	Conflicts about disclosure Rejection, fears of rejection
Accepting the "patient role"	Establish rapport, trust, mutual respect Encourage partnership, foster autonomy Elicit concerns, encourage questions Communicate patient tasks clearly	Patient tasks Patient responsibilities	Ambivalence, distrust Anger, rejection Oppositional behavior Testing limits
Initiating positive health behaviors	Identify harmful behaviors Refer for substance, psychiatric treatment Establish alliance for good health	Health promotion Harm reduction Lifestyle, behavior change	Anger, grief Difficulty changing behaviors Resistance to treatment

Table 9-1: Providing HIV Care at Emotional Milestones (continued)

<i>Health Care Provider Skills Required</i>			
<i>Patient Milestones</i>	<i>Be Able To</i>	<i>Educate Patient About</i>	
		<i>Show Empathy For</i>	
Appointments, adherence	Forge and maintain treatment alliance Understand barriers to treatment Discuss risk/benefit decision making Anticipate side effects	Importance of follow-up Medications, side effects Adherence skills Viral resistance	Anger, defiance, hostility Burden of adherence demands Fear of failure, self-blame Missed appointments, doses
Coping with physical symptoms	Identify symptoms, provide relief Encourage accurate description of symptoms Provide emotional support, compassion for distress	Etiology of symptoms Limitations of treatment Risks/benefits of treatment	Discomfort, distress, pain Breakthrough of denial Anger, impatience Fear of progression of illness
Confronting serious illness	Diagnose, treat, diminish suffering Tell bad news with empathy Recognize emotional impact, show compassion Listen	Illness, treatment specifics Prognosis Opportunities for change in behaviors; "lessons"	Anger, blaming self, provider Fear of dying Suffering Dependency needs
Improvement in health status	Consolidate lessons learned from illness Encourage health promotion behaviors	Realistic expectations Reassessing work limitations	Unrealistic expectations Return of denial
Transition to disability	Initiate discussion about disability Assess legal disability Provide emotional support	Realistic goals, expectations Advance care directives Disability entitlements Permanency planning	Grief, demoralization Anger, denial Loss of self esteem
Confronting death	Balance hope, discuss common fears Provide accurate prognosis, allow time to prepare Support appropriate denial for daily function Discuss palliative care, communication with "family"	Prognosis, likely course Palliative measures	Denial, anger, blame Fear, grief

Developmental psychologists have characterized fundamental differences in the way women and men think about themselves (Gilligan, 1993), with significant implications for clinical practice. Although any generalization about gender may be wrong in the individual case, two overarching observations derived from this research are important to understand the ways women and men tend to differ in their reaction to being HIV-positive. First, women more frequently define themselves in the context of their relationships to others; and second, while men more frequently fear intimacy, women more often fear separation (Surrey, 1982). Whether these differences are more evolutionary and transcultural, or derive from socialization and economic forces, an understanding of these differences is important to increase providers' sensitivity and to enhance their effectiveness in working with women living with HIV.

Although there are universal fears about dying alone and being abandoned when ill, it is not uncommon to hear HIV-positive men express fears about becoming dependent on others, whereas HIV-positive women tend to worry more about those who are dependent on them as their illness progresses. Men often lose self esteem if they are not able to continue working, or feel anger and may wish to distance themselves from others whom they feel obligated to support; women more frequently lose self esteem if they are unable to continue taking care of others. Many women with HIV are single mothers and feel shame or guilt if they are unable to take care of their children as they feel they should.

These reactions may lead women to accept being the target of anger or abuse, or to suppress their own anger, in order to avoid finding themselves alone; they may continue to use drugs for fear of losing a substance-using partner; or they may feel guilty about taking time away from responsibilities for others in order to address their own needs. It may be difficult to self-motivate and establish good self-care independently when "no one" will benefit from these efforts except for the woman herself. In a study of delays in seeking care among HIV-positive individuals, women were 1.6 times more likely to delay medical care than men; having a child in the household increased the likelihood of delay (Stein, 2000). Women who have been abused, are poor, or have in other ways experienced powerlessness in their lives may be even less convinced that they are "worth it."

On the other hand, the motivation to take care of others may encourage some HIV-positive women to undertake major changes in their own behavior, such as giving up longstanding drug dependencies during pregnancy, or engaging in discussions that frighten them, such as about permanency planning or advance directives. Other women with HIV may take on the responsibility of bringing their children or partners into medical care despite significant barriers, including their own fatigue or ill health, and may demonstrate remarkable resourcefulness in seeking out additional avenues of support.

IX

The clinician should show respect for the degree of caring the woman demonstrates, and acknowledge the impact HIV has on the people she cares about. These are clinical opportunities to build trust and strengthen an alliance around common concerns. Giving permission for the HIV-positive woman to attend to her own needs, and in other ways “empowering” her, may over time be as important as instructions about what specific health behaviors to follow. The health care provider who first acknowledges her priorities in taking care of others, and then reminds her that she will not be able to continue that care unless she first takes care of her own health, is likely to be more successful in terms of her health outcomes. When the woman feels her values have been respected, and when sufficient trust has been established, the provider’s concerns will be experienced as caring and supportive, rather than as rejection or criticism.

In certain circumstances, such as in negotiating safe sex with an unreceptive partner, the provider may even be more directive, and encourage a woman to develop the necessary skills to be more assertive about her own health concerns. Developing these skills may also be helpful within the healthcare setting. In the HIV Cost and Services Utilization Study (HCSUS) of HIV-infected U.S. adults in medical care, women with CD4 counts below 200 cells/mm³ were less likely to receive effective combination antiretroviral therapy than men (Shapiro, 1999).

C: SURVIVING WITH HIV: HIV-POSITIVE WOMEN IN THE CONTEXT OF POVERTY, SEXUAL ABUSE, AND SUBSTANCE ABUSE

POVERTY

The majority of women with AIDS in the United States are unemployed, and 83% live in households with incomes less than \$10,000 per year. Only 14%, aged 15-44 years, are currently married, compared to 50% of all women in the United States. Twenty-three (23%) of HIV-positive women live alone, 2% live in various facilities, and 1% are homeless. Approximately 50% have at least one child less than the age of 15 years. The majority of women with AIDS in the U.S. are from minority racial and ethnic groups, with African Americans and Latinas comprising over three-quarters of cases. (Bozzette, 1998; Shapiro, 1999; Barkan, 1998) (See Table 9-2 for a comparison of women and men in HCSUS.) They are frequently without easy access to medical care. Poverty and the related experiences of racism, sexism, and stigmatization are the dominant themes in their lives.

Poverty and homelessness can be as devastating to the person and personality as the physical sequelae of HIV. For many women who are living on the street or in transient residences, are feeling overwhelmed by the needs of their children, or are battered within their relationships, illicit drugs may seem to be the best antidote. In the book *Women, Poverty and AIDS* (Farmer, 1996), which contains a comprehensive discussion of these

issues, Shayne and Kaplan state that “safe sex is an economic compromise for many poor women who rely on sex as a source of employment, as a means to establish ownership or proprietary rights in relationships, or as a means of getting tangible supports, generally short in supply.”

Table 9-2: A Demographic Comparison of HIV-positive Women and Men*

	<i>Women</i>	<i>Men</i>	<i>Level of Significance</i>
African American	54%	27%	< .001
Unemployed	76%	59%	NA
Incomes < \$5000/yr	30%	17%	< .001
Without medical insurance	85%	63%	< .001
<35 yr old	44%	31%	< .001

** Analysis based on 1996 figures of men vs. women living with HIV/AIDS; women were 26% of 231,4000 reported cases*
NA, not applicable.
Source: Bozzette, 1998.

It is hard to make the medical treatment needs for HIV relevant unless the woman feels her provider recognizes and has some understanding of her daily struggles for survival. Women may feel that their medical providers are simply adding to their burdens by asking them to prevent transmission to others (especially when they may have little choice in safer sex practices) or to adhere to complicated medical regimens.

In one study investigating ways to improve health care utilization, a sample of HIV-positive women from a needle exchange program and from a correctional facility indicated that “shelter and food/clothing ranked first among unmet needs for services” (Thompson, 1995). Poverty and unemployment were also viewed as more serious problems than HIV/AIDS by a group of women in treatment at a state psychiatric facility (Weinhardt, 1998).

More than one-third of a nationally representative sample of HIV-positive individuals in care went without or postponed care at least once in a six-month period for one of four competing subsistence needs: needing the money for food, clothing or housing; not having transportation; not being able to get out of work; and being too sick. Having at least one competing subsistence need was associated with never having received antiretroviral therapy (Cunningham, 1999).

There are many concrete services such as transportation, child care, food programs, income and employment support, and housing that can increase the ability of HIV-positive women to participate in health care. Many women who have substance abuse disorders with psychiatric



comorbidity may qualify for entitlement programs that they have not explored. Vocational rehabilitation programs are often facilitated by medical or psychiatric referrals. Community-based programs for people with HIV often include food banks and vans, and sometimes offer childcare or emergency shelter. Lack of housing is a major factor in medical illness and should be considered in developing an individual treatment plan. For example, residential programs that engage clients in substance abuse treatment contracts can provide both housing and incentives to abstinence from substance abuse.

CHILDHOOD SEXUAL ABUSE AND ADULT VICTIMIZATION

Sexual abuse and domestic violence are experienced within the lifetimes of a significant portion of American women, regardless of their economic status, ethnicity, or HIV status. When childhood sexual abuse is defined as physical contact of a sexual nature with children less than 14 years of age, prevalence estimates range from 28% to 36% (Wyatt, 1986). Although childhood abuse research is limited by the methodology of self-report, sampling, and definitional issues, it shows remarkably consistent high lifetime prevalence rates of childhood sexual abuse and adult physical or sexual assault for women who are HIV-positive or at risk for HIV.

A history of childhood sexual abuse is also associated with multiple HIV transmission and risk behaviors. In a study of 3,346 women, those who had a history of childhood sexual abuse were more likely than those who had not to report problems with alcohol, use of drugs, receiving money or drugs in exchange for sex, unwanted sex, a greater number of unprotected sex acts, a greater number of partners, and a greater proportion of sex acts accompanied by drugs or alcohol in the past 90 days. Analyses suggested that for these women with a history of childhood sexual abuse, participation in non-sexual risky behaviors "may be a bridge to participation in sexual behaviors that increase the risk of HIV infection" (NIMH Multisite HIV Prevention Trial Group, 2001). In a study of street-recruited women from three different major urban sites, with demographics similar to a large portion of the population of women with HIV, 12% of 918 women reported that they had been sexually assaulted in the previous 12 months (Wong, 1993). In comparison with those who were not sexually assaulted, rape was associated with higher rates of sex for drug exchange, reporting more than 100 lifetime sex partners, smoking crack, and twice the likelihood of being infected with HIV and syphilis.

Sexual assault in adult women is estimated to be two to four times as likely for women who are survivors of childhood sexual abuse. A study of 327 women with or at risk for HIV (Zierler, 1991) found that 35% of women with HIV were sexually assaulted as adults. Forty-five percent of women who reported rape as adults had been sexually abused during childhood or as teenagers. Among women with HIV, adult sexual assault was associated with more sexual partners, unprotected sex involving drugs, earlier age of injection drug use, teen pregnancy, sexually transmitted infections, and need for gynecologic surgery.

In a study of 230 HIV-positive women in New York City, 50% experienced abuse in childhood, 68% as adults, and 7% reported physical assault or rape in the previous 90 days. History of childhood abuse was significantly correlated with adult and recent trauma (Simoni, 2000). In the HCSUS study, 20.5% of women with HIV in care reported domestic violence or physical harm since diagnosis (Zierler, 2000), and in the prospective HIV Epidemiology Research Study (HERS) cohort, the incidence of abuse among HIV-positive women with CD4 count >350 cells/mm³ was 6.92 per 100 person-years (Gruskin, 2002). Among 357 men and women living with HIV/AIDS, 68% of women (and 35% of men) reported a history of sexual assault since age 15 (Kalichman, 2002). A recent study of 1645 subjects enrolled in the Women's Interagency HIV Study (Cohen, 2000) found that among both HIV-positive and seronegative, at-risk women, two out of every three women (67% and 66%, respectively) had experienced domestic violence during their lifetimes, and almost one out of three (31% and 27%, respectively) had been sexually abused as children. There was no significant difference in prevalence associated with race, ethnicity, education level, or marital status, although domestic violence was more frequently reported among older, unmarried, unemployed women.

Multiple studies have also established a relationship between childhood sexual abuse in women and adult-onset depression (Weiss, 1999). In a study of 236 women ages 36-45, increasing severity of abuse was associated with increasing risk for depression (Wise, 2001). Both HIV-positive and at-risk women have higher rates of depression than the general population, and depression increases with physical symptoms (See below). HIV-positive men and women who are survivors of sexual assault report greater anxiety, depression, and evidence of borderline personality disorder (Kalichman, 2002).

There are major implications from these findings for medical care, psychiatric and substance abuse treatment, and HIV prevention efforts. HIV-infected and at-risk women who have experienced childhood and/or adult sexual and/or physical abuse or other domestic violence see HIV and their relationship to the health care system through the prism of those experiences. These experiences also influence their likelihood of continuing risky sexual or substance using behaviors.

Women with a history of childhood sexual abuse may be susceptible to a variety of misperceptions. A directive style of recommending medical treatment, for example, may be perceived as coercive. A treatment with major side effects or a surgical procedure may be experienced as abusive intrusions in their lives or bodies. A friendly relationship with a health care provider may take on unwarranted sexual overtones. Efforts at health education may not be heard when the individual is suddenly lost in thought or actually dissociating because of sudden memories of abuse. Pain may be amplified because of experiences of physical abuse and risk being dismissed as drug-seeking.

Clinicians, in turn, may have particular responses to women who have been abused and should understand their vulnerability to unproductive "countertransference" reactions, such as being provoked into becoming the anticipated abusive figure or feeling compelled to rescue the



individual. The clinician must ask in order to know. A simple and direct question should be used: e.g., "Would you mind if I ask if you have ever been the victim of physical or sexual abuse?" or "Has anyone ever hurt you physically or abused you sexually?" "Is there anyone in your life right now who makes you feel unsafe?" These questions should routinely be asked as part of the medical history. If there is a positive response, the details of current abuse must be explored. If there is a negative response, the possibility of an abuse history should nevertheless be kept in mind.

Medical care, treatment, and prevention efforts should be conceptualized with attention to the impact of violence and trauma in their lives (Fullilove, 1992). Lack of trust, low self esteem, and feelings of powerlessness are frequently experienced. Supportive measures, such as having a female provider, participation in support groups, receiving supportive psychotherapy or treatment with psychiatric medications, assistance with social resources, or receiving vocational rehabilitation can increase trust and self esteem and ultimately empower these women. Education about prevention should be a part of comprehensive care when there is high risk for continuing transmission behaviors.

ILLICIT DRUG USE

As many as one-third of HIV-positive women exposed to HIV through heterosexual contact use noninjection drugs, and the use of these drugs increases the likelihood of high-risk sexual behaviors (Klein, 1997). Women who use drugs by injection may be more likely to follow as a second user of shared needles, increasing their risk of HIV acquisition, as well as acquisition of hepatitis B and C (Bennett, 2000).

There is a high rate of psychiatric comorbidity among women with HIV who use drugs and/or alcohol (see Chapter X on Substance Abuse). Each factor can exacerbate the other and relapses, in turn, are often associated with increased medical morbidity. In the HCSUS database, co-occurring psychiatric symptoms and drug dependence and/or heavy alcohol consumption were found in an estimated 13% of persons with HIV. Sixty-nine percent of those with substance-related problems also had psychiatric symptoms, and 27% of those with psychiatric symptoms had a substance-related problem (Galvan, 2003). A three-year longitudinal study of HIV-positive intravenous drug users (IDUs) found that 47% had experienced at least four episodes of major depressive disorder, while less than 40% of IDUs with current major depression received treatment (Johnson, 1999).

Investigators using a National Survey of Veterans found that the combination of substance abuse and post-traumatic stress disorder (PTSD) increased the rate of HIV infection almost 12-fold, compared to those without either disorder (Hoff, 1997). Because of the association between a history of sexual violence, substance abuse and PTSD, a similarly increased rate of HIV may be expected among women with this constellation of conditions.

Active substance abuse has been associated with nonadherence with antiretroviral therapy and general medical care. Medical providers caring for substance-using women with HIV should consider both psychiatric assessment and substance abuse treatment in the plan of care. The combination of psychiatric and substance abuse treatment when there is comorbidity has been shown to be effective (Lyketsos, 1997); if treatment for both problems is not offered at the same time, a relapse in one condition may destabilize the other.

III. NEED FOR MULTISERVICE CLINICAL PROGRAMS

Women with HIV who have multiple diagnoses and require a variety of services to be adequately supported through their illness. The varied needs of these women require specific multiservice program components (Morrow, 1997) and care provider training (Table 9-3) for effective comprehensive care. The clinical issues in these diverse subpopulations of HIV-positive women with complex histories and comorbidities can be managed best through such programs, which are responsive to both their clinical and concrete needs. Some of these services may be available through community-based AIDS service organizations and require close coordination with medical care.

<i>Common Clinical Issues for HIV-positive Women</i>	<i>Clinical Program Response</i>
Lack of trust; fears of abandonment	Continuity of care; nonjudgmental attitude; patience; female providers
Chronic low self esteem	Respect, acceptance, listening, time
Complex personal situations	Multiservice coordination: housing; transportation; vocational rehabilitation and education; linkage to entitlement programs
Responsibility for children and others in household	Child care, respite programs; integrated pediatric and women's care; permanency planning and advance directives assistance
Stigmatization	Awareness of care provider reactions; social support groups
Continuing high-risk behaviors	Prevention education via the primary health care provider
Feelings of powerlessness; lack of assertiveness and skills	Case management; outreach support; patient education; new skills training
Domestic violence; exploitive relationships	Women's shelters; domestic violence counseling; legal aid; psychotherapy
Substance use and psychiatric comorbidities	Psychiatric and substance abuse treatment programs integrated with medical care

Optimally, treatment for formal psychiatric and substance use disorders can be available on site (Kobayashi, 2000) and integrated with primary medical care. Savings from unnecessary emergency room visits and



preventable hospitalizations may help offset the labor-intensive costs of these multiservice programs. If a broad array of services is not provided for these populations with such a complex layering of needs, routine medical care is likely to be complicated by intermittent follow-up, medication nonadherence, frequent presentations in crisis in emergency room settings, and suboptimal medical outcomes.

IV. PSYCHIATRIC DISORDERS

Psychiatric disorders among women with HIV infection require diagnosis and treatment. According to the HCSUS, a national probability sample of HIV-positive adults receiving medical care, the prevalence of anxiety and mood disorders, illicit drug use, significant alcohol use, and use of psychotropic medications among individuals with HIV is significantly higher than in the general population (Bing, 2001; Orlando, 2002; Galvan, 2002; Vitiello, 2003). A detailed diagnostic interview of the 57% in this sample who initially screened positive for a psychiatric disorder or illicit drug use in the previous six months estimated that 29.1% of all HIV-positive patients had a major psychiatric disorder: anxiety disorders (20.3%); mood disorders (17.2%); major depression (15.3%), panic disorder (12.3%), and PTSD (10.4%) (Vitiello, 2003). An analysis of data from 847 women in the HCSUS reported that younger age, having HIV-related symptoms, using avoidant coping strategies, reporting increased conflict with others, experiencing prior physical abuse, needing income assistance, and putting off going to the doctor because of caring for someone else increased risk for psychiatric morbidity (Sherbourne, 2003).

If women with these disorders do not receive appropriate treatment, their participation in medical follow-up or their ability to adhere to complicated medication regimens can be compromised. HIV-positive women with untreated psychiatric disorders may also engage in high-risk behaviors, potentially increasing risk of transmission to others or personal risk of being exposed to other STIs.

A. DEPRESSIVE SYMPTOMS AND MOOD DISORDERS

Women across cultures and around the world have lifetime incidence rates of major depressive disorders twice that of men. In the U.S., the incidence of major depression in the general populations is approximately 10-15% (American Psychiatric Association, 2000). Two large scale longitudinal natural history cohort studies of HIV-positive women (WIHS, HERS) used the Center for Epidemiologic Studies Depression Scale (CES-D) score of 16 or higher to reflect "probable cases of depression." These studies suggest rates of depressive symptoms or disorders in HIV-positive women (42-51%) that are more than twice the rate found with HIV-positive men or the general population (Cook, 2002; Ickovics, 2001). In the WIHS cohort, HIV-positive women also reported poorer mental health quality of life than either physically well or chronically ill members of the general population or than HIV-positive men across all participating sites.

A longitudinal cohort study of 93 HIV-positive women and 62 HIV-negative women without current substance abuse found that HIV-positive women were four times more likely (19.4%) to meet clinical criteria for current major depressive disorder than HIV-negative women (4.8%), with significantly more anxiety symptoms (Morrison, 2002). The HCSUS study (N = 2,864) found that HIV-positive individuals with probable mood disorders had significantly lower scores on health-related quality of life measures (Sherbourne, 2000). Among a sample of 234 African American men who have sex with men (159 HIV+) and 135 African American women (100 HIV+), there was a high prevalence of anxiety spectrum disorders (38%) and mood disorders (23%) in both groups, and significant rates of PTSD (50%) among the women (Myers, 1999).

Table 9-4: Common Clinical Misperceptions Regarding Psychiatric Issues

<i>Psychiatric Issue/ Disorder</i>	<i>Clinical Misperceptions</i>	<i>Remember to Ask About</i>
Major depression	"Anyone with HIV would be depressed or grieving," forgetting biologic depression	Vegetative symptoms (early morning awakening, diurnal mood variation, appetite disturbance); anhedonia more than sadness
Bipolar mood disorder	"Depressed mood must mean depression," forgetting bipolar symptoms	Hypomani/manic symptoms (history of racing thoughts, hyperactivity, no need for sleep, grandiose plans, irritability)
Psychosis	"The patient seems normal," forgetting hallucinations and paranoia	Psychotic symptoms: "Do you ever hear your name called, turn around and no one is there?" "Ever feel that strangers are talking about you as you walk down the street?"
Delirium	"The patient is clearly schizophrenic or psychotic" forgetting acute medical etiologies	Distractibility, disorientation, dysarthric speech; inability to sustain, focus attention; misperceptions; mumbling or muttering
Sexual abuse/ assault history	"Too personal; may embarrass or offend"	"Were you ever sexually, physically abused in childhood? Assaulted as an adult?" Do not ask details.
Anxiety, panic, agoraphobia	"Must be drug-seeking"; "Anyone would be anxious"	Panic symptoms, sense of doom, tachycardia (repeated episodes), impairment of function; avoids crowded places
Domestic violence	"Seems like a nice person"	"Is there anyone in your life now or in the past who makes you feel unsafe?"
Suicidal ideation	"May plant the thought in their mind, provoke it"	"Have you ever felt like hurting or killing yourself? Have a plan? " Have the means?

IX

A meta-analysis of 10 published studies found that the frequency of major depressive disorder was nearly two times higher among HIV-positive individuals than HIV-negative controls (Ciesla, 2001).

Depressive symptoms may result from a myriad of depressive disorders, including bereavement, adjustment issues/disorders, post-traumatic stress disorders, borderline personality disorders, major depressive disorder or bipolar depression, and can present with numerous comorbid conditions, such as substance use disorders that can cause secondary organic mood disorders. From a clinical perspective, depressive symptoms require careful differential diagnostic assessment because of different treatment requirements (See Tables 9-4 and 9-5).

Isolating and characterizing the extent to which some depressive symptoms may derive from an organic mood disorder directly related to HIV infection of the central nervous system is a difficult task. A specific role for an HIV-related central nervous system effect on psychiatric symptoms, however, is implied in the HCSUS study, which found that patients who initiated or maintained ARV therapy had fewer psychiatric symptoms 8 months later, and this was significantly related to higher CD4 cell counts, fewer opportunistic infections, and fewer HIV-related symptoms (Chan, 2003). Similarly, in a Canadian study of 234 HIV-positive participants who were depressed at baseline (52% of the total), an analysis of change in the CES-D before and after initiating protease inhibitor-containing HAART regimens found a significant improvement in depressive symptoms, after controlling for CD4 count, employment status, income, and age (Low-Beer, 2000).

B. IMPACT OF DEPRESSION AND MENTAL HEALTH SERVICES ON ANTIRETROVIRAL THERAPY, ADHERENCE, OUTCOME, AND COST

According to a number of recent studies, women with HIV who do not have access to mental health services and/or whose depressive symptoms and disorders are not treated are less likely to be on antiretroviral medication, less likely to be adherent to antiretroviral medication, and more likely to have a poor medical outcome at more cost.

ACCESS TO MENTAL HEALTH SERVICES:

In the HERS study, 38% of HIV-positive women and 35% of high risk HIV-negative women reported needing mental health services in the prior six months and, of those, only 67% of HIV-positive and 65% of HIV-negative women actually received services (Schuman, 2001). In the WIHS cohort, 50% of HIV-positive women reported contact with a counselor or other mental health professional at one or more study visits, but at baseline, there was less likelihood of use of mental health services among women with no college education and who were African American (Cook, 2002). An estimated 27.2% of HIV-positive men and women in the HCSUS took

psychotropic medications, including antidepressants (20.9%), anxiolytics (16.7%), antipsychotics (4.7%), and psychostimulants (3.0%). Of patients with major depression or dysthymia, 43.2% reported receiving antidepressants and 34.3% reported receiving anxiolytics (Vitiello, 2003). In the HCSUS study, 61.4% of adults in HIV care used mental health or substance abuse services. Although the HIV population sampled had high mental health utilization compared to the general population, socioeconomic factors associated with poorer access to health services predicted lower likelihood of using mental health outpatient services, raising concerns that these are the same subpopulations with limited rates of antiretroviral usage (Burnam, 2001).

ACCESS TO AND ADHERENCE WITH ANTIRETROVIRAL THERAPY:

Women have significantly lower rates of HAART utilization than men (Shapiro, 1999). Among 273 HIV-positive women in the HERS study, 80 women had CD4 counts below 200/mm³, and of these only 23% were on HAART (Gardner, 2002). In the WIHS study, women with significant depressive symptoms were much less likely to be on HAART regimens, as were women with poor mental health quality of life. However, if women had recently received mental health services, they were significantly more likely to be on HAART (Cook, 2002). In an analysis of merged Medicaid and surveillance data from New Jersey for HIV-positive women and men, patients with depression who received antidepressant treatment were more likely to receive antiretroviral treatment than those with untreated depression (Sambamoorthi, 2000). HIV-positive women who were depressed and were treated with antidepressants were almost twice as likely to be on ARV therapy compared to those who were depressed and not yet treated with antidepressant medication (Turner, 2001).

The presence of depression or other mood disorders may also affect adherence to antiretroviral therapy, when this is prescribed. Patients in the HCSUS with depression (Odds Ratio, OR=1.7), generalized anxiety disorder (OR=2.4), or panic disorder (OR=2.0) were more likely to be nonadherent than those without a psychiatric disorder (Tucker, 2003).

MEDICAL OUTCOME:

After controlling for potential confounding variables, women with chronic depressive symptoms also had a more rapid decline in CD4 counts compared with women with limited or no depressive symptoms (Ickovics, 2001). Depressed women with HIV were found to have increased mortality. Participants in the HERS study with depressive symptoms were nearly twice as likely to die as those without, after controlling for clinical evidence of declining health over time. Among respondents with no reported HIV-related symptoms at baseline, those with chronic depressive symptoms were 3.6 times more likely to die than those with



limited or no depressive symptoms, although unmeasured mediators of this effect could include adherence, healthcare utilization, and psychiatric treatment. For women whose CD4 count was less than 200, HIV-related mortality for those with chronic or intermittent depressive symptoms was 54% and 48% compared with 21% for those with limited or no depressive symptoms. Evans et al. suggest that depression may decrease natural killer cell activity and lead to an increase in viral load (Evans, 2002).

COST:

After controlling for socioeconomic and clinical characteristics, HIV-positive New Jersey Medicaid recipients diagnosed with depression and treated with antidepressant medications had a 24% reduction in total monthly health care costs compared to those with depression who remained untreated (Sambamoorthi, 2000).

C. NEUROPSYCHIATRIC DISORDERS

HIV-associated dementia (HAD) is characterized by significant changes in cognitive, motor, and behavioral function consistent with a subcortical dementia. HIV-associated minor cognitive-motor disorder (MCMD), seen at earlier stages of illness, is associated with at least two of the following: impaired attention or concentration, mental slowing, impaired memory, slowed movements, lack of coordination, personality change, and acquired cognitive-motor abnormality on neurological or neuropsychological testing.

Antiretroviral therapy has had a dramatic effect on the neuropsychiatric disorders associated with HIV/AIDS. Median survival following the diagnosis of AIDS dementia complex (HAD) increased to a greater extent than that for all other AIDS illnesses, from 11.9 months in 1993-1995 to 48.2 in 1996-2000, in a study in Australia (Dore, 2003). A study based on the semiannual administration of a neuropsychological battery to women in the HERS study with CD4 counts less than 100 /mm³ demonstrated that antiretroviral therapy, particularly when taken for more than 18 months, had a significant impact on neurocognitive function compared to those women not treated with HAART, with improved verbal fluency, psychomotor, and executive functions (Cohen, 2001).

However, there have been reports of increased incidence of HIV encephalopathy over time with increasing antiretroviral use and increased prevalence of HIV encephalopathy at the time of death. This may indicate that, although there is longer survival after initial HIV infection in the HAART era and effective combination therapy decreases overall prevalence of central nervous system opportunistic infections, these therapies may be less active in preventing direct HIV-1 effects on the brain (Neuenburg, 2002).

It is important to remember that symptoms of neuropsychiatric disorders can be confused with depression. If a patient has a low CD4 count without prior antiretroviral therapy, it may be appropriate to assess the response of these symptoms to a standard antiretroviral regimen before initiating antidepressant medication (See Chapter IV). Finally, both psychotropic and antiretroviral medication can cause neuropsychiatric symptoms as side effects. See Treisman (2002) for a thorough discussion of these issues.

V. DIAGNOSIS OF MAJOR DEPRESSIVE DISORDER

Major depressive disorders are frequently undiagnosed (Asch, 2003) and once diagnosed, are often under-treated. Care providers may project their own feelings and think "I'd be depressed too, under the circumstances," and not think about intervening with medication. Substance disorders are sometimes missed as contributors to the depression, and bipolar disorder is often not recognized when depression is the presenting symptom.

Normal grief or sadness does not require treatment with medication. The central feature of a major depressive disorder is the loss of pleasure in all activities or "anhedonia," rather than sadness alone. Waves of grief are usually accompanied by lighter moments or even laughter as the most acute grief subsides. Sadness for other reasons, such as a major disappointment, is also responsive to environmental change such as an enjoyable activity, and the mood will be quickly reversed if the source of the disappointment changes.

This is not the case in a major depressive episode, where the world has no joy regardless of the activity or turn of events, and where the outlook is gloom and doom regardless of the likelihood of a positive change. There may be obsessive rumination on past wrongs, or preoccupation with guilt or regrets that are impossible to balance with any feelings of accomplishment or hope. In addition to depressed mood, anhedonia, and hopelessness, major depressive disorders are usually accompanied by vegetative or biologic symptoms: low energy and psychomotor retardation; sleep disturbance (hypersomnia or insomnia), early morning awakening (around 2:00 AM to 4:00 AM); appetite disturbance (hyperphagia or hypophagia); decreased libido and, constipation. Finally, there may be cognitive changes such as decreased attention and concentration, social withdrawal and tendency toward isolative behavior, diminished range of affect, uncharacteristic irritability, and increased use of drugs or alcohol. In the most severe cases, psychotic symptoms such as delusions and hallucinations may be present.

The mood of a major depressive disorder is often worse in the morning, whereas the sadness of adjusting to difficult events tends to worsen over the course of the day, followed by a new day which is filled with more hope. A family history of mood disorders is often present. The

constellation of depressive symptoms develop together over a course of weeks or months and can help to differentiate major depressive disorders from similar disturbances related to medical illnesses. Hopelessness indicates severe depression and is the most consistent predictor of completed suicides. The suicidal ideation associated with bipolar depression can be particularly dangerous. A combination of psychotherapy and antidepressant medication has been shown to be therapeutic for HIV-positive patients with major depressive disorders (Markowitz, 1998).

Some of the clinical misperceptions that get in the way of evaluating major depression and other psychiatric disorders are listed in Table 9-4 (page 359), along with reminders for complete assessment. For the complete diagnostic criteria of each disorder, see the DSM-IV-TR of the American Psychiatric Association (2000).

Condition	Differentiated from MDD by:
Bipolar disorder	Racing thoughts, increased energy, decreased need for sleep, irritability or angry outbursts, hypersexuality (these may coexist with depressed mood in a mixed bipolar state)
Grief	Onset associated with the loss; responsive to positive changes in the environment with enjoyment or less sadness; decreasing severity over time; preoccupation with deceased; "psychotic" symptoms related to deceased such as seeing, being visited by the deceased; rare suicidal intent although reunion fantasies may exist
Adjustment disorder with depressed mood	Sadness is rarely as profound; little anhedonia; no vegetative symptoms; identifiable precipitant; responsive to environmental change; suicidal ideation and intent may still occur; severe cases may respond to antidepressants
Organic mood disorder	Identifiable etiology linked by time; may be associated with cognitive deficits; test for specific medical conditions such as TSH, B12, VDRL or RPR, CNS evaluation; no family history
Dementia	Less concern with cognitive decline; more gradual changes; may respond with laughter; worse at night; specific neurological deficits; CT or MRI scan often abnormal
Delirium	Fluctuating mental status with altered level of consciousness; distractibility; inability to focus or sustain attention; dysarthric speech; agitation; medical etiology; usually acute onset
Medication- or substance-induced mood disorders	Onset with use of: steroids, anticholinergics, sedative-hypnotics, anticonvulsants, antiparkinsonians, beta-blockers, anti-TB meds; sympathomimetics; azidothymidine, stavudine; all illicit drugs (urine toxicology screen, medication history)
<i>TSH, thyroid-stimulating hormone; VDRL/RPR, nontreponemal serologic tests for syphilis.</i>	

VI. PSYCHOPHARMACOLOGY FOR THE HIV-POSITIVE WOMAN: GENERAL GUIDELINES

Numerous studies have indicated that psychotropic medications are safe and effective for HIV-positive individuals and do not adversely affect the immune system (Ferrando, 1999; Rabkin 1999; Repetto, 2003; Robinson, 2002). Standard antidepressant medications are generally well tolerated. While specific medications and common clinical dosing ranges are listed in Table 9-6 and are discussed below, the following general guidelines should be kept in mind when approaching psychotropic medications with the woman with HIV:

- **Start low, go slow:** There is evidence that for antipsychotic medication, women in general require lower doses than men. Use slow upward titration as with geriatric patients. (ADA, 2004; Seeman, 2004).
- **Expect the unexpected:** HIV-positive patients often experience unusual side effects, or common side effects at low doses, or complicated drug-drug interactions.
- **Dynamic monitoring:** Changes in weight, metabolism, other medications, or medical illness episodes require frequent updating and reevaluation of dosing or choice of medications; this is particularly important with increased weight or abdominal girth, new onset of hyperlipidemia, or hyperglycemia. (see below and chapter XIV Pharmacology).
- **Interdisciplinary coordination:** Psychiatrists and primary health care providers should be in regular communication with each other about clinical updates, dosing changes, and major medical events.
- **Suspect substances:** Depression may be complicated by alcohol, anxiety by withdrawal syndromes, mania by psychostimulants; patients often forget that when their consumption has decreased, their CNS sensitivity to the effects of these substances increases over time.
- **Address medication adherence:** Use medication boxes, simple regimens, written instructions, coordination with antiretroviral therapies, and patient education. Non-adherence or discontinuation may diminish the overall treatment effect if not specifically targeted (Ferrando, 1999).
- **Potential drug-drug interactions** are a concern in prescribing psychotropic and antiretroviral medications. The primary cytochrome P450 systems at issue for psychiatric medications are CyP2D6 and CyP3A4: The major CYP450 drug-drug interactions to keep in mind are included in Table 9-7.

Common potential side effects of all of the antidepressant medications include agitation, irritability, sedation, sexual dysfunction, weight gain, headache, gastrointestinal distress, dry mouth, and activation of mania. There may be discontinuation syndromes with paroxetine and venlafaxine so these drugs should be tapered when increasing or decreasing the dose. Venlafaxine may

also cause hypertension. "Second generation antipsychotics", as listed in Table 9-6, are routinely recommended over traditional antipsychotic medications such as haloperidol, except for acute or short-term use, because of potential improvement of "negative" (affect, social interaction) as well as "positive" (hallucinations, delusions) psychotic symptoms, and lower associated incidence of extrapyramidal side effects such as dystonia, akathisia and the long-term risk of dyskinesia. However, recent concern about the association of olanzapine, clozapine (not recommended for first-line use) and, to some extent, quetiapine and risperidone, with weight gain and possible increased risk for diabetes and dyslipidemias, necessitates extreme caution in using these agents in conjunction with antiretroviral medications which may also be associated with hyperlipidemia and lipodystrophy, hyperglycemia and weight gain. Hyperprolactinemia may occur with quetiapine or olanzapine, with associated sexual side effects or galactorrhea.

Tolerance, dependence and withdrawal syndromes, including rebound anxiety, can complicate the use of benzodiazepines, especially alprazolam, and patients should be warned about sedation, cognitive effects and slowed reflexes, especially with regard to driving when using these agents.

Adverse effects with mood stabilizing drugs include potential significant weight gain with both valproic acid and lithium, still considered first line agents for mood stabilization. Depression may increase with valproic acid when some patients experience more "antimanic" than true mood stabilizing effect. Valproic acid may also be associated with more serious adverse effects, including hepatic dysfunction, thrombocytopenia or pancreatitis. Lithium may be superior for patients with clinical history dominated by clear cycles of mania. Because lithium is excreted through the kidneys, patients are at risk of toxic lithium levels if they become dehydrated due to vomiting or diarrhea, excess sweating or use of diuretics. Carbamazepine and oxcarbazepine are related compounds which may be helpful in primary or adjunctive mood stabilization, although both may be sedating. Oxcarbazepine may be associated with hyponatremia, but has the advantage of fewer drug-drug interactions and does not require monitoring with blood levels. Carbamazepine has been associated with rare instances of severe hematologic and dermatologic complications, but has been safely used in the setting of HIV infection with careful clinical monitoring. Lamotrigine interacts with both valproic acid, which doubles lamotrigine levels, and with carbamazepine, which cuts lamotrigine levels in half; lamotrigine has also been associated with severe rash upon occasion.

Finally, patients who experience severe or unusual side effects, have multiple diagnoses or require multiple medications, or are not responding at routine doses with initial medications should be referred for psychiatric consultation.

Table 9-6: Common Psychiatric Medications	
Disorder	Medications and common dosing ranges*
Major depressive disorder (with or without anxiety)	Citalopram (Celexa) or Escitalopram (Lexapro) 10–40 mg (SSRI) Fluoxetine (Prozac) 10–60 mg (SSRI) Paroxetine (Paxil) 10–40 mg (SSRI) Sertraline (Zoloft) 25–200 mg (SSRI) Bupropion (Wellbutrin-SR) 100–1000 mg; usually AM and midday Mirtazapine (Remeron) 15-30 mg Venlafaxine (Effexor-XR) 37.5–225 mg
HIV-related depression/ fatigue (with or without minor cognitive motor disorder)	Methylphenidate (Ritalin) 10–60 mg in divided doses, AM and midday
Bipolar mood disorder	Carbamazepine (Tegretol) 400–1200 mg in divided doses, titrated slowly by blood levels (4–12 mcg/ml) Gabapentin (Neurontin) 600-1800 mg in divided doses Lamotrigine (Lamictal) 25 mg, then 50 mg daily for two weeks each; then 100 mg daily for one week, followed by 200 mg daily Lithium carbonate 600–1800 mg or Lithium CR 450mg – 1350mg in divided doses titrated by blood levels (0.6–1.0 mEq/L) Oxcarbazepine (Trileptal) starting at 150–300 mg bid for one week, titrated very slowly 300–1200 mg in divided doses Valproate/valproic acid (Depakote) 500–2000 mg in divided doses, titrated by blood levels (50–100 mg/mL)
Psychotic symptoms (also severe PTSD, Bipolar disorder)	Ziprasidone (Geodon) 40–240 mg (with food) twice daily Aripiprazole (Abilify) 10–30mg Risperidone (Risperdal) 0.5–6 mg once to twice daily Quetiapine (Seroquel) 25–600 mg twice daily Olanzapine (Zyprexa) 2.5–20 mg
Anxiety disorders (also PTSD) and Panic attacks	Paroxetine (Paxil) 10–40 mg Sertraline (Zoloft) 25–200 mg Buspirone (Buspar) 15–30 mg in divided doses Lorazepam (Ativan) 1–6 mg in divided doses Alprazolam (Xanax) 0.75–4 mg in divided doses Clonazepam (Klonopin) 1–4 mg in divided doses
Insomnia	Trazadone (Desyrel) 25–100 mg Benadryl 25–100mg Lorazepam/Clonazepam at night dose Temazepam (Restoril) 15–60 mg Zolpidem (Ambien) 5–10 mg
Alcohol dependence	Disulfiram (Antabuse) 250–500 mg daily to three times/week
Alcohol withdrawal	Tranxene 15–30 mg q 2–6 hr
Opiate dependence	Methadone 60–120 mg
Opiate withdrawal	Methadone 5–40 mg in divided doses, tapered by 5 mg/day Clonidine 0.3–0.6 mg in three divided doses
SSRI=selective serotonin reuptake inhibitor; PTSD=Post Traumatic Stress Disorder * Many psychiatric medications are now available in extended release and rapidly dissolving, as well as liquid and parenteral forms.	
Source: Modified from Schatzberg, 1998	



Table 9-7: Pharmacokinetic Drug Interactions between Psychotropic Drugs and ARVs			
Drug	CYP Substrate	CYP Inhibitor	Pharmacokinetic data/comments
Amitriptyline (Elavil) Nortriptyline (Pamelor) Desipramine (Norpramin) Imipramine (Tofranil) Clomipramine (Anafranil) Doxepin (Sinequan)	2D6		RTV decreased desipramine clearance by 59% in vitro. RTV increased amitriptyline levels*. NFV increased desipramine levels*.
Mirtazapine (Remeron)	2D6		Increases in serum level of mirtazapine may be seen with RTV co-administration.
Paroxetine (Paxil)	2D6	2D6	Increases in serum level of paroxetine may be seen with RTV coadministration.
Venlafaxine (Effexor)	2D6	2D6 (weak)	Increases in serum level of venlafaxine may be seen with RTV co-administration.
Fluoxetine (Prozac)	2D6	2C19, 2D6, 3A4 (weak)	DLV Cmin increased by 50%, RTV AUC increased by 19%*.
Citalopram (Celexa)	2C19		Drug interactions unlikely w/ antiretrovirals.
Sertraline (Zoloft)	2C19	2D6 (weak)	Drug interactions unlikely w/ antiretrovirals.
Bupropion (Wellbutrin, Zyban)	2B6> 3A4		Clinically important drug interactions w/ PIs unlikely (preliminary in vitro data show weak inhibition by RTV).
Trazodone (Desyrel)	3A4		Increases in serum level of trazodone may be seen with PI coadministration. Decreases in serum level of trazodone may be seen with EFV or NVP co-administration.
Nefazodone (Serzone)	3A4	+3A4	Increases in serum level of nefazodone may be seen with PI co-administration. Decreases in serum level of nefazodone may be seen with EFV and NVP co-administration. Nefazodone may increase serum level of PIs and NNRTIs.
Fluvoxamine (Luvox)	2D6	+3A4	Increases in serum level of fluvoxamine may be seen with RTV co-administration. Fluvoxamine may increase serum level of PIs and NNRTIs.
Haloperidol (Haldol)	3A4>2D6, 1A2		Increases in serum level of haloperidol may be seen with PIs. Decreases in serum level of haloperidol may be seen with EFV and NVP.
Perphenazine (Trilafon) and thioridazine (Mellaril)	2D6 (2D6 inhibitor)		Increases in serum level of perphenazine and thioridazine may be seen with NFV and RTV.
Olanzapine (Zyprexa)	1A2>2D6		RTV decreased olanzapine AUC by 50%*
Escitalopram (Lexapro)	2D6		No drug interaction with RTV Interaction with other PI and NNRTI unlikely

Table 9-7: Pharmacokinetic Drug Interactions between Psychotropic Drugs and ARVs (continued)			
<i>Drug</i>	<i>CYP Substrate</i>	<i>CYP Inhibitor</i>	<i>Pharmacokinetic data/comments</i>
Quetiapine (Seroquel) Ziprasidone (Geodon)	3A4		Increases in serum level of quetiapine and ziprasidone may be seen with PI co-administration. Decreases in serum level of quetiapine and ziprasidone may be seen with EFV and NVP co-administration.
Aripiprazole (Abilify)	3A4, 2D6		Increases in serum level of aripiprazole may be seen with PI co-administration. Decreases in serum level of aripiprazole may be seen with EFV and NVP co-administration.
Risperidone (Risperdal)	2D6>3A4		Increases in serum level of risperidone may be seen with RTV co-administration.
Alprazolam (Xanax)	3A4		Alprazolam AUC decreased by 12%*. Alprazolam clearance decreased by 59% and t1/2 increased by 200%*.
Triazolam (Halcion) Midazolam (Versed)	3A4		RTV increased triazolam AUC 20% and increased t1/2 by 12-fold*. Co-administration with PIs and EFV is contraindicated.
Zolpidem (Ambien)	3A4		RTV increased zolpidem AUC by 27%*
Chlordiazepoxide (Librium) Clorazepate (Tranxene) Estazolam (ProSom) Flurazepam (Dalmane) Clonazepam (Klonopin)	3A4		Increases in serum level of chlordiazepoxide, clorazepate, estazolam, clonazepam, and flurazepam may be seen with PI co-administration.
Lorazepam (Ativan) Temazepam (Restoril) Oxazepam (Serax)	Glucuronidation		Interaction unlikely Lorazepam was not affected by EFV*
Diazepam (Valium)	1A2 and 2C9> 3A4 and 2C19		RTV may decrease serum level of diazepam
Carbamazepine	3A4	+3A4	May decrease serum level of PIs and NNRTIs. Consider TDM**.
Oxcarbazepine		-3A4	May decrease serum level of PIs and NNRTIs. Consider TDM** (especially at high dose oxcarbazepine).
Lamotrigine	Phase II Glucuronidation		RTV, NFV, LPV/r may decrease lamotrigine serum concentration.
* Interactions based on pharmacokinetic (PK) data. If no clinical PK data available, drug-drug interaction predictions are based on pharmacology principles.			
** TDM = Therapeutic Drug Monitoring			
Source: Paul Pham, <i>The John Hopkins University School of Medicine, Baltimore, MD, 2003.</i>			

VII. EVALUATION OF SUICIDE RISK

Women are significantly more likely to attempt suicide than men, but men are significantly more likely to complete the suicide (male:female ratio of at least 4:1). Caucasians commit suicide at twice the rate of African Americans and Hispanics. It is estimated that 90% of individuals have a psychiatric disorder at the time of suicide and 45–79% of those have major depression. Fifteen percent of individuals with a mood disorder commit suicide (Buzan, 1996).

Women more commonly attempt suicide by overdose, whereas men use more violent means, such as firearms or hanging. Women who have few social supports, have been widowed or divorced, or who have a history of sexual abuse are at increased risk for suicide. Women with children attempt suicide less frequently. Any risk factor is increased by the presence of alcohol, psychosis, or an organic mental syndrome.

It is likely that suicide rates are decreasing among individuals with HIV (Marzuk, 1997). This may be due to a global or specific treatment effect of antiretroviral therapies (Chan, 2003), which can improve organic mood disorders and cognitive function (Ferrando, 1998), in addition to increasing longevity and hope.

To assess suicide risk, the clinician must inquire about it (see Table 9-8). Knowing that this does not increase the likelihood an individual will attempt suicide. The clinician should practice a standard way of asking, such as “Have you ever had thoughts of hurting yourself?” or “. . . of ending your life?” or “Do you ever feel that life is not worth living?”

Table 9-8: Risk Factors in the Evaluation of Suicide Risk

- Significant suicidal ideation
- Specific intent or plan; available means
- Hopelessness
- Previous suicide attempts
- Depressed mood, mood disorders
- Family history of suicide or mood disorders
- Schizophrenia, psychosis (not necessarily command hallucinations)
- Organic mental syndromes
- Intoxication with alcohol, other substances
- Recent major loss, particularly through suicide
- Preoccupation with death
- Fantasies of reunion through death
- Homicidal rage
- Caucasian race

VIII. CARE PROVIDER ISSUES

One of the most important relationships the woman living with HIV has is the relationship with her health care provider. The dynamics of this relationship can have significant impact on the experience of the HIV-positive woman, and she will be affected not only by what the clinician communicates about HIV disease and treatment, but by how the information is communicated and how the provider relates to her. The practitioner who is able to establish a trusting relationship with the patient may find that the strength of their relationship can motivate the HIV-positive woman as much as lectures about viral load. Care providers, in turn, may experience, and should be aware of, a variety of potential reactions to their patients.

Women who use/abuse drugs or alcohol may provoke strong reactions in care providers, commonly frustration and disapproval, particularly when the woman is pregnant or has children. Providers may feel anger when the woman's learned helplessness, particularly in sexual situations, results in her submitting repeatedly to unsafe sex, or provide inadequate pain control in response to provocative and insistent behavior on the part of the patient, in order to try to assert control. As is the case with other medical conditions, providers may personalize nonadherence with medications or medical follow-up as an affront to their good intentions or perceive it as a lack of commitment to treatment, rather than adherence to different priorities. Appointments missed to take care of children or because of problems with transportation may be misinterpreted as poor motivation for treatment. Providers who may then convey frustration or disappointment to a patient (e.g., with her nonadherence to medication) may find that she does not return because she has personalized this as a rejection.

On the other hand, providers may also collude with the HIV-positive woman's feelings of powerlessness and try to take control over things she can actually handle herself with sufficient support. Protective concerns and anger at an abusing partner may tempt the provider to cross professional boundaries and try to rescue the patient. Frank disregard or avoidance of medical treatment may be mistakenly excused without exploring the real meaning of the behaviors. Care providers might assume that a woman is missing visits because she is overwhelmed with the care of her children when she is actually angry at a particular provider, or so frightened about the illness that she avoids treatment. Initiating multiple medications may be the point at which she is forced to break through the denial and confront her illness.

For the female health care provider, the experience of taking care of women with HIV can be both more rewarding and more depleting than general medical care. Personal identification with the patient may work positively to increase empathy, or negatively to increase projection of one's own values and expectations on the individual. Female providers may also experience amplified grief because of the death of a patient with whom they have developed a genuine connection.

Providers who are either prone to experience patient deaths as their own clinical failures, or who have deep compassion for the suffering of their patients, may be vulnerable to experiencing professional burnout, particularly if subjected to multiple, sequential losses. The practitioner who can cope with these challenges, however, may find personal and professional satisfaction in providing a combination of important services to a subpopulation of women who remain profoundly underserved.

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X. SUBSTANCE ABUSE

Henry Francis, MD and Victoria A. Cargill, MD, MSCE

I. SUBSTANCE USE AND ABUSE

Substance use is more prevalent in the United States than is generally appreciated. Statistics described in the 2002 National Survey on Drug Use and Health (NSDUH) give the following picture on drug use in American men and women (SAMHSA, 2002). Approximately 46% of the American population will use an illegal drug in their lifetime. It is estimated from the NSDUH data that in the general population, 10.3% of men and 6.4% of women have used illegal drugs in the last month. Over the past year, 35 million Americans will have used an illegal drug. Only a fraction of drug-using persons are truly drug-dependent (also called drug-addicted). It is estimated that 7.1 million people meet the definition of illicit drug dependence, defined as compulsively continuing drug-seeking and drug-using behavior even in the face of negative consequences, including health, social, family, legal or work problems.

The general rates of legal drug dependence dwarf the amount of illegal drug addiction. In 2002, 120 million persons reported consuming alcohol in the last 30 days and 71.5 million persons used a tobacco product. At least 54 million of the alcohol consumers are dependent on alcohol through binge or very heavy drinking. The alcohol-dependent individuals are almost three times as numerous as the number of illegal drug users. In contrast to illegal drug use rates where almost twice as many men as women use illegal drugs, alcohol consumption rates are nearly equal for men and women in the general population. However, women were much less likely to be binge drinkers. It is important to note that rates of drug and alcohol use are equal in adolescent males and females (12–17 yr. old), suggesting a trend toward comparable substance use patterns for men and women. Regular use of cigarettes (nicotine dependence), was nearly equal for men and women.

Unfortunately, the majority of alcohol and/or drug dependent women and men, who could benefit from substance abuse-related emotional/psychologic and health treatment, never receive any form of therapeutic intervention. In 2002, only 7.5% of women who needed treatment for an alcohol problem and 20.4% of women who needed treatment for an illegal drug problem actually received care at a specialty facility for these problems.

This chapter will focus on drug and alcohol dependence as a disease, discuss associations with a variety of comorbid conditions, review the epidemiology of substance abuse in the United States, and outline ways to identify and treat substance abuse in women.

II. EPIDEMIOLOGY OF SUBSTANCE ABUSE

The frequency and danger of drug and alcohol dependence and behaviors of drug and alcohol use are greatly underestimated by the American public and health care professionals. The two commonly used legal drugs, alcohol and tobacco, are more frequently consumed than all the illegal drugs combined (Table 10-1). Marijuana and cocaine (including crack cocaine) are the most frequently used illegal drugs. Inhalants are used predominately by adolescents. A more recent trend in adolescents is to use club drugs like g-hydroxybutyrate, ecstasy (MDMA), Rohypnol, ketamine, methamphetamine, and LSD at all-night parties called “raves” or “trances.” Surprisingly, heroin, which is viewed as a highly prevalent drug, is actually one of the least favored drugs of preference in the U.S. population.

Table 10-1: Prevalance of Drug use

<i>Drug</i>	<i>Alcohol</i>
Alcohol	155,476,000
Tobacco	84,731,000
Marijuana	25,755,000
Cocaine	5,902,000
Hallucinogens	4,749,000
Inhalants	2,084,000
Stimulants	3,181,000
Heroin	404,000

Source: Adapted from the 2002 National Survey on Drug Use and Health (SAMHSA, 2002); past year use

The rates of illicit drugs used vary slightly by ethnicity (Table 10-2) and in a major way by gender. Estimates for gender-specific drug use indicate that women are almost 50% less likely to use illicit drugs compared with men. The male-to-female illicit drug use rate relationship is consistent throughout all ethnic groups. Ethnic comparisons of drugs used demonstrated that the highest rates of drug use occur in young adults aged 18–25.

White American men and women have higher rates of alcohol use than African Americans or Hispanic Americans (Table 10-3). For

all alcohol-using groups, alcohol consumption is highest in young adults (18–25 yr).

Table 10-2: Illicit Drug use Estimates by Age and Ethnicity in the US

<i>Percent US Population</i>			
<i>Age (yr)</i>	<i>White</i>	<i>Hispanic</i>	<i>African American</i>
12–17	24.0	20.8	18.5
18–25	39.6	27.0	30.9
26 or older	10.2	10.5	13.5

Source: Adapted from the 2002 Survey on Drug Use and Health (SAMHSA, 2002); past year use

Table 10-3: Alcohol use Estimates by Age and Ethnicity in the US

<i>Percent US Population</i>			
<i>Age (yr)</i>	<i>White</i>	<i>Hispanic</i>	<i>African American</i>
12–17	20.1	10.9	16.6
18–25	66.8	49.8	48.3
26 or older	57.5	46.1	43.6

Source: Adapted from the 2002 Survey on Drug Use and Health (SAMHSA, 2002); past month use

III. SUBSTANCE ABUSE AND HIV

Substance abuse is a major risk behavior for acquisition of HIV infection. The most recent HIV/AIDS statistics in the US show that 26% of women living with HIV/AIDS at the end of 2002 were infected through injection drug use (IDU). Non-injection drug use (NIDU) is also associated with increased risk of HIV infection, most likely related to high risk sexual behaviors. Use of illicit drugs and alcohol abuse are generally associated with larger numbers of sexual partners, increased rates of STIs, decreased rates of condom use, increased likelihood of sex with an injection drug user and, for illicit drugs, increased risk of exchange of sex for money or drugs (Woods, 2000; Molitor, 1998; Word, 1997; Sanchez, 2002). Crack cocaine use has been associated with increased likelihood of engaging in anal sex (Gross, 2000). Although IDU-related HIV transmission is most closely related to sharing injection equipment, a significant portion of transmission is related to sexual behaviors. Even after controlling for other potential risk factors, HIV infection rates tend to be higher among individuals who abuse alcohol (Petry, 1999). Individuals who abuse one drug or alcohol are more likely to use/abuse other substances as well. Over half of cocaine-dependent and 17–50% of heroin-dependent individuals abuse alcohol and alcohol use is associated with needle sharing in both heroin- and cocaine-abusing persons (Petry, 1999).

While under the effects of these substances, individuals have impaired decision-making ability or a reduced ability to understand or evaluate their actions. Disinhibition with drug use is known to decrease compliance with safer sex precautions or drug paraphernalia hygiene. Sex and drug-related HIV risk behaviors are strongly associated in women. Women acquire HIV, hepatitis B and C, and STIs often through sexual partnerships with injection drug users.

Among HIV-infected women, substance abuse is common. Although learning that she is HIV-infected may provide a woman incentive for stopping drug or alcohol use in order to better care for herself, it may also be more difficult to curtail substance abuse because of feelings of despair and hopelessness about the diagnosis of HIV. HIV status did not affect use of heroin or cocaine in a large cohort of HIV-infected and high-risk HIV-uninfected women followed for over 6 years (Macalino, 2003). In HIV cohort studies, 40–80% of individuals consume alcohol and rates of alcohol dependence are increased (Kresina, 2002).

The coexistence of substance abuse and HIV has a number of implications. The stigma and discrimination associated with drug and alcohol abuse, as well as the disorganization often seen in the lifestyle of those with active substance abuse, can lead to denial, delay in diagnosis of HIV, and reluctance to seek care. The signs and symptoms of drug and alcohol dependence, as the comorbidities associated with these conditions, may overlap with the signs and symptoms of HIV, further complicating and delaying early diagnosis and care. Such delays have been associated with increased morbidity and mortality in drug-using populations. The

comorbidity associated with substance abuse, such as alcohol-induced liver cirrhosis or IDU-related hepatitis C, may accelerate HIV progression and/or significantly complicate HIV management. Active substance abuse is consistently associated with poor adherence to medical care and to antiretroviral medications. Individuals who are heavy alcohol users are one-fourth as likely to achieve virologic suppression on HAART as non-drinkers (Miguez, 2001). Both alcohol and methadone have potential drug-drug interactions with some antiretroviral agents, possibly increasing toxicity or decreasing effectiveness of ARV drugs.

Primary care providers are uniquely positioned to identify early indications of drug use-related HIV risks and signs of other comorbidities and to engage drug users in treatment at earlier stages of drug dependence. New and younger initiates to injection drug use engage in particularly high-risk behaviors for acquisition and transmission of infectious diseases and HIV (Carneiro, 1999). In primary care settings, interventions can be put in place to prevent further transmission (Anderson, 1996) of HIV or other infections. Misconceptions about the legal, social, and health implications of testing positive for HIV reduce early detection efforts, particularly among patients at high risk (Harvey, 1999).

IV. COMORBIDITY RELATED TO SUBSTANCE ABUSE

Substance abuse is associated with a number of medical consequences and comorbid conditions, some of which are listed in Table 10-4. These conditions represent only a few of the many disease states either directly associated with substance abuse or exacerbated by substance abuse. Excessive alcohol use places women at risk for cirrhosis, epilepsy and dementia, psychiatric disorders, cardiomyopathy, peptic ulcer disease, pancreatitis, malnutrition, and malignancies. Intravenous drug use continues to be implicated in a number of infectious diseases, such as hepatitis and endocarditis, and smoking tobacco is the most common cause of lung cancer and airway diseases, and has been implicated in other malignancies such as cervical carcinoma (Waggoner, 1994).

Table 10-4: Medical Conditions and Sequelae Associated with Drug and Alcohol Abuse

<ul style="list-style-type: none">• HIV• STIs• Tuberculosis• Hepatitis (A, B, C, D and GBV-C)• Bacteremia	<ul style="list-style-type: none">• Endocarditis• Cirrhosis• Cancer• Cellulitis• Thrombophlebitis• Poor nutrition	<ul style="list-style-type: none">• Pneumonia• Cutaneous abscesses• Cognitive dysfunction• Septic emboli• Trauma
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The comorbid conditions related to substance abuse may delay diagnosis of HIV and complicate management of both HIV and substance abuse. Hepatitis C is a marker of poorer outcomes for HIV and has been associated with decreased survival and increased HIV progression. Some

have postulated that HCV, rather than being the primary cause of poor outcomes, may be a marker of later access to care and injection drug use, based upon a cohort of 823 HIV infected patients with and without HCV co-infection. (Greub, 2000; Tedaldi, 2003; Sulkowski, 2002). Both HIV infection and alcohol abuse have been reported to accelerate hepatitis C-induced liver disease and when all three are present together, this effect may be magnified. End-stage liver disease has become the leading cause of death in specific patient populations with HIV infection, and coinfection with viral hepatitis and alcohol abuse appear to be the major risk factors for progression of liver disease and death (Kresina, 2002).

Treatment with highly active antiretroviral therapy (HAART) is associated with improved outcomes in patients with substance abuse and comorbidities such as hepatitis coinfection (Benhamou, 2001). This underscores the importance of timely identification and treatment of substance abuse and its sequelae, as well as HIV. In both substance abuse treatment programs and primary care clinics, strategies are needed to identify HIV and manage HIV and comorbid conditions associated with HIV and/or substance abuse or have established linkages into appropriate care.

V. SUBSTANCE ABUSE IN WOMEN

Women who use drugs and alcohol have different risk factors for initiating use, have accelerated progression to dependence (Zilberman, 2003), and have an increased vulnerability to the medical and psychosocial consequences of substance use as compared to men, and as such require different approaches for the diagnosis and management of drug use and its sequelae. Women need treatment plans and care sites that address their personal, social, and familial needs, but most addiction diagnosis and treatment paradigms have been based upon the experiences in treating male users. Family circumstances, stigma, community environment, social status, and the nature of her primary relationships all affect the treatment of substance abuse in women. Several studies suggest that women drug users are more socially isolated, depressed, and dependent upon partners than their male counterparts (Sanders-Phillips, 2002). Women who have experienced violence, whether sexual or physical, are more likely to use alcohol, as well as marijuana or crack cocaine (Fullilove, 1992; Miller, 2000). These women, often due to imbalances in the power of their relationships, as well as a past history of abuse, are less likely to insist upon condom use, placing themselves at risk for HIV and other STIs (Fenaughty, 2003; Amaro, 2000).

Underlying psychiatric conditions, such as depression or other psychiatric disorders, may influence initiation or continuation of substance use ("self-medicating" depression). The prolonged use of drugs or alcohol in this setting can exacerbate, rather than improve, these problems. Female drug and alcohol users as a group are more likely to suffer from depression and anxiety disorders than the general population or other medical groups. The strong association between drug use and alcohol abuse and mental health disorders is evident in environmental and genetic predisposition to

addictive, impulsive, and compulsive behaviors and personality disorders. A conservative estimate is that over 50% of drug or alcohol-dependent women have one or more comorbid mental health conditions. Successful treatment of the drug or alcohol dependence is unlikely until their mental illness is treated.

Prevention intervention strategies for women with substance abuse must include both contextual relevance (eg, dealing with an IDU sexual partner) and real-world appropriate planning, such as condom use strategies in the setting of drug/alcohol intoxication. In addition to treatment of the underlying substance abuse and HIV, if present, treatment and prevention of comorbid conditions (eg, STIs, hepatitis C) are important, as these may facilitate sexual and perinatal transmission of HIV. Although they are growing in number, still relatively few treatment facilities accommodate women who are pregnant or have small children. Those sites that can address the medical, drug and alcohol use, and living circumstance challenges simultaneously will have the greatest appeal and utility for drug and alcohol-abusing women.

VI. IMPACT OF SOCIETAL PERCEPTIONS AND BELIEFS

Numerous social, moral, personal, and situational beliefs adversely affect a substance-abusing woman's health. Historically, U.S. society's response to drug addiction is punitive, stigmatizing, and prejudiced against drug users and their families. The negative public sentiment surrounding illicit drug use is especially evident in criminal justice sentencing practices. Health providers often share these views of drug users as unreliable and noncompliant. Value-laden judgments may affect provider willingness to treat this population and influence the care provided and therapeutic regimens prescribed. Providers may also be reluctant to raise the subject of substance abuse treatment with patients because of misconceptions about the effectiveness of treatment.

Women with drug and alcohol abuse are more likely to experience poor health and are less likely to access services, receive treatment, or seek health care, partially because of the stigma of substance abuse. Suspicion, fear, and distrust of the health care system result in reluctance among drug users to disclose medically necessary information. Negative sanctions, such as mandatory HIV testing during pregnancy and incarceration of drug-using pregnant women for child abuse, have intensified fears about contact with the health system. For economically disadvantaged women with HIV and drug abuse problems, the fear of discrimination, retribution, loss of housing, or loss of children may become more important than seeking or engaging in health services (Sly, 1997) and may keep them from receiving personally tailored prevention messages.

Individuals who are drug or alcohol dependent, even though they may exhibit dysfunctional behavior, retain the right to be evaluated as individuals and to be treated with respect and equality, regardless of conflicts in values or beliefs between patient and care provider.

VII. IDENTIFICATION OF SUBSTANCE USE/ABUSE

A. DIAGNOSIS BY HISTORY

Identification of substance use can be a challenge, given the myriad of illnesses it can mimic. However, the biggest barrier to identification is denial. Given the stigma associated with substance use, as well as the stereotypes associated with substance use, health care providers must entertain the diagnosis in all patients. Substance use must be a diagnosis to be excluded in the differential diagnoses of many medical conditions. Table 10-5 lists clues to a possible alcohol and drug abuse diagnosis. These clues include erratic behavior, agitation, disorientation, doctor “hopping,” child custody loss, and frequent unexplained accidents.

Table 10-5: Clues to Drug and Alcohol Abuse

<i>Medical History</i>	<i>Behavioral Clues</i>	<i>Social History Clues</i>
<ul style="list-style-type: none"> • HIV infection • Endocarditis • Hepatitis B or C infection • Septic emboli • Septic thrombophlebitis • Pancreatitis • Cirrhosis 	<ul style="list-style-type: none"> • Agitation • Somnolence • Disorientation • Erratic behavior • Doctor “hopping” • Frequent unexplained accidents 	<ul style="list-style-type: none"> • Inability to retain employment • Child custody loss • Seemingly unexplainable financial difficulties • Relationship distress

The diagnosis of drug and alcohol dependence is made by taking a careful history of drug and alcohol use, as well as a directed medical and psychosocial history; performing a complete physical evaluation; and laboratory testing for the presence of drugs and/or alcohol, or for the complications of drug and alcohol abuse.

The most commonly used instruments to detect and assess drug and alcohol abuse are the CAGE survey, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) alcohol/drug abuse/dependence diagnostic criteria, and the Addiction Severity Index.

If the provider cannot get a sense of the patient's substance use from unstructured questions, the CAGE survey offers a nonthreatening alternative approach. The CAGE survey is a four-question format intended to be used in primary care and other non-substance abuse-related health care facilities.

1. Have you felt that you ought to **C**ut down on your drinking or drug use?
2. Have people **A**nnoyed you by criticizing your drinking or drug use?
3. Have you ever felt bad or **G**uilty about your drinking or drug use?
4. Have you ever had a drink or used drugs first thing in the morning (**E**ye opener) to steady your nerves, get rid of a hangover, or to get the day started?

There are several other simple alcohol-screening instruments, including TWEAK, T-ACE, Michigan Alcoholism Screening Test (MAST), Alcohol Use Disorders Identification Test (AUDIT), and Rapid Alcohol Problems Screen (RAPS). TWEAK (an acronym for Tolerance, Worry about drinking, Eye-opener, Amnesia, and Cut down on drinking) and AUDIT perform better than CAGE in women (Bradley, 1998). Both TWEAK and T-ACE have been validated for alcohol screening in pregnancy (Russell, 1994).

Screening tests like these can be very useful for getting substance-addicted patients into a trajectory for substance abuse care. Otherwise, these patients may be seen in different parts of the health care system for other problems, while the substance abuse is not identified or addressed.

Some patients will come to medical attention because of substance intoxication or withdrawal. As with substance abuse in general, entertaining the diagnosis and recognizing the constellation of signs and symptoms is critical to recognition of intoxication and withdrawal syndromes. Alcohol intoxication may be characterized by inebriation, sedation, ataxia, and slurred speech. However, this extreme of behavior is witnessed in only a subset of patients. Of the 113 million Americans age 12 and older who reported alcohol use, 33 million reported binge drinking (meaning they drank 5 or more drinks on one occasion 5 or more days during the past 30 days) (SAMHSA, 1999). Alcohol withdrawal can vary from agitation to the more florid syndromes associated with delirium tremens. This includes labile blood pressure, autonomic instability, visual hallucinations, and death. It should be noted that delirium tremens may be fatal if untreated. The mortality may be as high as 35%, but with early recognition and treatment, that risk decreases to 5% (Grossman, 2001).

Opiate intoxication is associated with sedation, including somnolence or "nodding." There has been a resurgence in heroin popularity, with an estimated 81,000 new heroin users in 1997 (SAMHSA, 1999). Opiate withdrawal is characterized by the loss of central nervous system depression. These signs include piloerection, vomiting, diarrhea, agitation, irritability, and sweating. Cocaine, and its alkaline cheaper form, crack, are highly addictive. Intoxication with cocaine is associated with euphoria, as well as profound hypertension (secondary to vasoconstrictive effects). Increased pulse rate and dilated pupils are also associated with cocaine intoxication. Cocaine/crack withdrawal is associated with irritability, agitation, and mood lability.

The DSM-IV criteria for drug dependence are developed for the 11 classes of commonly abused drugs (including alcohol) and include 7 major criteria (Table 10-6). DSM-IV criteria determine dependence by finding evidence of physical or psychologic dependence on a drug or tolerance to it, disruption of social life patterns, and disregard of the negative medical consequences of using drugs. A person is considered to be drug dependent if they fulfill 3 of the 7 criteria within a 12 month period.

Table 10-6: DSM-IV Drug Dependence Criteria

- | |
|---|
| • Presence of drug withdrawal symptoms/syndrome |
| • Escalation of drug doses or reduced effect of the same dose |
| • Persistent inability to reduce or control drug use |
| • Increased time obtaining and using the drug |
| • Personal and business activities reduced by drug use |
| • Substance taken in larger amounts or for longer than intended |
| • Knowledge of drug use's negative health and personal effects, yet continuing to use drugs |

Source: Adapted from DSM-IV, 4th edition, 1994.

The Addiction Severity Index (ASI) (NIH, 1995) is most commonly used to help health care givers assess the severity of the drug and/or alcohol addiction in persons who are already determined to have a drug use problem and for whom a treatment plan must be developed. The ASI is a detailed, 1-hr assessment of environmental, historical, physiologic, and drug-related factors contributing to that individual's drug use. The specific areas of evaluation include drug and alcohol use, psychiatric problems, legal problems, family/social issues, and employment/ support concerns. Physical and psychologic signs of drug use and changes in medical and mental health status are also assessed. The data accumulated by ASI information is useful for developing treatment plans that include lifestyle change goals. The ASI is also a useful instrument for assessing progress at different follow-up points because it is time-based and yields quantitative composite scores for each problem area.

B. DIAGNOSIS BY LABORATORY AND CLINICAL EXAMINATION

Substance abuse disorders are erratically diagnosed on physical examination for a number of reasons including: 1.) caregivers' lack of interest 2.) lack of awareness of drug use signs or 3.) the signs may be subtle. Most drug and alcohol-dependent persons have jobs and lead a "normal" life, without the stereotypic dysfunction of severe alcoholism or injection and noninjection drug use. Cocaine snorting can be suspected by seeing a damaged nasal mucosa; hypodermic marks or "tracks" suggest injection drug abuse, although the absence of visible marks does not rule this out. The single most useful examination is of the eyes. Nystagmus is often seen in abusers of sedatives/hypnotics or cannabis. Mydriasis is often seen in persons under the influence of stimulants or hallucinogens or in withdrawal from opiates. Miosis is a classic hallmark of opioid effect. Evidence of multiple minor (or past major) injuries can also be a clue to possible substance abuse.

Drugs may be detected in almost any fluid or tissue in the body. The most common samples for drug tests are urine, blood, saliva, hair, sweat, and breath (Wolff, 1999). Urine testing is the most available and useful testing format. There are test kits that can be used in offices and at home and require simple collection of a urine sample. Urine test limitations, however, are numerous. These limitations include the ability to detect only recent drug or alcohol use, as seen in Table 10-7. Adulterated urine samples and changes in the acidity of the urine may prevent quantification of illegal drugs in urine. Blood testing is available to many caregivers but is more expensive and more cumbersome than urine analysis. Blood testing is more accurate at quantitative detection of drugs in the user. Saliva may also be useful and correlates well with drug levels in the blood. Hair analysis is a more recent technology and may be a future tool for drug detection. It has the advantage of detecting drug use over a 1–3-mo period, depending on a person's hair growth rate. The reasons that the test is not used widely are that cosmetic hair treatments, i.e., hair bleaching, may change drug level results, in addition to other factors such as hair pigmentation and hair growth rate. Sweat testing is another noninvasive test that is more useful for monitoring drug relapse during drug treatment. It is designed to continuously monitor a person's drug use over a period of time by placing a special absorbant pad on the skin. The pad collects microscopic amounts of sweat produced by the body over time and is analyzed later for presence of drugs. Breath testing is commonly used to estimate the concentration of alcohol in an alcohol user and is a reliable reflection of blood alcohol.

Table 10-7: Duration of Drug Detection

<i>Drug</i>	<i>Duration of Detection</i>
Alcohol	6–10 hours
Amphetamines	12 hours
Barbiturates	2–30 days
Valium	4–5 days
Cocaine	24–72 hours
Heroin	24–72 hours
Marijuana	3–30 days
Methaqualone	4–24 days
Phencyclidine (PCP)	3–10 days
Methadone	3–5 days
Sex, food, gambling	N/A

Overall, the urine tests are the most reliable tests for clinicians to use. However, test results may be difficult to interpret for the inexperienced care giver because the results may be confounded by secondary drug exposures, chemical characteristics of the drugs to be detected, drug level variations in different body tissues and fluids, and test method variations. Drug testing properly used is a useful adjunct to clinical and behavioral drug use assessment and a useful but limited drug use screening tool. Drug tests should not be used as the sole criteria for detecting substance use but, properly used, they are helpful during drug therapy, and follow-up.

VIII. TREATMENT READINESS AND HARM REDUCTION

Substance abusers vary in their readiness to change their behaviors. Providers who are attuned to the patient's stage of readiness (precontemplative to action-oriented) will have the greatest success in facilitating behavior change (Prochaska, 1992). Motivating factors for treatment readiness in women are most commonly associated with difficulty in raising their children or in response to interventions by social services departments (Brady, 1999). Unlike men, women are more likely to express their treatment readiness in nonsubstance use settings, especially in mental health care sites (Lex, 1991). For that reason, drug and alcohol treatment readiness should be evaluated in all health care settings.

For persons who are not ready for addiction treatment, caregivers can provide harm reduction interventions, aimed at reducing the damaging effects or harm resulting from risk behaviors and practices such as the sharing of syringes and other drug injection equipment and/or unsafe sex practices resulting from the use of drugs and alcohol (Des Jarlais, 1995). Comprehensive strategies that can effectively target high-risk populations consist of a hierarchy of risk reduction approaches that, depending on the composition and needs of the populations being served, may include needle exchange programs or community outlets providing condoms (Sumartojo, 1996). Sexually transmitted infection prevention programs, education programs, social and work skills building programs, and health and drug/alcohol use treatment programs should be provided through community resources. Programs targeting drug- and alcohol-using populations and subpopulations are all useful in preventing diseases such as HIV, STIs, hepatitis, and tuberculosis and should eventually lead to encouraging the substance user to seek help in stopping drug or alcohol use (Needle, 1997).

A patient's history and behavior may be more predictive of treatment readiness, potential for engaging in care and adhering to therapeutic regimens than provider judgments based on gender, race, or ethnic background. There is a direct relationship between patient adherence with substance abuse treatment and the quality of the patient-provider relationship; however, the lack of physician training in the care of injection and other drug or alcohol abusers and the negative attitudes about drug use pose significant barriers (Laine, 1998).

IX. TREATMENT OF SUBSTANCE ABUSE

A. TREATMENT PROGRAMS

The most effective treatment programs are comprehensive, multidimensional, and can be effectively delivered in outpatient, inpatient, and residential settings. In addition to behavioral (counseling, cognitive therapy, or psychotherapy) and/or pharmacologic therapies, the patient may need other medical services, family therapy, family planning, violence prevention, parenting instruction, vocational rehabilitation, and social and legal services (Table 10-8).

<i>Personal Needs</i>	<i>Treatment Needs</i>
<ul style="list-style-type: none"> • Family services • Housing and transport • Financial services • Legal services • HIV/AIDS services • Educational services • Medical services • Vocational services • Child care services • Mental health services • Family planning services 	<ul style="list-style-type: none"> • Behavioral therapy • Clinical and case management • Intake and processing • Treatment plans • Pharmacotherapy • Continuity of care • Substance use monitoring • Self-help/peer support groups • Substance education

Treatment programs should also provide repeated assessments for HIV, hepatitis B and C, tuberculosis, and other infectious diseases, as well as noninfectious diseases like diabetes and hypertension, and counseling and referral for relevant mental health treatment.

The most successful treatment occurs when the environmental, social, behavioral, medical, and addiction problems are found early and treated over a long period of time (more than a year). Though it would be desirable to detect and treat drug use and alcohol abuse early after onset, when patterns of use are more easily treated or modified (Coates, 1998), most drug treatment modalities target more advanced stages of dependence, when medical or legal interventions are needed. Most patients do not seek treatment until symptoms and associated consequences are severe. Women's drug use problems tend to occur at an older age of onset and develop more rapidly than in men. Women also often learn of their HIV infection and other comorbid conditions much later than men. The late diagnosis of drug use and other diseases may result in shorter survival. The confluence of factors that complicate health care for female substance abusers underscores the importance of early engagement and retention of women in care.

Effective treatment of drug dependence produces reductions in drug use by 40–60%, significant decreases in criminal activity during and after treatment, and increases in full-time employment. Effective treatment also reduces risk of HIV transmission (as well as other infectious diseases) by a reduction in risky behavior. Methadone treatment programs have consistently been linked to lower rates of HIV infection (Metzger, 1993). Similarly harm reduction interventions also play an important role in decreasing risky behavior. In a prospective study of 259 untreated injection drug users, syringe exchange programs demonstrated a two to six-fold decreased odds of HIV risk behavior. These findings were most pronounced for those individuals without other sources of syringes (Gibson, 2002). Establishing accessible care in primary care settings offers countless opportunities to initiate prevention and treatment interventions targeted to

adults, adolescents, and other population groups at risk for drug and alcohol abuse and associated problems. Easy health access for women is particularly important because their motivation for drug use/alcohol abuse is most often to cope with negative mood or anxiety (McCaul, 1999). Providers should be accessible and should monitor individual triggers for stress and levels of stress sufficient to produce drug use complications or relapse.

B. PHARMACOLOGIC INTERVENTIONS

Today even the most severe physical withdrawal symptoms can be managed with appropriate pharmacologic treatments, reducing the complications of physiologic dependence in the treatment of drug dependence. Drugs for alcohol and sedative-hypnotic dependent persons are important for controlling and preventing serious medical consequences of drug withdrawal while other medications like methadone can help stabilize a patient and facilitate a return to productive functioning. Other important pharmacologic interventions include the treatment of comorbid conditions common in drug and alcohol abusing populations. Use of antidepressants in psychiatrically impaired substance abusers is as important as therapies directed to the effects of the drugs of abuse.

The pharmacologic treatments for drug use are well known but not well understood by many health caregivers. Several classes of medications may be used to treat, modulate, or prevent drug use.

OPIATE ADDICTION

Opiate agonist drugs like methadone, 1-a-acetyl-methadol (LAAM) and buprenorphine are used as opiate substitutes for opiate-dependent persons. These three drugs, used to treat addiction, block the ability of the illicit drugs to attach to opiate receptors, therefore decreasing a person's craving for the drug without causing euphoria. This is the most misunderstood medical approach to addiction treatment. Although methadone, LAAM, and buprenorphine are addictive, they are successful in helping addicts to stop their negative and harmful behaviors associated with drug use and begin to concentrate on developing the skills to discontinue drug use entirely. It is the drug craving that is associated with drug use relapse and criminal behavior and it is its prevention that makes substitution medications work successfully as part of a drug treatment program. Methadone suppresses withdrawal for 24 hr (four to six times the duration of the effects of heroin) and decreases or eliminates drug craving; it is not sedating, can be dosed once a day, and can be administered orally. Furthermore, it is medically safe even when used continuously for 10 years or more.

LAAM is a newer synthetic opiate resembling methadone. LAAM can block the effects of heroin for up to 72 hr with minimal side effects when taken orally. Its long duration of action permits dosing just three times per week, thereby eliminating the need for daily dosing and take-home doses for weekends.

Buprenorphine is a partial opioid agonist which has recently been approved by FDA for office-based and program-based treatment of opiate addiction. Some of the advantages of using buprenorphine are milder withdrawal symptoms, lower risk of overdose, and availability to patients in the offices of physicians trained and certified in the use of the medication. If used in the proper dosage, buprenorphine is as effective as methadone or LAAM.

These substitution medications are not a cure for drug dependence but important adjuncts to care. It has been shown that while an opiate user is on methadone, she is much less likely to commit a crime and more likely to succeed in completing a drug treatment program. When combined with behavioral therapies or counseling and other supportive services, these pharmacologic approaches are highly effective for treating heroin addiction, particularly in those with long-term dependence and repeated prior treatment failures.

Antagonist medications like naloxone and naltrexone block the effects of morphine, heroin, and other opiates. As antagonists, they are especially useful as antidotes. Naltrexone, with a duration of action ranging from 1 to 3 days depending on the dose, blocks the pleasurable effects of heroin and is useful in treating some highly motivated individuals, such as professionals who do not want to lose their jobs. It is also successful in preventing relapse by former opiate dependent individuals released from prison on probation.

ALCOHOL ADDICTION

Antabuse (disulfiram) is used in the context of alcohol abuse treatment to cause negative effects when the patient consumes alcohol. The drug interferes with alcohol metabolism, causing the production of acetaldehyde, a noxious chemical that causes severe flushing, nausea, and vomiting. The effectiveness of therapy is dependent on patient adherence to a daily medication dose. Acamprosate (Putzke, 1996) is a newer drug currently used in Europe that increases alcohol abstinence and decreases craving by affecting g-aminobutyric acid and glutamate brain receptors. Naltrexone also has been found to decrease alcohol craving and relapse. It was approved in 1994 by the FDA for the treatment of alcohol dependence (Volpicelli, 1992; Anton, 1999).

COCAINE ADDICTION

There are no effective medications for treating cocaine addiction but in some cases treating comorbid mental health problems may improve chances of stopping cocaine use in the cocaine or crack-dependent person. Pharmacologic therapies have been specifically targeted at decreasing the dysphoric effects of cocaine withdrawal. Unfortunately, studies examining antidepressant medications targeting numerous neuron targets and multiple generations of antidepressant medications such as fluoxetine, sertraline, maprotilene, phenelzine, trazodone, and

lithium have not proven successful in assisting a person to permanently stop cocaine or crack use (McCance, 1997). Dopaminergic agents such as bromocriptine, amantadine, haloperidol, bupropion, and others have also not been proven to be effective. However, in studies using desipramine, carbamazine, and bupropion, the mental health effect of these drugs was clinically helpful for a patient's successful drug cessation in drug treatment programs (Kranzler, 1999).

DETOXIFICATION

Detoxification is used either to prevent serious medical or psychological complications of drug withdrawal from alcohol or sedative hypnotics or to ease the symptoms of withdrawal from the other drugs that do not have withdrawal syndromes with any significant morbidity or mortality (all other drugs of abuse) (Prater, 1999). In either case, detoxification protocols are not treatments for drug use but are part of a drug use treatment strategy.

Detoxification of alcoholics and sedative hypnotic users will prevent severe and sometimes fatal complications of drug withdrawal. For alcoholics, chlordiazepoxide (Librium) sedation is an important part of patient therapy. In most persons with alcohol dependence detoxification with a benzodiazepine can be completed on an outpatient basis with supportive care. However, about 10% of alcohol-dependent persons will have sufficiently severe withdrawal symptoms, histories of withdrawal complications, or other comorbid illnesses that require in-patient management. If a woman is pregnant, Librium should not be used. Alternative medications, especially for persons with severe liver disease are lorazepam (Ativan) and oxazepam (Serax). In conjunction with the sedatives, thiamine to prevent Wernicke-Korsakoff syndrome and clonidine or β -blockers to control noradrenergic symptoms may be helpful. Withdrawal from sedative hypnotics is characterized by severe, chronic anxiety, which may need long-term controlled, tapering doses of sedatives. Carbamazine (Tegretol) and valproic acid have also been used to control anxiety in sedative-hypnotic patients (Eickelberg, 1998).

Detoxification for other types of drug abuse is useful for diminishing the symptoms of drug withdrawal but does not have any long-lasting beneficial effect on the drug user. For example, clonidine (Gold, 1979) and lofexidine (Bearn, 1996) are used in this way because they decrease the adrenergic symptoms of opiate withdrawal. These measures are short term and do not address the true underlying problems of drug use. Even though the effects of detoxification are only short term, it is one of the few drug use interventions reimbursable in most health systems (O'Brien, 1997).

NEW PHARMACOLOGIC APPROACHES

The combined use of antagonist-agonist medications has been evaluated for drug treatment, with the biologic objective of preventing activation of opiate receptors and other drug use-related cell receptors. Research has found that treating nicotine-addicted persons with mecamylamine prevents smoking relapse (Rose, 1994). This may be a useful adjunct therapy for persons in tobacco cessation programs.

Anticraving medications are used to prevent a person from wanting to take the drug. The biology and psychology of craving and its prevention are not well understood but it has been proven to be effective in treating addiction to nicotine. Bupropion (Wellbutrin, Zyban), an antidepressant medication, has been successfully used to treat cigarette craving (Ferry, 1999).

Vaccines against addictive drugs are intended to block the binding of illicit drugs to their cellular receptors. Although no vaccines are currently available for human use, there is evidence that a vaccine against cocaine may be possible to develop. Much future research is planned in this area.

C. COGNITIVE/BEHAVIORAL INTERVENTIONS

Behavioral and cognitive interventions are a vital part of drug and alcohol addiction treatment and prevention. Cognitive-behavioral therapies are based on the assumption that learning processes play an important role in the development of drug use and dependence and therefore are important in efforts to reduce use and dependence. Behavioral methods are employed to identify high-risk relapse situations, extinguish triggers to drug use, develop self-monitoring of use behavior, and establish competing coping responses. By learning to recognize situations conducive to substance use, patients can develop individual coping strategies to avoid circumstances that place them at risk for relapse. Perhaps the single most important factor for short- and long-term relapse prevention is the learning and application of individual coping skills. Avoidance of other drug users and drug use environments are key tools for maintaining abstinence. Brief interventions with as little as 5 minutes of education and counseling about safe drinking guidelines, the consequences of alcohol on health, the patient's medical status, and the improvements that may occur if alcohol use is stopped or reduced, have been shown to be effective in reducing alcohol consumption and its medical and social consequences in general medical settings and may be of use in HIV clinics as well (Petry, 1999). Five to 15 minute interventions have also been shown to be effective in increasing smoking cessation rates (Dolan-Mullen, 1999).

There are at least 11 research-validated therapies using a variety of behavioral, social, and incentive-based systems to treat drug use (NIH, 1999). The objectives of the different programs include removing patients from stressful environments to get care (short-term and long-term residential homes), providing alternatives to pharmacologic treatment (outpatient drug-free programs), and providing community-specific interventions (community-based programs for drug users and recently released criminals). There are several psychotherapy programs, based on the patient's willingness to recognize drug use as a problem and to stay off drugs, with or without incentives.

The 12-step self-help groups/meetings are important nonmedical, behavioral drug use intervention and prevention activities used by 10–15 million Americans in 500,000 or more groups (Goldsmith, 1989). These

meetings emphasize fellowship and provide support for maintaining abstinence from alcohol, other drugs, or addictive behaviors like overeating. These programs are not intended to replace medical and behavioral drug use treatments but are meant to add to their effectiveness. The largest 12-step groups are Alcoholics Anonymous; Narcotics Anonymous, for all drug users including alcoholics; Al Anon, to support family and friends of alcoholics and drug users; and Overeaters Anonymous (Chappel, 1999). In 1976, Women for Sobriety was established as a 12-step program to help women, when it was recognized that Alcoholics Anonymous did not address adequately the specific needs of alcohol-dependent women (Katkulas, 1996). Rational Recovery, a self-help group based on cognitive/behavioral principles, is also available in many large cities.

X. PREDICTORS OF DRUG TREATMENT RETENTION AND THE DURABILITY OF TREATMENT GAINS

Predictors of treatment retention include high motivation, legal pressure, receiving psychologic counseling while in treatment, no prior violations of the law, and an absence of other psychologic problems (NIDA, 1998). Specific characteristics, such as injection drug use, age, race, socioeconomic status, level of education, and occupation do not predict adherence to drug treatment programs. The most accurate predictors of drug program retention and medication adherence are health care beliefs, health care access, familiarity of the treatment setting, availability of case management social support, and perceived support from the clinical staff.

Provider and patient recognition of the chronic nature of drug addiction and the need for long-term treatment is essential to successful and durable addiction care. It has also been shown that lasting reductions in drug use are greater for patients who remain in treatment for a minimum of 3 mo or longer (Simpson, 1997) and are treated with a combination of medical, behavioral and cognitive treatments.

Available treatment options continue to expand, providing therapeutic combinations that, when appropriately matched to patients' specific treatment needs, can increase the patient's chances of staying drug-free (McLellan, 1997). Treatments taking care of a patient's specific social and personal needs increase an individual's chances of successfully completing the treatment program and have improved posttreatment outcomes. Treatment for women that is woman-focused and targets the unique needs of women, including their children; interpersonal, cultural, and contextual issues; and employment and housing considerations are also known to increase effectiveness (Metsch, 1995). Participation in these programs enables women with children to develop stronger life and social skills to ensure stable independent living practices (Hughes, 1995).



XI. RELAPSE

Drug addiction is a chronic disease characterized by periodic drug use relapses. Although many treated persons relapse, it is wrong to conclude that treatment has failed or that the individual is hopeless. Like diabetes, hypertension, or other chronic diseases, the individual with a substance abuse problem will need frequent and long-term follow-up to maintain a drug-free state. Not surprisingly, simultaneous treatment for concurrent medical, mental health, and drug use problems offers significantly higher rates of success. The interventions that successfully address comorbidity maximize linkages between school, community, clinic, and other health service delivery systems. Woman-focused HIV prevention interventions include overcoming gender, cultural, and power barriers that increase risks, such as learning negotiation strategies for gaining partner acceptance for condom use, dealing with parenting responsibilities, and resolving interpersonal conflicts. The relative success and durability of approaches that have multiple and mutually reinforcing outcomes depend on coordination among professional and material resources in a rational, systematic, and cost-effective manner.

Treatment should be judged by the same criteria used for other chronic disease interventions: Will it help lengthen the time between relapses, ensure the individual can function in society, and minimize long-term physical damage?

XII. SUBSTANCE ABUSE IN PREGNANCY

It is difficult to determine the true prevalence of substance abuse by pregnant women. Stigma, criminal laws regarding child endangerment, and denial all contribute to the epidemiologic conundrum. Cross-sectional studies at large urban centers, given the high-risk populations served, may overestimate community drug use health problems. In 1990, a Centers for Disease Control and Prevention study in Rhode Island revealed a statewide prevalence of illicit drug use of 7.5% (CDC, 1990). A cross-sectional study in Florida revealed that 15% of unselected women had evidence of recent drug or alcohol use on urine toxicologic screening (Chasnoff, 1990). Punitive approaches to the problem of substance abuse during pregnancy risk threatening privacy rights. These approaches further serve as deterrents to health-seeking behavior, and may further threaten the health of women and children.

The sequelae of substance use in pregnancy is beyond the scope of this chapter, however, a few specific drugs will be highlighted.

Smoking tobacco during pregnancy is associated with increased perinatal mortality, bleeding complications in pregnancy, low birth weight infants and preterm delivery and a possible increase in behavioral and learning problems among school-aged children whose mothers smoked during pregnancy (ACOG, 1997; Milberger, 1996). It is estimated that there could be as much as a 10% reduction in fetal and infant deaths if all pregnant women stopped smoking (Kleinman, 1988).

Alcohol use in pregnancy is associated with risk of fetal alcohol syndrome. This congenital syndrome is characterized by three findings: growth retardation, facial abnormalities, and central nervous system dysfunctions. Skeletal abnormalities and structural cardiac defects are also seen in the fetal alcohol syndrome, but it is the performance deficits that are most obvious. Decreased IQ, fine motor dysfunction, and hyperactivity are all common findings (ACOG, 1994).

Cocaine use in pregnancy poses maternal as well as fetal hazards. Some of these stem from the intense vasoconstriction associated with cocaine (malignant hypertension, cardiac arrhythmias, and cerebral infarction). Cocaine has been associated with premature rupture of membranes, preterm labor and delivery, growth retardation, cognitive development delays, and placental abruption. There are also documented cases of in utero fetal cerebral infarction (MacGregor, 1987).

Opiate addiction during pregnancy also poses serious risk to the mother as well as the fetus. Newborn infants of narcotic-addicted mothers are at risk for several complications, including the potentially fatal narcotic withdrawal syndrome. Withdrawal syndromes may appear 24 hr after birth, but may be delayed as long as 10 days after birth (Levy, 1993).

Beyond the medical ramifications for the mother and the fetus, substance abuse in pregnancy raises the specter of the legal system. There have been at least 200 women, in 30 states, criminally prosecuted for using illicit drugs or alcohol during pregnancy (Jos, 1995). Actions such as these have the potential to turn the provider into a law enforcement officer, and ultimately to drive away from prenatal care the very women who most need it. The conundrum of substance abuse in pregnant women and how society can best approach the problem continues. Providers should focus on screening and assessment of substance abuse and referral of pregnant women with drug and/or alcohol abuse into care and treatment.

X

XIII. ANTIRETROVIRAL THERAPY IN SUBSTANCE ABUSERS

There is often a lack of compassion toward people who have contracted HIV through stigmatized behavior, such as drug use (Hajela, 1998). Such sentiments are compounded by perceptions about adherence among drug users and the threat to public health associated with nonadherence leading to multidrug-resistant strains of HIV or other infectious diseases (Gourevitch, 1996). These assumptions may lead to blanket denial of appropriate antiretroviral therapy to individuals with a past or current history of substance abuse.

Although active substance abuse (including alcohol, cocaine, and heroin) is associated with nonadherence, patient readiness for antiretroviral therapy must be carefully assessed on an individual basis, and those who have been treated for drug dependence may be even more adherent than the general population or other medical groups. However, drug users are less likely to receive care, and injection drug users are among those least likely to receive antiretroviral therapies even when these treatments

are available and free (Shapiro, 1999). Demographic characteristics of patients, including race/ethnicity, sex, age, and socioeconomic status are generally not predictive of medication adherence, although depression and low literacy have been associated with poorer adherence to HAART (Stone, 2001). Another challenge in the management of HIV infection in a substance-abusing woman is to recognize the potential for drug interaction between methadone, as well as street drugs, and antiretroviral therapies. The clinical experience in this area is limited; however, there are well-recognized drug interactions between certain antiretroviral therapies and methadone. Of the nucleoside reverse transcriptase inhibitors, only abacavir has been associated with an increase in methadone clearance. Both nevirapine and efavirenz are associated with significant decreases in the methadone level with opiate withdrawal a common consequence. As this increases the potential for heroin relapse, it is essential that this potential outcome be discussed with patients in advance of the prescribing of these therapies, with a clear plan to address this possibility with the patient's drug treatment provider (ie, increasing methadone dose). Alterations in methadone levels have been seen with the protease inhibitors; however lopinavir/ritonavir has been associated with decreases in methadone levels and subsequent opiate withdrawal (see Table 10-9).

With newer ARV agents and dosing schedules allowing once-a-day antiretroviral regimens, the possibility of directly observed therapy (DOT), particularly in the setting of methadone clinics, offers a practical solution to concerns about adherence for patients in these settings.

Table 10-9: Drug Interactions Between Antiretroviral Drugs and Methadone		
<i>Drug</i>	<i>Effect</i>	<i>Recommendation</i>
Nucleoside Reverse Transcriptase Inhibitors		
Zidovudine (ZDV)	No data	Unchanged
Lamivudine (3TC)	No change in drug concentrations	Unchanged
Didanosine (ddl)	EC ddl level unchanged; buffered ddl AUC decreased 63%	No change EC ddl; may consider increase in buffered ddl dose or maintain standard dosing
Stavudine (d4T)	D4T level decreased 27%	No dose adjustment
Zalcitabine (ddC)	No data	Unchanged
Abacavir (ABC)	Increase in methadone clearance	Close clinical monitoring; may require increase in methadone dose

Table 10-9: Drug Interactions Between Antiretroviral Drugs and Methadone (continued)		
<i>Drug</i>	<i>Effect</i>	<i>Recommendation</i>
Nucleotide Reverse Transcriptase Inhibitors		
Tenofovir (TDF)	No data	Unchanged
Non-nucleoside Reverse Transcriptase Inhibitors		
Nevirapine (NVP)	NVP level unchanged; methadone level significantly decreased	Close clinical monitoring; may require increase in methadone dose
Efavirenz (EFV)	Methadone level significantly decreased	Close clinical monitoring; may require increase in methadone dose
Delavirdine (DLV)	No data	Unchanged
Protease Inhibitors		
Indinavir (IDV)	No change in methadone levels	Unchanged
Ritonavir (RTV)	Methadone level decreased 37%	Close clinical monitoring; may require increase in methadone dose
Saquinavir (SQV)	Methadone AUC decreased 20%, when co-administered as SQV 400 mg bid	No dose adjustment for this regimen, but monitor and titrate to methadone response, if necessary
Nelfinavir (NFV)	NFV may decrease methadone levels, but minimal effect on maintenance dose	Close clinical monitoring; may require increase in methadone dose
Amprenavir (APV)	Methadone level decreased 13%; APV Cmin decreased 25%	Monitor and titrate methadone if needed
Fos-Amprenavir (fAPV)	Presumably similar interaction to APV	Monitor and titrate methadone if needed
Lopinavir (LPV)	Methadone AUC decreased 53%	Close clinical monitoring; may require increase in methadone dose
Atazanavir (ATV)	No data	Unchanged
<i>AUC area under the curve concentration</i>		
<i>Cmin trough level</i>		
<i>EC enteric-coated</i>		
<i>Source: Adapted from Table 21, DHHS, 2004.</i>		

XIV. CRIMINAL JUSTICE SETTINGS

Women are the fastest growing segment of the prison population, and their drug-related crimes are increasingly more serious (FBI, 1997). Criminal justice reports show that substance use is implicated in the incarceration of 80% of men and women in state, federal, and local prisons. Persons either violated drug laws, stole property to buy drugs, have a history of substance abuse or addiction, or engaged in some combination of these (Maruschak, 1997). The more prior convictions an individual has, the more likely s(he) is to be drug dependent.

The most serious offense for 40% of women in state and federal prisons is the violation of drug laws. The enactment of mandatory sentencing policies has been associated with a 10-fold increase in the number of women incarcerated for drug crimes between 1986 and 1996.

Statistics show alcohol present in 31% of crimes, a combination of alcohol and other drugs in 16%, and other drugs alone 9%. A recent study confirms that alcohol has a high association with violent crime: twenty-one percent of violent felons in state prisons committed their crimes while under the influence of alcohol alone.

State officials have estimated that 70–85% of inmates need some level of substance abuse treatment; however, only about 13% actually receive treatment (Harlow, 1997). Those individuals with substance abuse histories are also more likely to have a history of physical and sexual abuse (National Minority AIDS Council, 1997). Criminal justice reports attribute the overwhelming majority of AIDS cases among inmates to injection drug use, with an incidence of new AIDS cases among inmates 17 times higher than that in the general population.

Inmates who have received appropriate treatment in prison are 50–60% less likely to be arrested again during the first 18 mo after release. For each offender who successfully completes treatment and returns to the community as a sober citizen with a job, it is estimated that reduced crime and arrest, prosecution, and incarceration costs, health care savings, and potential earnings accrue in the first year after release (Califano, 1998). One study found that total savings can exceed costs by a ratio of 12 to 1; another found that for every \$1 invested in drug treatment, there is a return of up to \$7. Levels of criminal activity have also been shown to decline by two thirds from the period before treatment to a comparable period after treatment.

XV. CONCLUSION

Drug and alcohol abuse have strong associations with HIV and other comorbid medical and psychiatric problems. Substance abuse may increase risk for HIV and other STI acquisition/transmission; may delay identification of HIV and entry into care; and may complicate management of HIV and other disorders. Women with substance abuse problems have special needs and require unique approaches to management. Health care providers should screen all women (including pregnant women) for drug and alcohol use/dependence and be knowledgeable about appropriate referrals and linkages. HIV prevention and treatment interventions should be part of comprehensive substance abuse treatment services and all HIV-infected women with drug and/or alcohol abuse problems should have access to substance abuse treatment.

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XI. ADOLESCENTS¹

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Adolescence is a time of significant cognitive, emotional, and physical development and is often characterized by exploration and experimentation. As adolescents explore intimacy and sexuality and develop autonomy, it is also a time of heightened vulnerability, including risk for HIV infection. This chapter focuses on young women as it reviews the epidemiology of HIV/AIDS in adolescents and provides guidelines for HIV counseling and testing, medical and psychosocial care, and strategies for linking HIV-infected and at-risk youth to care.

I. EPIDEMIOLOGY

Adolescents are at high risk for HIV infection. Worldwide, one out of every two new cases of HIV—half of 5 million new infections in 2001—occurred in youth ages 15–24. In developing countries, women are becoming infected at significantly younger ages than men, with a higher percentage of young women in their teens and early twenties having HIV than women in any other age groups (UNAIDS, 2002). In the United States, (CDC, 2001) more than half (53%) of adolescents newly infected with HIV are female, and 50% of all new infections, or some 20,000 new cases per year, are estimated to occur in youth ages 13 to 24. In addition, 19% of U.S. AIDS cases are reported in young adults in their twenties. Given a 10-yr period, on average, from initial infection to clinical manifestations of AIDS, most of these young people were likely infected during their teens.

Compared with adults, female adolescents represent a much higher proportion of HIV/AIDS cases. In 2001, adolescent girls ages 13–19 yr accounted for 48% of incident adolescent AIDS cases, whereas female adults made up 26% of incident adult AIDS cases. At highest risk are African American youth, who made up 66% of cumulative teen HIV cases through 2001, while representing only 15% of the U.S. adolescent population (CDC, 2001).

A. SEXUAL RISK

The majority of adolescent females (51%) with AIDS were infected through heterosexual intercourse. Moreover, an additional 30%, who are classified as having “no identified risk” because they were unable to identify their partners’ risk, are also assumed to have been infected through heterosexual encounters (CDC, 2001). This is consistent with

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widespread lack of awareness of their potential risk for HIV infection among sexually active adolescents and adult women. For example, of adolescents known to be HIV positive, 75% of young women are unable to identify their partners' risk factors (Futterman, 1993). Furthermore, for many adolescents "having sex" means heterosexual vaginal intercourse and some adolescent females may engage in receptive anal intercourse in the belief that this preserves their virginity and is safer (Haglund, 2003). A much smaller proportion of female youth (13% of 13–19-yr-olds and 25% of 20–24-yr-olds) were infected through injection drug use, compared with 39% of adult women with AIDS. Adolescents who were infected perinatally account for a small but growing number of adolescents with HIV/AIDS, and some are not diagnosed until adolescence.

Clinicians working with adolescents have noted additional risk factors for youth. A significant proportion of adolescents with HIV have experienced childhood sexual abuse; of adolescents screened at the Adolescent AIDS Program at Montefiore Medical Center, 25–40% report having been sexually abused (Futterman, 1993). Childhood sexual abuse has been associated with subsequent feelings of powerlessness in sexual situations and increased risk for unsafe sexual activity.

Moreover, 20% of sexually infected HIV-positive youth seen in an adolescent program reported having a parent who is also HIV-infected (Chabon, 2001). Further research is needed to assess parental influence on their children's HIV status. Nevertheless, children of parents with HIV generally live in the same high-prevalence neighborhoods as their parents and may also face increased risk as a sequela of parental illness or substance abuse. Clinicians should ascertain a history of sexual abuse or forced sex as well as parental HIV history when taking a history with adolescents.

B. SEXUALLY TRANSMITTED INFECTIONS AND PREGNANCY

Sexually active teens are also at risk for pregnancy and other sexually transmitted infections (STIs). According to the 2001 Youth Risk Behavior Survey, nearly half (43%) of all U.S. female high school students are sexually active (including 60% of 12th-graders), and 9% report having been pregnant (CDC, 2002). Approximately 1 million teens become pregnant each year, 74–85% of them unintentionally. Both STIs and pregnancy are markers for unsafe sexual activity and, in addition, STIs (both ulcerative and inflammatory) increase susceptibility for HIV infection. Two thirds of the 12 million cases of STIs reported in the United States each year occur in youth under age 25, and 1 out of 4 are reported in adolescents. Younger teens, particularly females, are least likely to be considered at risk or to be screened, particularly if they are asymptomatic, which is the case with the majority of STIs in women. For example, chlamydia is asymptomatic in three fourths of infected women, whereas approximately half of gonorrhea infections in women have no symptoms. This is especially salient because adolescent women have the highest age-specific incidence rates for both gonorrhea and chlamydia; 79% of reported cases of chlamydia occur in young women (46% in 15–19-yr-olds and 33% in 20–24-yr-olds).

C. HEIGHTENED VULNERABILITY FOR INFECTION

Adolescents are at risk for HIV and STIs as a result of the interplay between behavioral, biological, and socioeconomic factors (Institute of Medicine, 1997).

BEHAVIORAL RISK

During adolescence, sexual activity is often initiated, risk-taking and experimentation are normative, and many sexually active adolescents fail to take appropriate prevention precautions, despite basic knowledge of HIV transmission and prevention. During their last sexual encounter, nearly half of 9th-through 12th-grade girls did not use condoms, whereas 11% reported having more than 3 sexual partners. Many teens follow a pattern of sexual “serial monogamy” and may not consider themselves as having multiple partners. More than 1 in 5 (20–24%) of female high school students report episodic heavy drinking or current marijuana use, which can impair judgment and increase potential for high-risk behaviors. Most high school seniors have used alcohol, and 1 out of 4 students report having 5 or more drinks at least once during the past 30 days. About 25% smoke marijuana, 15% report using inhalants, and more than 1 in 50 have injected illegal drugs (CDC, 2002).

Specific populations of teens are at especially high risk, including adolescents who are lesbian, bisexual and transgender, homeless or runaway, injection drug users, mentally ill, and youth who have been sexually or physically abused, incarcerated, or in foster care. These youth experience increased vulnerability and multiple health and social problems as a result of abuse and neglect and lack of services and care. Lesbian and bisexual females may view themselves at lower risk but those who are sexually active with gay male peers are at risk for infection because of higher HIV prevalence among gay males (Ryan, 1998).

BIOLOGICAL RISK

Several biological factors also contribute to heightened risk in adolescent females. During puberty, the cervix undergoes physical maturation that makes the cellular lining less susceptible to infection as the single-layer columnar epithelium of the cervix is replaced with thicker multilayered squamous cells. Until this occurs, the cervix is much more vulnerable to STIs, particularly chlamydia and gonococcus, which have an affinity for columnar cells and have also been shown to facilitate STI transmission. At the same time, male-to-female transmission of STIs is much more efficient than female-to-male transmission given the larger surface area of the lower female genital tract and mechanics of sexual intercourse, which can result in mucosal trauma to women. In addition, STIs which facilitate HIV transmission are more likely to remain asymptomatic in women, and thus unrecognized and untreated, for a longer period of time.

SOCIOECONOMIC RISK

Adolescents are the most uninsured and underinsured group in the United States and are the least likely to receive office-based medical care or to use primary care services. Twenty-five percent of youth ages 15–29 have no health insurance and approximately 1 in 5 suffers from at least one serious health problem. Poverty, poor access to care, and lack of education and prevention skills further increase vulnerability to HIV. Additional barriers include mistrust of the health care system, fear of inappropriate disclosure, and providers' lack of understanding of adolescent rights to confidentiality and care without parental consent for sensitive health issues.

Moreover, many adolescents use emergency and walk-in facilities for acute care needs. As a result, they lack a primary care provider who can ensure ongoing care and address prevention and health promotion needs. Because adolescence is a time when help-seeking behaviors and attitudes about health and self-care are formed, the experiences adolescents have with health care providers are especially important. They form the basis for future provider-client interaction, communication patterns, and relationships.

II. HIV CARE FOR ADOLESCENTS

Cornerstones of adolescent care include consent policies, confidentiality, accessibility, outreach, and linkage to care and prevention. Even though youth prefer health care settings that are geared to their needs, most teens will not receive care in adolescent programs. Although most facilities are unable to offer the ideal “one-stop shopping” for teens, quality care can be provided by identifying a staff member and/or provider team who wants to work with adolescents and by adapting adult and family programs to meet an adolescent's needs. This can be done by accommodating walk-ins because youth do not often plan ahead, addressing payment barriers, and providing flexible appointments that will not conflict with school or work.

A. CONFIDENTIALITY AND LEGAL ISSUES

All states have laws that allow minors to consent to treatment without parental consent for specific health services including emergency care, STIs, or reproductive health and substance abuse treatment services. In many, but not all, states, this includes the right to consent for HIV counseling and testing. However, not all providers are aware of these rights or understand their significance for adolescents, and these rights vary by state and the medical service provided. Most importantly, lack of confidentiality may cause adolescents to avoid or delay needed care. Even though parental consent may not be needed to provide an HIV test or HIV-related care, providers should carefully assess an adolescent's cognitive capacity to understand the implications of having HIV disease and should encourage them to involve a supportive adult in their care.

B. COUNSELING AND TESTING

Although most youth do not think they are at risk for HIV infection, they prefer providers to initiate discussion concerning HIV prevention and risk assessment. All adolescents should receive HIV prevention education, and sexually active adolescents should routinely receive HIV counseling and be offered HIV testing with informed consent (Committee on Pediatric- AIDS, 2001). This enables providers to identify HIV-positive youth and provide ongoing medical care and support services, while relieving anxiety and reinforcing preventive behaviors for youth who are HIV negative. For adolescents who are not sexually active, counseling provides an opportunity to talk about sexual readiness, delaying intercourse, and low-risk ways to explore intimacy. New protocols for rapid, simple HIV counseling and testing are being developed for use in health care settings (www.adolescentaids.org; CDC, 2003).

New testing options such as those that test for antibodies in oral fluids or urine are helpful with youth who are afraid of needles and allow providers to offer testing in a variety of settings including mobile vans, school-based clinics, and drug treatment programs. Same-day testing is now FDA approved and is useful by eliminating the need for a return visit for results, but will require careful planning for the delivery of HIV-positive results. Meeting adolescent needs for flexibility, accessibility, and low- or no-fee HIV testing is important in overcoming primary barriers to accessing care and can serve as an entry point to care. Like other underserved populations, adolescents are generally diagnosed with HIV/AIDS late in the course of illness, relatively few receive care for HIV disease, and most do not know they are infected. Thus, ensuring access to HIV counseling and testing is essential in enabling adolescents to receive ongoing treatment and care.

Although counseling and testing for adults has generally been based on one initial pretest counseling session with providers, a “one-shot” approach to counseling is not effective with all at-risk youth. Two short counseling sessions before testing, using personalized risk reduction plans, can increase condom use and prevent new HIV and other sexually transmitted infections. Pre- and posttest counseling provide an opportunity to promote preventive health behaviors and to assess substance use and family planning needs, while providing basic information on HIV, obtaining consent, and conducting a comprehensive risk assessment (Table 11-1). More extensive guidelines are also available for adolescent HIV counseling and testing in all health settings (Chabon, 1998). Because adolescents may have misconceptions about aspects of HIV transmission and prevention, providers should assess their capacity to understand basic concepts of HIV disease and viral transmission. Effective HIV counseling for adolescents should be culturally sensitive and tailored to an adolescent's developmental needs. In addition, providers should take special precautions to ensure confidentiality in institutional settings such as foster care, residential treatment, or detention.

Table 11-1: Teen AIDER (Assess, Inquire, Discuss, Educate, Readiness) Interview for HIV Counseling, Testing, and Risk Reduction
<i>Assess and Inquire</i>
<p>Create a confidential atmosphere</p> <ul style="list-style-type: none"> • Assure youth about confidentiality of visit and ability to consent for testing per local laws • Assure youth that testing is their choice • Acknowledge that it can be embarrassing to discuss sexual behaviors • Help youth to identify supportive adult who is aware that youth is being tested
<p>HIV/AIDS Knowledge</p> <ul style="list-style-type: none"> • Allow adolescent to verbalize understanding of HIV, clarify misconceptions, and fill in gaps in knowledge • Assess feelings about testing and previous HIV testing experiences • Inquire if youth knows anyone with HIV/AIDS (e.g., sexual partner, family member)
<p>Sexual Risk Assessment</p> <ul style="list-style-type: none"> • Assess sexual behaviors without making assumptions about sexual orientation; not all youth are heterosexual and not all youth who have engaged in same-sex behavior self-identify as lesbian or gay • Assess number of partners, age differential, and partner's known risks • Assess frequency of substance use in the context of sexual behavior • Assess consistency of condom use and obstacles to use such as unassertiveness, desire to become pregnant, fear of violence, and religiosity • Assess for history of sexual abuse or rape
<p>Substance Use and Other Risk Assessment</p> <ul style="list-style-type: none"> • Assess level of drug and alcohol use and reasons and context in which use occurs • Review risk of impaired judgment that may lead to unsafe sex • Assess potential need for drug treatment • Assess violence and substance use in home and community
<i>Discuss and Educate</i>
<ul style="list-style-type: none"> • Discuss abstinence • Discuss sexual activities that don't involve exchange of body fluids (outercourse) • Demonstrate proper male condom, female condom, and dental dam use on anatomical model and provide opportunity for practice • Rehearse effective ways to communicate risk reduction with sexual partner(s) • Discuss harm-reduction strategies for youth using drugs • Develop a personalized risk-reduction plan • Discuss postponing sex for youth who are not sexually active • Determine referral needs (e.g., medical, psychosocial, school/vocational, substance abuse, reproductive health, legal, housing, psychiatric)
<i>Readiness For HIV Testing and Referral</i>
<ul style="list-style-type: none"> • Adolescent should be informed about both anonymous and confidential testing • Provide education about partner notification programs and other options for disclosure to partners • Assess understanding of meaning of a positive and negative test result • Assess understanding of benefits of early intervention • Determine with youth if testing should occur at this time and obtain informed consent • Strategies for coping (how to relieve stress and anxiety during the testing process) • Arrange follow-up appointment and method for confidentially contacting youth, if needed

Source: Adapted with permission from: Chabon B, Futterman D. Adolescents and HIV. *AIDS Clin Care* 11: 9–16, 1999.

Knowledge of appropriate condom use and widespread availability of condoms are especially important in promoting risk-reduction behaviors among youth. All facilities that provide health care for adolescents should make condoms available and providers should demonstrate condom use with anatomical models. Adolescents have difficulty using condoms during intercourse for several reasons, including: 1) lack of knowledge about effective use; 2) lack of communication and social skills; 3) lack of availability of condoms at the time of sexual activity; and 4) impulsive behavior exacerbated by drug or alcohol use. Gender and power imbalances in relationships make condom use especially difficult for adolescent women whose partners are older and who are just beginning to develop communication and negotiation skills. Helping youth identify their personal values may increase self-esteem and help them resist pressures to engage in sexual risk behaviors (Table 11-2).

Table 11-2: Factors Associated with Condom Use

<i>Encourages Use</i>	<i>Discourages Use</i>
<ul style="list-style-type: none"> • Knowledge about condoms • Belief in effectiveness • Discussion with health care provider • Self-esteem/self-efficacy • Communication/negotiation skills • Availability/accessibility 	<ul style="list-style-type: none"> • Drug/alcohol use • Relationship power imbalances • Peer pressure • Lack of effective sex education • Lack of media/cultural support

C. PREVENTION

Promoting abstinence and risk reduction among adolescents is especially challenging because developmental characteristics encourage concrete, short-term thinking and experimentation and increased reliance on peers. Thus, successful primary and secondary programs for adolescents are those that provide interventions to increase self-esteem and self-efficacy, build social skills, and provide basic information geared to the adolescent's developmental level, using a peer support model. For high-risk youth, the AIDS Risk Reduction Model (Catania, 1990) has been widely used to foster primary and secondary prevention, based on the premise that behavior must first be acknowledged as risky before youth will initiate change.

School-based programs that provide comprehensive health education in conjunction with school health clinics offer optimal opportunities to reinforce positive health behaviors and ensure routine screening for a range of health and mental health concerns. But they are especially important in reducing risk and identifying sexually active youth who are at risk for STIs and pregnancy. A comprehensive review of school-based programs designed to reduce risky behavior in teens found that adolescents who received AIDS education were less likely to engage in sexual activity and more likely to practice safer sex than peers who lacked AIDS education in school (Kirby, 1994). In particular, successful

programs include skills building, reinforcement of values and norms to prevent unprotected sex that are based on age and experience levels, and discussion of social influence and pressure. School clinics also offer an important venue for access to condoms and appropriate instruction on condom use. Although not widely available, school clinics provide an important site for HIV counseling and testing for in-school youth, given new rapid testing options. Ultimately, successful prevention must also involve society and the media—until youth see abstinence, condom use, and safer sex discussions incorporated into sex scenes in music videos and movies, they will not believe that this is a social norm.

Adolescents who are HIV-infected are also in need of risk reduction counseling to prevent transmission of HIV to uninfected sexual partners and to prevent acquisition of other STIs or reinfection with other HIV strains.

D. LINKING YOUTH TO CARE

Linking at-risk youth to care is essential in meeting their needs for risk-reduction education and appropriate ongoing HIV medical and psychosocial care. Barriers to care include stigma associated with HIV, lack of independent transportation, dependence on parents for health insurance or other financing for care, and feelings of vulnerability. Most HIV-infected youth do not know they are infected, and many providers are not aware of available community service agencies that can address their multiple mental health and social service needs. Community outreach is a primary component in ensuring access to care for youth with HIV disease. Peer-based outreach services are frequently employed, as adolescents are more likely to listen to their peers. Unlike adult women who have more opportunities to obtain HIV testing and to access care related to their reproductive health needs, adolescents who are not pregnant require proactive outreach efforts to promote HIV testing and engage them in care. This includes city-wide campaigns to encourage testing and to make it more widely available, with direct linkages to adolescent health care facilities. One such initiative — a social marketing campaign spanning the continuum from HIV prevention through testing to care — was developed by the Adolescent AIDS Program at Montefiore Medical Center in New York City in 1996. “HIV. Live with it. Get Tested” was designed with marketing experts, health providers, and most importantly youth themselves, to combine media advertisements such as posters and radio and TV ads with community outreach in settings where at-risk youth access information and are likely to congregate. Using teen language for sexual activity (e.g., “Knockin’ Boots” or “Gettin Busy”) to promote testing and care services through a coalition of adolescent HIV programs and community-based youth agencies, the initiative is intended to help adolescents link the concept of having sex with HIV risk and the importance of HIV testing. The initiative focuses annual activity around a “Get Tested! Week” launched with a youth-led Town Hall meeting and peer outreach (Futterman, 2001; www.adolescentaids.org).

E. HIV CLINICAL AND PSYCHOSOCIAL CARE

Although the natural history of HIV infection in adolescence is still being defined, the course of disease appears to follow that of adults. A national prospective study with sites in 13 cities—AMHARN—was funded by NIH and HRSA to identify the course of disease in adolescents, including its spectrum, manifestations, effects of puberty, and developmental and psychosocial interactions (Rogers, 1998; Rudy, 2001). Initial findings suggest that adolescents may have greater potential for immune reconstitution than adults as a result of residual thymic function, which underscores the need for aggressive outreach efforts and access to early effective treatment and has also identified a high prevalence of sexually transmitted infection in this population.

PHYSICAL EXAM, LABORATORY TESTS AND IMMUNIZATIONS

Physical examinations for adolescents should follow guidelines used for adults; however, providers should use Tanner staging of puberty (characterizing breasts, genitalia, and pubic hair) to interpret blood values and prescribe medications (Schneider, 1998). Because sexually active adolescents are at very high risk for STIs, providers should routinely screen with cervical cytology, and for chlamydia, gonorrhea, syphilis, and hepatitis B and C, and follow tuberculosis screening guidelines for adults with HIV infection. Pregnancy testing should be performed when indicated by history or exam findings, but should always be considered with missed menses, abnormal bleeding, or development of pelvic pain. Adolescents require more immunizations than adults (Table 11-3). Because immunizations may briefly boost viral load, they should be scheduled on the same day as or after viral load measurements. At present, CD4 counts and viral load measurements are interpreted as for adults and used to guide treatment.

Table 11-3: Immunizations for Adolescents

• Measles, mumps and rubella (MMR) booster
• Diphtheria-tetanus toxoid (dT) booster
• Hepatitis B vaccine (3 in series)
• Hepatitis A vaccine (2 in series) (not routine; recommended for males who have sex with males)
• Influenza (yearly)
• Pneumococcal vaccine
• Hib (optional)
• Varicella zoster vaccine for contacts (not currently approved for HIV+ persons)

Source: Reprinted with permission from: Hoffman ND, Futterman D, Myerson A. Treatment issues for HIV+ adolescents. *AIDS Clin Care* 11:17-24, 1999.

HIV TREATMENT

Information from clinical trials is limited because few adolescents have participated in existing clinical trials. While adolescent trials are under development, HIV and opportunistic infection treatment and prophylaxis recommendations for postpubertal adolescents currently follow clinical guidelines for adults. Because pubertal changes may affect pharmacokinetics, dosage is based on Tanner staging rather than age. For example, pediatric dosing should be used for adolescents who have entered/are in early puberty (Tanner stage I/II), whereas dosing for adolescents in midpuberty (Tanner III/IV) should be based on whether or not they have completed the growth spurt. Adolescents who have completed puberty (Tanner V) should receive adult dosages.

Treatment adherence, which is challenging for adults, can be especially challenging for adolescents, who struggle with a range of developmental tasks that require them to balance dependence with increasing autonomy. As with any successful work with adolescents, the first step in promoting adherence is establishing a solid therapeutic alliance. Providers must develop a systematic approach that facilitates adherence by addressing four areas of interaction, including building trust, assessing and facilitating readiness, helping teens initiate and practice the new treatment regimen, and providing ongoing support for adherence (Table 11-4). This approach addresses barriers to maintaining a complex medication schedule for adolescents, such as lack of privacy in school, home, or residential settings, the need to develop a reminder system, and the incongruity of having a serious illness while exhibiting few visible indicators of disease. For example, the most common reasons for missing medication by youth in a Los Angeles adolescent HIV/AIDS program include forgetfulness, side effects, the inconvenience of having to take so many pills, and the fact that taking the medication is a continual reminder of being HIV infected (Belzer, 1998).

AMHARN has designed a multilevel adherence initiative, Project TREAT (Treatment Regimens Enhancing Adherence in Teens), to address medication adherence in adolescents. A monograph describing the model has been developed for providers and is available from HRSA (Schietinger, 1999; Rogers, 2001). Based on Prochaska and DiClemente's Transtheoretical Model of Change, Project TREAT acknowledges the uniqueness of each adolescent's readiness for treatment. The model has developed specific interventions and materials (video and audio tapes and booklets) for each stage of readiness to facilitate successful adherence. (The Stages of Change are: Precontemplation, Contemplation, Preparation, Action, Maintenance, and Relapse.) Practice regimens with vitamins help youth rehearse their medication regimen, while enabling them to problem-solve potential barriers without risking underdosing. Medications must be integrated into the adolescent's daily routine. Ideally, adolescents should be prescribed a daily or twice-daily medication regimen. Many providers also initiate treatment without using protease inhibitors; these are incorporated into later regimens after the adolescent has demonstrated effective adherence, to avoid risking potential cross-resistance to protease inhibitors.

Table 11-4: Adherence: Using your EARS

Engage
<ul style="list-style-type: none"> • Establish therapeutic alliance and build trust; goal is active participation by adolescent in all aspects of treatment • Address immediate needs (health, housing, insurance, family, and partners) • Educate about HIV infection: transmission, disease course, and benefits of medications
Assess
<ul style="list-style-type: none"> • Stage HIV infection • Assess mental health and cognitive abilities • Assess physical ability to take medicines • Assess support systems and disclosure issues: family and friends • Assess readiness to begin medications
Readiness
<ul style="list-style-type: none"> • Decide with adolescent on regimen that integrates clinical needs with lifestyle—show different pills/combinations • Solidify support systems: family and/or treatment buddy • Practice chosen regimen with surrogate vitamins; distribute medications into a weekly medication planner, program one-day pill timer with the adolescent • Address adherence barriers discovered in practice run
Support
<ul style="list-style-type: none"> • Provide ongoing support with frequent clinic visits and phone contact • Acknowledge and address side effects • Develop strategies to ensure tolerability and regularity • Facilitate interactions with other youth taking medications

Source: Reprinted with permission from: Hoffman ND, Futterman D, Myerson A. Treatment issues for HIV+ adolescents. *AIDS Clin Care* 11:17–24, 1999.

PSYCHOSOCIAL ISSUES

The Adolescent AIDS Program has identified five key issues that adolescents with HIV/AIDS must address in coping with their changing health status: 1) receiving an HIV diagnosis; 2) disclosing an HIV status to parents, partners, and others; 3) coping with HIV disease; 4) becoming symptomatic; and 5) preparing for death (Kunins, 1993).

1. **Receiving an HIV diagnosis:** Providers should instill a sense of hope and encouragement when giving adolescents an HIV diagnosis. Asymptomatic youth must learn to balance healthy denial and preoccupation with HIV infection. Concrete thinking makes it difficult for some youth to integrate the concept of disease latency and asymptomatic infection. Support is essential in helping youth integrate this life-changing information. Individual and peer group interventions with psychologists and social workers can help facilitate adjustment. Psychotropic medication may be needed to manage preexisting psychiatric problems and for anxiety and depression that may accompany the diagnosis.
2. **Disclosure of HIV status:** After learning their diagnosis, adolescents must decide who to inform and when to disclose their HIV status. Telling their parents is difficult for many adolescents who fear losing their love and support. Fear of rejection and loss

of confidentiality is also a concern in disclosing to sexual partners. Providers should offer to help with disclosure and offer guidance in determining when it is safe and appropriate for the youth to disclose her HIV status. Role-playing and working through scenarios ahead of time can help the adolescent manage potential fears and concerns.

3. **Coping with HIV:** Adolescents also need guidance in learning how to interpret changes in their viral load and CD4 counts. Since fluctuation in results may cause some youth to panic, providers can help by explaining that variation is common and significant changes will not prevent them from leading satisfying and productive lives.
4. **Becoming symptomatic:** The appearance of HIV-related symptoms can be especially disturbing for adolescents who may have only superficially acknowledged their HIV status. For some youth, becoming symptomatic may encourage them to fight HIV and may enhance treatment adherence and self-care. Others, however, may feel overwhelmed and may lose their motivation to live. When symptoms occur, providers should explore their meaning, correct misconceptions about their significance, and ensure that adequate services and support are available.
5. **Preparing for death:** Many adolescents have limited experience with death and have naive perceptions about what to expect. Introducing the topic by talking about living wills and health care proxies before HIV becomes too advanced is a practical way to help youth begin to deal with issues related to death. When clinically appropriate, providers can help adolescents explore their feelings about dying by discussing options for dying in the hospital or at home, talking about funeral or memorial services, and exploring child custody or permanency planning with adolescent parents.

MENTAL ILLNESS AND SUBSTANCE USE

Mental illness and substance abuse are important comorbidities for HIV-positive adolescents. Accurate screening and diagnosis are essential in helping adolescents cope with their disease and successfully maintain their treatment regimen. Case studies of adolescents and young adults with HIV indicate a high prevalence of depression, bipolar disorder, and anxiety, often predating their HIV diagnosis. Similarly, many adolescents with HIV report alcohol and drug abuse. Of adolescents in the REACH study, 14% percent of females and more than 25% of males report weekly use of alcohol during the past 3 mo. During the same period, 7% of females and 20% of males reported using hard drugs (Rogers, 1998; Murphy 2001). In addition, as already noted, a high proportion of HIV-positive male and female youth report childhood sexual abuse (see Chapter I on Epidemiology and Natural History), which has many psychological and behavioral sequelae, including depression, posttraumatic stress disorder, substance abuse, suicidality, and risk for HIV infection.

III. SUMMARY

The high risk of adolescent females for HIV infection makes the development of realistic prevention programs a vital necessity. This includes wider availability of prevention skills building and the routine offering of HIV counseling and testing to sexually active teens in all programs that provide adolescent care. Although most youth will not receive services in adolescent programs, services can be readily adapted to provide a “youth-centered” approach, by such basic accommodations as offering flexible hours and low or no payment for services and care as well as providers who are knowledgeable about adolescents. Relevant clinical trials should be made available to adolescents, and there should be wide dissemination of information to health care providers about providing adolescent-related HIV care, such as use of Tanner staging for determining appropriate dosage. Youth at high risk for HIV should be identified and engaged in primary care as soon as possible, and outreach programs are an important component for programs that seek to link HIV-positive youth to care. Adolescents with HIV need intensive individual and group support to maintain health and reduce transmission to others. Health care providers in all settings that serve adolescents need to assist in making services visible, flexible, affordable, confidential, culturally appropriate, and available for all adolescents.

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XII: PALLIATIVE AND END-OF-LIFE CARE

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I. INTRODUCTION

This chapter is meant to provide ideas for coping with symptoms that impact quality of life throughout HIV disease and to prepare for issues faced near the end of life. Aggressive palliative care anticipates, prevents, and relieves suffering on emotional and spiritual levels as well as the physical. Because of gaps in traditional medical education related to end-of-life issues (Weissman, 1998), information in this chapter focuses on care near the end of life which is consistent with the new definition of palliative care (Hanson, 1997). Much documentation needs to be done in palliative care because the practice comes from an oral tradition. The challenge to readers is to share successes and failures in order to expand the literature especially for those living in countries with fewer resources.

Hospice, an early form of palliative care, developed in London during the late 1960's when Dame Cicely Saunders proposed using an *interdisciplinary* team to focus on the "relief of suffering" rather than simply on long-term survival for persons living with advanced cancer. This care was ideally delivered *in the home* and focused on *relieving physical symptoms* that might impede successful psychosocial and spiritual life closure prior to death (Saunders, 1966). In 1980, the World Health Organization defined palliative care as:

"The active total care of patients whose disease is not responsive to curative treatment. [It] . . . affirms life and regards dying as a normal process, . . . neither hastens nor postpones death, . . . integrates the psychological and the spiritual aspects of care, . . . offers a support system to help patients live as actively as possible until death, . . . and offers a support system to help the family cope during the patient's illness and in their own bereavement." (Doyle, 1998)

There are many differences between patients with cancer, who eventually learn that their disease is no longer being contained by treatment, and patients with HIV/AIDS, who suffer from a more episodic illness with very difficult to predict endpoints. In HIV disease palliative care is best woven into the general fabric of care from the time of diagnosis (Bloomer, 1998; Dudgeon, 1995). A small group of HIV providers, invited by the Health Resources and Services Administration (HRSA) of the Department of Health and Human Services, which oversees the Ryan White CARE Act, have attempted to define what this care should be in HIV disease:

". . . that care which is patient- and family-centered and optimizes quality of life by active anticipation, prevention, and treatment of suffering through respectful and trusting relationships formed with an interdisciplinary team throughout the continuum of illness: addressing physical, intellectual, emotional, social, and spiritual needs and facilitating patient autonomy, access to information, and choice." (Unpublished meeting report, HIV/AIDS Bureau, HRSA, 1999.)

As HIV disease becomes a chronic rather than terminal illness, management must be accomplished in the overall context of life (Breitbart, 1996). Good supportive care means “to be safe and not to be hurt, to be given refuge or sanctuary, to be comforted and accepted, to belong, and to give and receive love” (National Hospice Organization, 1997). Adjusting goals may be challenging for health care workers who use only a “cheerleading” approach to support. Involving the patient and her support system in decisionmaking affords her a sense of control over her disease that ultimately extends to the end of life (Fogel, 1993; Newsham, 1998). All staff must learn to value the impact of symptoms on the woman’s daily life as much as they do viral load and the CD4 cell count.

HIV disease has been associated with shame and a negative stigma (Chung, 1992; Abercrombie, 1996; Sowell, 1999) resulting in the isolation of many who are infected, especially women. Those who suffer from the disease are frequently without social support or the financial means, including health insurance, necessary for coping with their disease (Chung, 1992; Cohen, 1998; Nannis, 1997; Pergami, 1993; Sowell, 1997). As the traditional care giver, a woman may not have anyone else to care for her. She may have also suffered many personal losses leaving her emotionally drained and unable to provide care for someone else (Sarna, 1999). She must cope with knowing that she will one day be dying herself and that she must make provisions for her children and other dependents who will be left behind.

II. QUALITY OF LIFE

The overarching goal of palliative care is to relieve or reduce suffering and promote quality of life. With HIV disease, the unpredictable and episodic course of illness makes it difficult to estimate an individual’s prognosis. Use of combination therapy has decreased mortality rates by 23–90% depending on the population examined (Pezzotti, 1999; Sendi, 1999). Quality of life (QoL) alone has become an important outcome measure and providers now need to pay more attention to pain, fatigue, anorexia, and other symptoms that can be present even when the disease markers are improving (Barroso, 1999; van Servellen, 1998). Each provider must become adept at anticipating symptoms related to therapies and offering the woman a mechanism for preventing or controlling these side effects.

Despite prolonged survival, physical and spiritual distress, psychological pain, and grief remain a part of the illness (O’Neill, 1997). There does come a point in illness when quality of life becomes more important than quantity of life. The transition away from aggressive, curative care can be as difficult for members of the health care team as it is for patients and families (Finucane, 1999).

Several studies have specifically considered quality of life in women with HIV disease (Farsides, 1995; Rosenfeld, 1996; Sowell, 1997). Sowell found that social, and particularly psychological, symptoms have a major impact. Quality of life has been affected by “HIV treatment, physical symptoms, psychological well-being and [change in] role functioning.” Sarna (1999) found that problems arise in four domains: physical, psychological, social, and sexual. Another study, however, noted that financial concerns were the number one disrupter. This is followed by “worry about family,” “distress at losing others,” and “worry about progression of disease.”

Routinely measuring quality of life throughout the disease alerts health care providers to changes and stresses that may not always be obvious during a busy clinic visit. (See example of a quality of life form at www.tmg-web.com/modules.htm; Module 22.) Completing questionnaires every 3-4 mo or at the time of a clinical change may help the woman communicate with her providers. These answers can assist providers by monitoring problems and targeting interventions more specifically (Sarna, 1999). Quality of life scales have traditionally reflected functional status; for example, the Karnofsky Performance Status assigns a global ranking that reflects activity during any given day. The Medical Outcomes Study (Wu, 1997) is frequently used in the HIV population and has been shortened for easier use in the clinical setting. However, many of these scales, because they are function based, may not be as useful as the woman becomes more debilitated and approaches end of life.

In advanced disease one's focus is often directed to psychosocial and spiritual concerns that can be addressed even while bedridden. When we are healthy, not being able to leave the bed might seem unbearable. Approaching death, priorities shift; relationships and momentary pleasures become more important. In fact, it is not unusual for people to feel that their quality of life is better during this period because they are unable to perform mundane tasks and thus more inclined to focus on personal goals. The Missoula-Vitas Quality of Life Instrument (available through Vitas Healthcare Corporation, phone (305) 350-6033) has recently been developed specifically for those with deteriorating functionality. With this form the patient notes the importance of each domain and scoring reflects how the change in each characteristic, such as symptom control and sense of well-being, affects the individual woman. It is always useful simply to ask the woman how she would rank her own quality of life and what things are most important to her at the present time.

III. SYMPTOMS THROUGHOUT DISEASE

Three symptom surveys of outpatients with HIV/AIDS (Carr, 1994; Ferris, 1995; Sims, 1995) are summarized in Table 12-1. As disease advances it may not be possible to eliminate the cause of a symptom, but the woman and her family should be educated about symptom management and thus be empowered to master these symptoms.

Fatigue, pain, and difficulty with sleep are three symptoms that occur throughout the course of HIV disease (van Servellen, 1998; Whalen, 1994) and are often overlooked by providers. Patients believe they "must put up with" these problems and may avoid acknowledging them to providers. Women do not want to appear less courageous in coping with their disease or to distract the provider. Women who have a history of past or current substance abuse may fear being labeled as "drug-seeking" or may fear relapse if given pain medication. On the other hand, providers often do not inquire about these symptoms because they may not know how to manage them or feel inadequate to address them.

Dame Cicely Saunders, the founder of modern-day hospice, introduced the term "total pain" (Saunders, 1966) which is a model for how to approach all symptoms. She recognized that each complaint has a physical, emotional, and even spiritual component. If pain, or another symptom, is difficult to relieve with usual measures, it may be that

the woman has assigned special meaning to the symptom. She may be afraid her disease is getting worse or that “it is God’s punishment.” Both of these beliefs can exacerbate any symptom. Particularly when a symptom seems difficult to control, it is useful to ask the patient: “What does the pain (or nausea or shortness of breath) mean to you?” or “Why do you think you have this symptom?”

Table 12-1: Common Symptoms in HIV Disease

<i>Symptom</i>	# 1	# 2	#3
Anorexia/weight loss	91%	31%	61%
Fatigue/weakness	77%	50%	
Pain	63%	52%	Total 84%
Shortness of breath	48%	22% (Respiratory problem)	11% (Dyspnea)
Nausea/GI upset	35%	28%	21%
Cough	34%	27%	19%
Anxiety/depression	32%	24% (Depression) 40% (Anxiety)	20% (Depression)
Skin breakdown	24%	24% (Skin problem)	42% (Skin problem)
Diarrhea		24%	18%
Confusion/dementia	43%		29%
Constipation	24%		18%
Fever	13%	27%	
#1 Ferris, 1995. #2 Carr, 1994. #3 Sims, 1995.			

A. IDENTIFYING AND DEFINING THE PROBLEM

Instead of a “review of systems,” it may be useful to think of a “review of symptoms” moving from the head down to the feet. All symptoms can be approached similarly (MacDonald, 1998) by asking about the character (what does it feel like); the location (including radiation to other parts of the body); what makes it worse, what makes it better; and are there any other symptoms associated. It is also useful to ask how symptoms limit or affect daily activity. Asking these questions lets the woman know that you are interested in the particulars of how this affects her life, that her perception of her daily comfort is as important to you as is her viral load.

In cancer patients with symptoms such as fatigue, it has been shown that just the act of asking and being aware of the importance of this symptom to the patient provides some relief from it. A problem often worsens when the patient tries to deal with it alone and her fear of what is causing it grows. Routinely using a checklist of symptoms such as the Memorial Symptom Assessment Scale

(Portenoy, 1994b) will alert the practitioner to issues facing the patient. A review of symptoms will also alert the provider to the appearance of new symptoms that might herald progression of disease.

B. QUANTIFYING SYMPTOMS

Two simple methods can be used to quantify symptom severity: 1) on a scale of zero to 10, where zero means the absence of any symptom and 10 is the very worst it can be, how would the patient score her pain or fatigue? and 2) the visual analog scale is a straight, 10-cm line upon which the patient can make a mark representing how severe the symptom feels with the left end of the line representing "not at all" and the right being "the worst" (see Table 12-2). Distance along the line can be measured in centimeters, resulting in a numeric figure to record in the medical record for comparison purposes. Actual numbers are unique to the individual reflecting her perception and should not be used to compare her with other patients. Quantification is a mechanism for judging effectiveness of therapy and may alert the provider to a change in disease status.

Table 12-2: Pain Intensity Scales	
<i>0 – 10 Numeric Pain Intensity Scale*</i>	
<i>Visual Analog Scale (VAS)†</i>	
<p>* If used as a graphic rating scale, a 10-cm baseline is recommended. † A 10-cm baseline is recommended for VAS scales.</p>	

Source: Adapted from Acute Pain Management Guideline Panel, 1992 (AHCP, 1994).

C. MANAGEMENT OF INDIVIDUAL SYMPTOMS

Effective symptom management is based on a thorough understanding of the symptom and education of the patient and family, allowing them to anticipate crisis episodes with appropriate planning. It requires a multidisciplinary approach. The goal is to help the patient "move from a feeling of helplessness to a feeling of supremacy over the symptom" and develop and retain as much control over her life and illness as possible through the use of practical advice and emotional support (WHO, 1998). Symptoms can be managed with medications and/or nonpharmacologic interventions. In general, the oral route for medications is preferred to the parenteral; treatment regimens are tailored to the individual.

FATIGUE

Scope of the Problem

This is the most frequent complaint of persons with HIV disease in a number of different series (Laschinger, 1999; van Servellen, 1998). Seventeen to 60% of persons, even before they are diagnosed with AIDS, have this complaint (Breitbart, 1998). "Chronic fatigue" is present when symptoms of disproportionate tiredness, unrelated to activity or exertion, last for 1 mo or more. Patients complain of "lack of energy, stamina, or endurance." Women with fatigue have complained of decreased stamina at work, lowered quality of work, and frequent absenteeism possibly putting their jobs at risk (Semple, 1993).

Once the problem and its meaning to the woman are well delineated, it is important to rule out and treat correctable etiologies (Table 12-3). Anemia, depression, fear of the unknown, hypothyroidism, adrenal or testosterone insufficiency (even in women), occult infection (particularly abscess or *Mycobacterium avium* complex [MAC]), end-stage renal, pulmonary, or cardiac disease, malnutrition, lack of exercise, and disease progression itself all cause asthenia and fatigue (O'Dell, 1996). In HIV disease, it is often a combination of these factors.

In a study of 438 ambulatory patients in New York City (52% of these had intravenous drug use as an exposure factor), Breitbart showed a significant correlation between fatigue and the presence of pain ($p < .0001$), higher psychologic distress and poorer QoL ($p < .0001$), more depressive symptoms on the Beck Depression Inventory ($p < .0001$), and greater hopelessness on the Beck Hopelessness Scale ($p < .0001$) (Breitbart, 1998).

• Adrenal/hormonal insufficiency	• Insomnia
• Anemia	• Lack of exercise
• Depression	• Malignancy
• Disease progression	• Malnutrition
• End-stage organ disease	• Medications
• Fear of the unknown	• Metabolic (low K/Mg)
• Hypothyroidism	• Occult infection (abscess/MAC)

APPROACH TO MANAGEMENT

It is important to work with the woman on ways to manage her fatigue even while the work-up is being pursued:

1. Showing interest in alleviating this symptom offers her emotional support, which in itself helps relieve the fatigue.
2. Referring her for a physical therapy assessment and prescription of simple strengthening exercises not only physically attacks the problem but allows her to begin to rebuild her own self-esteem.

3. Keeping a diary of what helps minimize her fatigue and what she can accomplish in a day as well as a daily numeric score (see quantifying symptoms, page 423) involves her in her own improvement and provides a better picture of how this symptom affects her daily life.
4. As each possible etiology is addressed, remind the woman to have realistic expectations in order to avoid becoming discouraged by false hopes.
5. Using a positive, encouraging tone and setting small goals are helpful.
6. Nurses are adept at helping women find ways to eliminate or modify energy-consuming activities.
7. For many people, addressing spiritual issues or supportive counseling at this time may also provide comfort and encouragement.
8. Making use of other health care practitioners not only helps the woman to cope with this exhaustion but also releases the provider to concentrate more on those physical aspects of management that need to be addressed.

Pharmacologic treatments include methylphenidate 2.5–5.0 mg in the morning and repeated in early afternoon or high-dose prednisone followed by a rapid taper. The latter therapy is usually needed only with very advanced disease when the concern for further long-term immunosuppression is not the most important aspect of management.

PAIN

Scope of the Problem

Breitbart (1996) has reported that pain in women with HIV disease is “prevalent, often severe, and highly distressing.” Laschinger (1999), in reporting a phenomenologic study, states that the “pain experience embodies more than physical pain” (not unlike the “total pain” of Saunders). For this reason, understanding and controlling pain in women with HIV disease can be quite difficult because the practitioner must tease out the myriad components in order to optimally manage this symptom.

Surveys of ambulatory populations with HIV disease have documented that the prevalence of pain is 40–60% (Breitbart, 1996; Lebovits, 1989; O’Neill, 1993; Singer, 1993). For those who have more advanced disease and may be bedridden, these figures increase to as much as 83%. However, of those who do have pain, only about 40% are actually treated and of those treated only about 40% ever have adequate pain relief and can still rate their pain as a “seven out of ten” in severity (Anand, 1994). These findings are universal and not limited to those with a history of substance abuse.

In HIV disease, pain can be caused by the disease itself, by therapies used to treat the disease, or by unrelated problems. The most frequent types of pain are abdominal pain and peripheral neuropathy (Anand, 1994; Newshan, 1998) or those caused by infections such as oral, esophageal, or genital/perineal herpes or fungus. Medications for treatment are based on location and type of pain.

As in cancer patients, up to 80% of persons with HIV disease having pain will experience more than one pain simultaneously (Singer,1993). It is not unusual for a patient who has obtained relief from one pain to notice another type of pain that has been masked by the now-relieved pain. It is important to listen to and believe the patient. Carefully document all pain components and their characteristics to avoid a picture of "pseudoaddiction" or a label of "drug-seeking," in which an individual who is only partially treated continues to ask for pain medication (Weissman, 1989).

One approach to pain management often neglected in the literature is the "phenomenologic," which means understanding the human experience of pain from the perspective of the patient. Before the use of protease inhibitors, Laschinger (1999) conducted a qualitative study of 22 Canadian patients, predominately gay men but with the one woman who had parallel experiences. They identified four substantive themes as components of pain: physical pain, painful losses, pain of not knowing, and social pain. The one additional factor found in the woman was that she also had concerns related to her children.

"Physical pain" included joint pain, headache, neuropathic and abdominal pain, and skin and mouth lesions. "Losses" referred to loss of energy, time, independence, and relationships. "Not knowing" meant the added anxiety of fearing that the pain might be life-threatening. And "social pain" reflected inability to continue to participate in usual activities. The woman's fears had to do with how the knowledge of her disease might impact her children's schooling and how her death would impact their futures. This is a small but important study because it records the actual feelings of patients as opposed to asking for a provider's perception of what pain means to the patient. Although only one woman was represented, the findings are in keeping with our clinical experience.

Neuropathic Pain

The HIV virus invades both central and peripheral nervous systems where it may be dormant for years or cause acute symptoms. The most common pain syndromes are headache and peripheral neuropathy. The etiology may be immune-modulated, infectious, or drug-related. Treatment should be based on the etiology and location of pain and often requires an adjuvant medication in addition to opioids.

Adjuvants for neuropathic pain are usually an anticonvulsant (e.g., carbamazepine or gabapentin), an antidepressant (e.g., nortriptyline), or an NSAID. One of these medications is started at the same time as the opioid; use of the former may allow use of lower doses of opioid and consequently fewer side effects, although constipation cannot be avoided. In the past, it was believed that opioids were ineffective for neuropathic pain but it is now known that this type of pain simply requires higher doses of opioids. Table 12-4 describes frequent etiologies of neuropathic pain.

Table 12-4: Neuropathies in Patients with HIV/AIDS	
<i>PREDOMINANTLY SENSORY NEUROPATHY (PSN) OF AIDS</i>	
<i>Immune-mediated:</i>	<ul style="list-style-type: none"> • Inflammatory demyelinating polyneuropathies (IDPs) • Acute (Guillain-Barré syndrome) • Chronic (CIDP)
<i>Infectious:</i>	<ul style="list-style-type: none"> • Cytomegalovirus polyradiculopathy • Cytomegalovirus multiple mononeuropathy • Herpes zoster • Mycobacterial (MAI)
<i>Toxic/nutritional:</i>	<ul style="list-style-type: none"> • Alcohol, Vitamin deficiencies (B6, B12) • Anti-retrovirals: ddl (didanosine), ddC (zalcitabine), d4T (stavudine) • Anti-virals: foscarnet • PCP prophylaxis: dapsone • Anti-bacterial: metronidazole • Anti-mycobacterials: INH (isoniazid), rifampin, ethionamide • Anti-neoplastics: vincristine, vinblastine
<i>Other Medical Conditions:</i>	<ul style="list-style-type: none"> • Diabetic neuropathy • Post-herpetic neuralgia

Barriers to Pain Relief

There are many reasons offered by providers throughout the world for not prescribing adequate pain relief (American Pain Society, 1999). Many societies fear “addiction” or diversion of medications. Health care workers often approach pain management with inadequate training in pain management skills (Field, 1997; Portenoy, 1994a). Without appropriate knowledge of the pathophysiology either of pain or of its relief, providers may have the same fears as the public, believing that treating pain can “cause” addiction or that they must “save” powerful pain killers for a time when they might be “more needed.” Also there may be the conviction that one should “bear the pain” to show strength or religious faith. All of these notions, while widely believed, have no basis in fact. See Table 12-5.

Principles of Pain Management

Pain, as with any symptom, should be described, quantitated, treated, and promptly reevaluated with appropriate dose modification of therapy. The AHCPR *Guidelines for Management of Cancer Pain* recognize that pain experienced by those with HIV disease is comparable with the chronic pain experienced by persons with cancer, which often requires management with opioids. Unlike blood pressure, which might be regulated over weeks, pain should be controlled within the shortest time possible to prevent the development of long-term symptoms such as depression and anhedonia.

It is useful to start with the WHO ladder approach, which uses non-opioids initially and progresses through combinations of therapies and next to stronger opioids depending on the patient’s response. (See Table 12-6.) However, in HIV

pain, opioids are frequently needed because of the severity of the pain, and there is growing literature that *the use of the "second step, or weak opioids" might best be bypassed in HIV-related pain*. This second step includes "combination" pain medications, those containing an opioid plus aspirin or acetaminophen, which may increase the risk of hepatotoxicity or bleeding in women receiving highly active antiretroviral therapy. Becoming familiar with one or two agents for pain relief makes pain management easier.

Table 12-5: Barriers to Pain Management
<i>Problems Related to Health Care Professionals</i>
• Inadequate knowledge of pain management
• Poor assessment of pain
• Concern about regulation of controlled substances
• Fear of patient addiction
• Concern about side effects of analgesics
• Concern about patients becoming tolerant to analgesics
<i>Problems Related to Patients</i>
• Reluctance to report pain
- <i>Concern about distracting physicians from treatment of underlying disease</i>
- <i>Fear that pain means disease is worse</i>
- <i>Concern about not being a "good" patient</i>
- <i>Reluctance to take pain medications</i>
- <i>Fear of addiction or of being thought of as an addict</i>
- <i>Worries about unmanageable side effects</i>
- <i>Concern about becoming tolerant to pain medications</i>
<i>Problems Related to the Health Care System</i>
• Low priority given to cancer and AIDS pain treatment
• Inadequate reimbursement
- <i>The most appropriate treatment may not be reimbursed or may be too costly for patients and families</i>
• Restrictive regulation of controlled substances
• Problems of availability of treatment or access to it

Source: Adapted from AHCPR, 1994.

**Table 12-6: Pharmacologic Approaches to Pain Management:
 WHO Three-step Ladder**

<i>WHO Three-step Ladder</i>	
Step 3: Severe Pain	↑ Morphine Hydromorphone Methadone Levorphanol Fentanyl Oxycodone ±Nonopioid analgesics ±Adjuvants
Step 2: Moderate Pain	↑ APAP or ASA + Codeine Hydrocodone Oxycodone Dihydrocodeine Tramadol (not available with ASA or APAP) ±Adjuvants
Step 1: Mild Pain	Aspirin (ASA) Acetaminophen (APAP) Nonsteroidal anti-inflammatory drugs (NSAIDs) ±Adjuvants
<p><i>"Adjuvants" refers either to medications that are coadministered to manage an adverse effect of an opioid, or to so-called adjuvant analgesics that are added to enhance analgesia.</i></p>	

Source: Adapted from WHO, 1986.

The following guidelines (including Table 12-7) are helpful in prescribing pain medication (American Pain Society, 1999):

1. Use a grading system (such as the scale of 0–10) to document pain severity and relief from pain for monitoring the effectiveness of therapy.
2. Start with a dose that will acutely relieve the pain. This may be given intravenously or subcutaneously to achieve a rapid response. Care should be taken to observe for any signs of respiratory depression in opiate-naïve patients.
3. Next, begin a low dose every 3–4 hr (based on the half-life of the drug) "around-the-clock" and **not** on an as-needed basis. The initial dose should be chosen based on the age, size, and renal/hepatic function of the patient. (Suggestions are given in any standard pain-management text such as *Principles of Analgesic Use in the Treatment of Acute and Cancer Pain*, 5th ed., available from the American Pain Society at <http://www.ampainsoc.org>).

4. In addition to the every 3-4 hr. "around-the-clock" dose, include provision for a supplemental, or "breakthrough," dose of about one sixth of the total daily opioid dose to be given every 1-2 hr between the scheduled doses should the pain not be controlled. This allows for development of a steady state drug level and avoids alternation of great pain intensity with somnolence. This is the same approach used to control hyperglycemia with a sliding scale of regular insulin based on glucometer readings; these doses are based on pain scores.
5. When pain is fairly well controlled, it is appropriate to change the patient to a long-acting pain medication for ease of administration. The dose is calculated by adding together the total dose taken in 24 hr and dividing by the half-life of the new preparation. For example, for a medication meant to be given every 12 hr: divide the total dose by two and this number will be your dose every 12 hr. Don't forget the breakthrough dose. This is a short-acting opioid, preferably of the same type as the long-acting one for use at times that the pain is not adequately controlled (equals 1/6 daily total dose).
6. Liquid formulations are useful for those with difficulty swallowing, as are rectal suppositories; "sprinkles," which can be mixed with soft food; or patches, which can be absorbed through the skin if adequate subcutaneous fat is present.

Table 12-7: Mnemonic for Assessment of Pain

A – Ask about pain regularly; Access systematically
B – Believe the patient and family
C – Choose treatment options appropriate to patient and setting
D – Deliver medications on an "around-the-clock" basis with adequate "breakthrough" doses
E – Evaluate results frequently; Empower patients and families to control

Source: Adapted from AHCPR, 1994.

Side Effects

Table 12-8 outlines several common side effects of opioids. Opioids usually cause drowsiness in the first 24-36 hr and patients should be advised that this will resolve. Use a low dose to initiate therapy but be prepared to increase the dose over the next 48 hr based on the patient's pain scores. Nausea is another common side effect in those first few days and can be treated with an antiemetic such as prochlorperazine or lorazepam. All opioids slow bowel motility and patients should be given a stool softener when pain medication is prescribed.

Many prescribers will use an antiemetic or methylphenidate to counteract these symptoms over a few days. Prolonged sleeping after the initial dosing may simply reflect the woman's need for rest, which has not been possible because of the pain. If side effects are pronounced over a longer period, it is best to talk with the woman about what else is going on and it may be useful to discuss analgesic use with a pain specialist and involve other team members.

Constipation	Requires prescription of stool softener at the time of prescribing opioid; tolerance does NOT develop
Drowsiness	Resolves after 24–36 hr; extended sleeping can be from exhaustion; may need psychostimulant, e.g., methylphenidate
Nausea	Prescribe antiemetic with first prescription; resolves in several days; may need around-the-clock dosing
Urinary retention	Uncommon side effect; change opioids or adjuvants
Itching/twitching	May indicate toxic levels due to decreased elimination; lengthen interval; rotate opioids

Although many providers fear respiratory depression, this is unusual unless an opiate-naive patient is given a large, parenteral dose initially. Most pain (85–90%) can be controlled with oral medications. If the patient is having severe pain in a controlled situation such as a hospital or hospice, an initial subcutaneous injection of morphine or hydromorphone may control the pain more rapidly. Once a patient is on an appropriate dose, side effects (except for the slowed bowel motility) generally resolve and patients return to their usual level of functioning, or even improved activity, because the pain is relieved.

With very high doses, twitching or myoclonus may occur and in this case, it is possible to alternate two different opioids (referred to as “rotating”) or to change to another drug entirely (Galer, 1992). If twitching develops, the patient may have decreased renal or hepatic clearance. In this case the dosing interval should be lengthened or different opioids can be used in an alternating fashion.

Opioid Conversions

Many opioid preparations are available. These drugs are not equivalent on a milligram-to-milligram basis and it is possible to see what appears to be “drug-seeking behavior” if the conversion dose chosen is too low. When changing from one medication to another, use a conversion chart to find the total dose in morphine-equivalent units and convert according to the table (see Table 12-9). There is no “ceiling effect” with opioids as there is with other medications such as acetaminophen, aspirin, or tricyclics; i.e., there is no toxic dose and the patient should be given whatever dose relieves her pain. Just as pain scores are individual, so are ultimate doses. It may be useful to seek the guidance of someone knowledgeable in pain management if you as the provider are not experienced with these medications.

Table 12-9: Dose Equivalents for Opioid Analgesics in Opioid-naïve Adults and Children ≥50kg Body Weight				
Drug	Approximate Equianalgesic Dose		Usual Starting Dose for Moderate to Severe Pain	
Opioid Agonist	Oral	Parenteral	Oral	Parenteral
Morphine	30 mg q 3–4 hr (repeat around the clock dosing) 60 mg q 3–4 hr (single dose or intermittent dosing)	10 mg q 3–4 hr	30 mg q 3–4 hr	10 mg q 3–4 hr
Morphine, controlled-release (MS Contin, Oramorph)	90–120 mg q 12 hr	N/A	90–120 mg q 12 hr	N/A
Hydromorphone (Dilaudid)	7.5 mg q 3–4 hr	1.5 mg q 3–4 hr	6 mg q 3–4 hr	1.5 mg q 3–4 hr
Levorphanol (Levo-Dromoran)	4 mg q 6–8 hr	2 mg q 6–8 hr	4 mg q 6–8 hr	2 mg q 6–8 hr
Methadone (Dolophine, other)	20 mg q 6–8 hr	10 mg q 6–8 hr	20 mg q 6–8 hr	10 mg q 6–8 hr
Oxymorphone (Numorphan)	N/A	1 mg q 3–4 hr	N/A	1 mg q 3–4 hr
Combination Opioid/NSAID Preparations				
Codeine (with aspirin or acetaminophen)	180–200 mg q 3–4 hr	130 mg q 3–4 hr	60 mg q 3–4 hr	60 mg q 2 hr (IM/SC)
Hydrocodone (in Lorcet, Lortab, Vicodin, others)	30 mg q 3–4 hr	N/A	10 mg q 3–4 hr	N/A
Oxycodone (Roxicodone, also in Percocet, Percodan, Tylox, others)	30 mg q 3–4 hr	N/A	10 mg q 3–4 hr	N/A

Source: Adapted from AHCP, 1994.

Pain Management with a History of Substance Abuse

Those who have used opioids in the past may have a higher tolerance and thus require higher than usual doses. “Addiction” is a psychological craving and the use of drugs “to get high” or despite personal harm should not be confused with tolerance. When treating someone who has previously abused drugs (or is doing so currently), it is useful to discuss the full plan ahead of time. The patient should understand that this is a two-way interaction, that she must be truthful about her pain and its severity/relief as the provider will endeavor to control the pain. Most people with an addiction history who have legitimate pain are thankful to have it dealt with in an adult manner and understand that this is not a time to engage in manipulative behavior. In fact, many are afraid to take narcotics for fear of relapse.

Seeking a higher dose of drug does not necessarily mean that the patient is “drug-seeking.” “Losing” or forging prescriptions, stealing from or having them “stolen” by others, visiting multiple providers for duplicate prescriptions and injecting oral formulations (Portenoy, 1994a) are signs that the patient may not be using the medication appropriately. She must understand that she will be given adequate drug to last for a clearly described interval, she cannot obtain refills on weekends, and there is only one provider who can write her prescriptions. Situations involving tampering with prescriptions or selling medication should be turned over to legal authorities and will sever the patient-provider supply of medication. Written contracts are used in some clinics but a well-documented discussion in the medical record is adequate.

Women with a history of substance abuse are often poorly emotionally defended and may have inadequate coping skills for even minor frustrations. Low self-esteem and little self-confidence can impact pain and make it worse. Breitbart noted that pain in women is more intense and that those with a history of opportunistic infections or intravenous drug use are “more likely to experience pain” (Breitbart 1996).

Management of pain is not easy and requires a great degree of trust on both sides. Being consistent, open, and fair are important attributes for the provider to model. Providing positive feedback, reducing harm through education, and attempting to understand individual circumstances are most helpful to the patient. Clearly, as a patient approaches the end of life, old habits and fears often resurface and, at this time, the patient may need more support than usual.

Gender Differences

There is a growing amount of literature suggesting that pain in women is undertreated. Breitbart reported that women with HIV disease appear to have “higher levels of pain intensity . . . [and are] more likely than men with AIDS to have their pain under-medicated” (Breitbart 1996).

SLEEP DISTURBANCE/INSOMNIA

Scope of the Problem

Insomnia and excessive daytime sleepiness are primary complaints in persons with HIV disease regardless of stage. Cohen et al. (1996) reported that fully two thirds of patients with AIDS have difficulty falling asleep without correlation with CD4 count. Insomnia includes difficulty falling asleep, difficulty staying asleep, and early morning awakening.

For women fatigue is not necessarily related to sleep patterns although it is important to document what the sleeping pattern is. Using questions similar to those in Table 12-10, try to determine the pattern of sleep problems, the frequency, associated events, and other factors listed below. Treatment should be tailored to the etiology. If you see patients in a busy setting, it is useful to have them fill out a card recalling specific characteristics of the symptom. A nurse can help the patient complete this card, leaving the provider to focus on therapy and documentation.

Table 12-10: Sleep Problems (Sample Questionnaire for Office Use)	
Do you have trouble <input type="checkbox"/> falling asleep? Or <input type="checkbox"/> staying asleep?	
Do you take naps during the day? <input type="checkbox"/> Yes <input type="checkbox"/> No How many hours _____?	
Do any of the following wake you up?	
<input type="checkbox"/> headache	<input type="checkbox"/> fever/night sweats
<input type="checkbox"/> bad or vivid dreams	<input type="checkbox"/> leg cramps
<input type="checkbox"/> problems breathing	<input type="checkbox"/> fear
<input type="checkbox"/> chest pain/heartburn	<input type="checkbox"/> another person in the house
<input type="checkbox"/> abdominal pains	<input type="checkbox"/> other _____
<input type="checkbox"/> need to pass urine	_____
<input type="checkbox"/> need to move bowels	_____
What have you tried for sleep?	
<input type="checkbox"/> Drug store product	<input type="checkbox"/> Counting sheep or other meditation
<input type="checkbox"/> Sleeping pill from friend	<input type="checkbox"/> Warm bath
<input type="checkbox"/> Hot milk	<input type="checkbox"/> other _____
<input type="checkbox"/> Reading	_____
<input type="checkbox"/> Music	_____

Assessment

Having the patient keep a sleep diary; bringing a family member to appointments to comment on sleep patterns; and clearly documenting bedtime, how long it takes her to go to sleep, and how long she can stay asleep provide the best picture of this problem. Include a full history of caffeine and alcohol intake and describe the environment and other factors that might affect sleep. Review current medications to eliminate these as a possible etiology that may cause insomnia, particularly NNRTIs and selective serotonin reuptake inhibitors taken at bedtime. Remember that injection drug users may have night sweats and abdominal pains as signs of withdrawal. Simple sleep-wake reversal may herald liver damage. Sleep disorder, classically early morning wakening, may be a symptom of depression (Nokes, 1999).

Management of Insomnia

Treat the underlying problem whenever possible starting with simple environmental modifications, e.g., fresh air; quiet (may need white noise emitter); avoiding exercise, heavy meals, large amounts of alcohol, or arguing just before bed. Plain acetaminophen or aspirin in low doses if not contraindicated may be helpful, as are short-acting hypnotics or sedating antidepressants, e.g., trazodone 50 mg qhs. When underlying depression is identified, appropriate treatment with an SSRI or a tricyclic antidepressant is indicated. (See Chapter IX on Psychiatric Issues.) Short-acting benzodiazepines are useful acutely but should be avoided long-term or in patients with dementia because they may increase confusion (Phillips, 1999). Physical interventions such as massage, relaxation exercises, and deep breathing are also beneficial.

PRURITUS

Generalized pruritus without a rash may be secondary to dry skin, hepatic dysfunction, or an allergic reaction. The rash with scabies in an immunocompromised host may be diffuse and might require biopsy if symptoms do not respond to empiric therapy.

Along with specific therapy for scabies, the patient should be given an antihistamine to break the cycle of itching. Low doses of an opioid are not uncommonly required to conquer this symptom. If the symptoms have been present for weeks, it may be necessary to follow the nighttime scabies treatment with 1% hydrocortisone lotion each morning.

If the itching is thought to be secondary to hepatic dysfunction, holding hepatotoxic agents and using an H2 blocker such as around-the-clock cimetidine for several days is helpful. As the hepatic enzymes return to normal, medications can be resumed at lower doses and/or with longer dosing intervals. This is true if the underlying pathology is not related to the lactic acidosis associated with some antiretroviral therapies. In this case consult a liver specialist before reintroducing medications. These patients are partially relieved with a 1% hydrocortisone lotion containing menthol.

HICCUPS

When intractable, this symptom can lead to poor oral intake and weight loss as well as to depression because of an interruption of all normal activity. Simple mechanical measures such as drinking out of the "wrong" side of the glass and swallowing up-hill against gravity may transiently interrupt these symptoms. The usual medical treatment is low-dose (12.5–25 mg) chlorpromazine orally. Metochlopramide, baclofen, amantadine, benzodiazepines, and haloperidol (Kaye, 1989; Woodruff, 1999) have also been described as useful although there is little evidence base for these recommendations. One treatable cause for this symptom is persistent and severe esophageal candidiasis, which requires aggressive therapy of this infection for relief. Malignancy impinging on the phrenic nerve can also cause hiccup and a chest X-ray is recommended to rule out a mass.

XEROSTOMIA (DRY MOUTH)

This condition can be secondary to medications such as antidepressants, anticholinergics, or HIV medications such as didanosine or zalcitibine. It is generally reversible if noticed soon enough and the drug is stopped. However, if this condition persists without detection and treatment, it may become permanent. Direct invasion of the salivary gland with HIV can also cause dry mouth. Treatment should be directed at the etiology.

Artificial saliva, drinking extra fluids with meals, and fluoride treatments administered by a dentist may be necessary to reverse this symptom. If it is not noticed in a timely manner, tooth decay and gingival disease may occur, resulting in caries and "sore" teeth. Left untreated, the patient may withdraw from society and become quite depressed because of the inability to be comfortable during a meal with others. Pilocarpine drops taken orally 4 times per day have been useful in this syndrome (LeVeque, 1993). However, the onus is on the provider to ask about the presence of this symptom on a regular basis to detect, treat, and reverse the problem.

DYSPNEA

In the original hospice studies in this country, dyspnea was one of the five symptoms correlated with a shortened life expectancy even when patients had no demonstrable disease in the cardiovascular or pulmonary systems. Dyspnea is an uncomfortable feeling of not being able to breathe although the oxygen saturation may be normal. Treatment should be directed at the presumed etiology using bronchodilators, diuretics, and steroids as necessary. In the hospice literature morphine has been used anecdotally as an aerosol with significant relief although this has not been formally proven to be useful; subcutaneous or oral morphine can also be used (start with 5 mg every 3–4 hr). Clinical trials are needed to compare aerosolized morphine with saline nebulizers, which some authors have found equally useful.

Benzodiazepines are desirable to interrupt the cycle of dyspnea and panic that sets in when an individual is having difficulty breathing. A long-acting drug such as lorazepam 0.5 mg can be given around the clock every 6–8 hr to minimize the anxiety in this setting.

IV. PROGNOSIS

The use of combination or highly active antiretroviral therapy and the ability to measure the existing human immunodeficiency viral burden have significantly impacted the course of HIV disease. With improved antiretroviral therapy, use of prophylaxis for opportunistic infections, and treatment by providers who are knowledgeable about HIV disease, patients can look forward to living longer and healthier lives. However, particularly in resource-poor nations, most will die of this disease. To set realistic goals, the provider must have some sense of the individual's expected survival time.

Being able to give the patient and family a realistic appraisal of life expectancy, particularly near the end of life, is an important adjunct to disease management. For example, if the woman has several months to live, this may be the best time to review and clarify who will help with decisionmaking as she becomes acutely or seriously ill. It is also a time to investigate and make decisions about guardianship as well as to make a will and determine general advance directives. Deciding which medications to discontinue and when depends upon the provider's projection of how long the patient has to live.

Although overall prognosis may be difficult to estimate, there are general signs that reflect advanced disease or failure of the immune system (National Hospice Organization, 1996). For example, repeated episodes of opportunistic infections, uncontrollable weight loss, or frequent hospitalizations all suggest that the woman is no longer "doing well." Once this decline begins and all antiretrovirals have been exhausted or the woman opts for no further aggressive therapy, it is reasonable to focus on issues related to life closure. As the woman becomes weaker, certain therapies may be withdrawn and attention should be directed toward psychosocial and spiritual tasks.

In 1996, before widespread use of combination therapies, the National Hospice Organization published *Medical Guidelines for Determining Prognosis in Selected Non-Cancer Diseases*, 2nd ed. (N.H.O., 1996) (Table 12-11), which described indicators for a shortened life expectancy in several chronic diseases including HIV/AIDS. When several of these indicators are present, one should consider the prognosis to be limited unless the use of new or unapproved therapies is possible.

Wasting syndrome based on loss of lean body mass (Kotler, 1989) and anemia are both independent risk factors for decreased survival (Moore, 1999). Median time to death can be related to the severity of each. Persistent oral thrush is also an independent predictor of progression of AIDS. Concurrent unresponsive malignancy or end-stage organ failure shortens the prognosis. Worldwide, hepatitis C is rapidly becoming a leading cause of death.

Although it is not well documented, the woman's personal goals may significantly affect life expectancy. The experience in hospice care is that people must have completed psychosocial and spiritual goals before being able to peacefully "let go." For women with children this may mean making reasonable guardianship arrangements called *permanency planning*. For others it may mean resolving a relationship or coming to terms with her life events or accomplishments. Saying goodbye to loved ones and to care providers is a last necessary step before death.

Table 12-11: Factors Associated with Shortened Life Expectancy

• CD4 persistently low	• Advanced disease: <50 cells/cc
• Viral burden remains 100,000 copies/mL despite combination therapy	
• Functional status <50 (Karnofsky Performance Status)	• Spending >50% of day in bed
• Failure of optimized therapy	• Multi-drug resistance or failure
• Desire to forego more therapy Often occurs after multiple hospitalizations	
• Anemia (hemoglobin <12)	• Persistent oral thrush
• Significant wasting	• Loss of >30% lean body mass
• Progressive hepatitis C	• Hepatic failure; drug intolerance
• Progressive multifocal leukoencephalopathy	• Progressive dependencies; dementia
• Unresponsive Kaposi's sarcoma involving an organ	• Progression despite therapy
• End-stage organ disease	• Renal, hepatic, or cardiac failure
• Persistent diarrhea >1 mo	• No response to treatment
• Unresponsive lymphoma/ other malignancy	• Acknowledgment by patient and family of poor prognosis
• Desire of patient for death	

Source: Adapted from Moore, 1999; N.H.O., 1996.

V. TELLING THE TRUTH AND BREAKING BAD NEWS

Communication skills are particularly important as the woman's health begins to decline. Being a good listener is paramount and there are concrete skills that can be learned.

Baile and Buckman discuss how to talk about difficult topics described in Table 12-12 (Baile, 1998). They note the importance of paying attention to the physical environment when having serious discussions with patients and families. It is important to have privacy, quiet, and lack of interruptions as much as possible. The provider should sit down to talk with whatever "family" the patient wishes to include. The use of touch may be comforting although it is important to gain permission first. Body language and eye contact are a part of the setting.

Table 12-12: Mnemonic for Breaking Bad News

S — Setting and listening Skills
P — Patient & family; Perception of condition
I — Invitation to patient to determine how much Information he/she wants to know
K — Knowledge; reviewing the facts
E — Explore Emotions & Empathize
S — Summary & Strategy

Source: Adapted from Baile, 1998.

When discussing emotionally laden issues or breaking bad news, it is best to ask what the perceptions are of those present, whether you are addressing the woman alone or her friends and family. "Before I talk, tell me how you think you are [she is] doing?" "What are your concerns at this time?" Not only does this help the provider to know where to begin but it provides a vocabulary to use in this discussion. Words used by them will suggest vocabulary as well as degree of comprehension. Avoiding jargon or strictly medical terms is helpful. In the case of bad news, it is useful to provide a *warning statement* such as "I have some bad news for you" or "This is a very difficult time and I want you to be prepared." Once the facts have been communicated, it is important to determine what the reaction is to this news. Providing a period of silence may help those involved to gather their thoughts before speaking (Weissman, 1998).

Listening skills include asking open-ended questions and repeating the last comment made by the patient or family member to clarify what has been said. *Acknowledge emotions* by using empathic responses even if the feelings themselves are unimaginable to you. After a period of discussion, develop a *strategic plan* with the patient or family by discussing expectations and goals. Use this time to reassure that there will be future conversations. *Summarize* what has been discussed and ask for any remaining questions.

VI. REALISTIC GOAL SETTING AND ADVANCE CARE PLANNING

We must all learn to think ahead to a time when we may not be healthy and able to care for ourselves. Women, in particular, need to make provisions for others they care for such as children or an elderly parent. Thinking ahead prevents confusion and also assures that no one person will be burdened with matters near the time of death. Each woman needs to select someone who will be able to manage her legal affairs and also someone to make medical decisions for her should she not be able to do so. This may be two different people but it is important for the woman to discuss her own wishes with that person early in her illness. By doing it at a time when she feels well, she can remain in control and make her own choices (see Table 12-13).

Table 12-13: Making Plans Ahead of Time

1. Appointment of Power of Attorney for health matters and for financial matters	These are two different issues; the healthcare POA does not last beyond the death; therefore, all plans must be made and executed ahead of time.
2. Appointment of guardian for children	Be certain that children & guardian are both aware of these plans.
3. If there are children left behind	Many people make a scrap book, write a letter, or even make a video to remind younger children who their mother was.
4. Make a will if there is anything you own that you would like to leave to a particular person	This includes money, a home, dishes from your grandmother, or jewelry that has a special meaning to you.
5. Discuss with family or friends how and where you would like to die	You can be involved in planning a funeral or memorial service; can pick out your clothes and pallbearers.
6. Discuss desires regarding care before death: <ul style="list-style-type: none"> • For nutrition and hydration • For cardiopulmonary resuscitation • For being kept alive on machines 	It may be helpful to think about what you might want in different situations. For example, if you would be bed-bound; if you were no longer able to care for yourself; if you would not be able to recognize people or carry on normal conversations.

A. IMPORTANCE OF MAINTAINING HOPE

To provide the most supportive and sensitive care throughout illness, the provider must understand the overall goals of the patient. As the woman moves through her disease it is necessary to intermittently discuss these, preferably while the patient is feeling well and able to feel more in control of her disease. Just as quality of life evolves, so do desired outcomes. Many medical providers seem to fear that having these discussions might “take away hope.”

Hope is not false expectation. It can be redefined in an acceptable way for the individual. Whereas hope for a long life may no longer be possible, hope for being able to leave good memories behind for children may be fulfilled by making a scrapbook, audio tape, or even a video. One can simply hope for days that are meaningful (Bennett, 1995). Multiple studies document that having a sense of spiritual (not necessarily religious) well-being has a positive effect on health (Colman, 1999).

Hope “. . . is the emotion upon which all the other emotions of elation are grounded. . . shaped by a glimpse of something not yet clearly within sight. . . always looks toward creative changes. . . an expression of the will to live. . . of an individual's trust in life. . . even terminally ill persons express the feeling that things will somehow get better. . . that as long as we live, we live for a better future” (Kast, 1991). It is not a commodity that one person gives to another but is within the individual and can be modified accordingly. Ernst Bloch in *The Principle of Hope* wrote:

“What matters is learning to hope. Hope does not abandon its post. It is in love with success rather than failure. Hope, superior to fear. . . reaches out; it broadens rather than narrows” (Bloch, as cited in Kast, 1991).

He apparently “saw hope in daydreaming, fantasy, and imagination.” Albert Schweitzer also believed that imagination was what allows the human to tolerate the present.

B. PERSONAL GOALS

In discussing goals, it is useful to ask the woman, “What aspects of your life are most important to you? What have you accomplished in your life that makes you feel proud?” This is also a time to determine which other persons she cares about and who provides her support. Frequently, it is a family anniversary or event, such as the birth of a grandchild, that comprise the woman's true goals.

Each of us has dreams. It is up to the provider or other members of the team to discover those and help the woman to see how they might be achieved. With HIV disease the young woman may not have had time to realize her dreams. In this case, the team must help her value the life she has had and to discover and acknowledge what it is that she wishes remembered about her life. She can also be assisted in grieving the loss of future. Sharing a funny story or memory of a special event helps the young woman know that she has left her mark.

C. ADVANCE CARE PLANNING

Once the provider understands what is important to the woman, it is much easier to talk about the kind of care she would like to receive near the end of life. Being able to hold her granddaughter may be more important than living another year. Once broad goals can be identified, the team needs to shift from a tactical approach to care to a more strategic one. Bennett (1995) refers to this as changing from a “cure-based approach to a psychosocial model.” It means to target an overall goal rather than to get bogged down in correcting the electrolytes. Being at home may be more pertinent than having the last potassium adjusted or receiving the final days of a course of intravenous antibiotics. Being free of pain and in a dry bed with loved ones present may be the ultimate goal.

Although the term “advance directive” makes sense to those in the health care environment, these words may be essentially meaningless to the woman and those who make up her support system. In trying to determine what the patient wants it is necessary to use concrete and explicit terms when discussing this topic. It is important to develop a “psychosocial success” register where psychosocial desires and resolutions can be formally recognized; this might be done during a case conference with staff.

VII. END-OF-LIFE ISSUES

A. PHYSICAL COMFORT NEAR THE END OF LIFE

When the patient is bedridden, it is comforting to be surrounded by photos or objects that remind her of events and people she would like to remember or that make her happy. Being in a home-like environment is the desired resting place for many (American Health Decisions, 1997). Attention to reducing noise, providing a fan or some means of air movement, serving small portions of food several times throughout the day rather than three large meals, and playing music or reading stories may all provide comfort. If the patient has a favorite pet or small children she might enjoy short visits with them.

Complementary therapies such as massage, guided imagery, or acupuncture are widely used and can provide comfort to those for whom they are familiar. Others may not appreciate being touched by strangers and it is always important to discuss these methods before introducing them. Likewise, incense or peppermint oil may be used to mask unpleasant odors; activated charcoal on a gauze pad or chlorophyll tablets can accomplish the same result.

Cultural beliefs and rituals become very important at this time. Use the rest of your team to discover what practices must be respected, because ignorance of these might inhibit a peaceful transition and leave bad memories for families and friends. For example, some cultures or religions require that the patient receive fluids or that the health care workers give the appearance of performing resuscitation attempts or efforts to prevent the actual death. Knowing these beliefs ahead of time will allow for the staff to prepare and conversations to be held that might preclude misunderstanding.

Once the patient and family have made the final decision for “No cardiopulmonary resuscitation (CPR),” many health care workers are at a loss for exactly what to do. Although fluids and antibiotics may be withheld, there are still many techniques that staff can employ to support the patient and family as a unit. It has been suggested that “Orders to Intervene” should be written.

Alexander, Perrone, and Reiss (Alexander, 1999) have developed a mnemonic for remembering simple medical orders that might be implemented as an example of these interventions (see Table 12-14). The care provider should recognize that despite the end of curative interventions, there is always something that can be done to comfort both patient and family. By reversing “No CPR” and writing orders for “RPC” the team can continue to offer support. *Reassurance* of continued involvement by the health care team, *presence* at the bedside on a predictable basis, and an attitude of *caring* that respects individual goals and comfort are the least that can be done. The *Oxford Textbook of Palliative Medicine*, 2nd ed. (Doyle, 1998) contains a wealth of knowledge for those who want to give good supportive care.

Table 12-14: Physician's Card
<i>Side One</i>
<p><i>Comfort Measures at LIFE'S END</i></p> <p>L – LIPS, mouth & eyes moistened; ice chips; artificial saliva /tears</p> <p>I – INCONTINENCE of bowel & bladder expected–use catheter; bed pad</p> <p>F – FEVERS expected: around the clock antipyretics (oral or suppository)</p> <p>E – ELIMINATE all but essential meds</p> <p>S – SYMPTOM management–be aggressive</p> <p>E – EATING less is expected; diet as desired</p> <p>N – NURSING call orders–revise</p> <p>D – DECUBITUS/skin care/turning q 2 hr</p>
<i>Side Two</i>
<p>Making the decision to write “Do Not Resuscitate” orders is often difficult but it does not mean that there is “nothing else to be done.” Once the order “No CPR” is written reverse your thinking and write orders for RPC:</p> <p>R – Reassurance</p> <ul style="list-style-type: none"> • you will continue to care for the patient and family • symptoms which interfere with good quality of life will be controlled • there are effective ways for coping with stresses and for grieving • patient and family concerns will direct how and where care is provided <p>P – Presence</p> <ul style="list-style-type: none"> • be there to hold conversations • visit on a regular basis • sit down and hold a hand • listen respectfully <p>C – Caring</p> <ul style="list-style-type: none"> • provide comfort measures • honor the individual • share laughter and touch <p>Facilitate “life review” and these important conversations:</p> <ul style="list-style-type: none"> • Thank you • Please forgive me • I forgive you • I love you • Goodbye

Source: Alexander, 1999, © University of Maryland, Baltimore, 1999 Palliative Care Program, Permission to reproduce for educational purposes granted.

B. CLINICAL TREATMENT

Treatments that have been used throughout active disease may need to be modified as the woman comes closer to dying. Using complex diagnostic procedures and prolonged courses of therapy may not be necessary at the end

of life and may be a significant burden to the patient. Short bursts of antibiotics may be all that is needed to arrest a symptom. Such judgments must be based on realistic prognosis as discussed earlier in this chapter. For example, a woman resistant to oral antifungal agents may need a brief course of intravenous therapy if this offers the quickest relief of her symptoms.

If there are high fevers and sweats presumed secondary to MAC she may no longer tolerate the usual combination of drugs, and single-agent or short-burst doses may be adequate to control symptoms at a time when a reduced pill count is the overriding goal. One of the difficult aspects of managing the end stages of illness is knowing when it is appropriate to discontinue certain therapies. Much of this decisionmaking is based on the provider's ability to provide realistic prognostic information to the patient and family. For example, prophylactic therapies might be discontinued in the last 3-4 weeks of life; they can easily be resumed should the woman become symptomatic.

C. CONVERSATIONS FOR THE END OF LIFE

Families often fear that discussing death might "scare" the dying person. However, most people know when they are dying and are relieved at being able to discuss their fears or beliefs. Women in particular often feel a need to "protect" those around them and may be more comfortable talking about their impending death with someone who is not a family member. Although most people feel awkward around someone who is very ill or dying because they "don't know what to say," there are a number of things to talk about.

Most people near the end of life want to know that their time on earth has been worthwhile. They want to know that they have been loved, that they will be remembered, and that they are forgiven for things they may have done wrong. One simple method for achieving these goals is to "do life review" which means to ask to hear stories of the person's life: what she is most proud of, what is the funniest thing that ever happened to her, what she is ashamed of or wishes she hadn't done. By asking these questions, the listener can reassure the person that those positive memories will stay alive. By talking about negative events, they can be minimized or forgiven.

An anonymous hospice nurse once said that there are five important conversations for the dying person to have to assure a peaceful death (Byock, 1997). These are "Thank you," "Forgive me," "I forgive you," "I love you," and "Goodbye" (Table 12-15). The last of these is the most difficult both for the dying woman and for those who will be left behind. But this is the most important conversation because the dying need to feel reassured that those left behind will be able to take care of themselves. This is especially true of women regarding spouses and children; it is accentuated when the woman is young and there are young children involved. Those being left behind must also say goodbye by giving the dying woman "permission to go," which represents their acceptance of the finality of the death. This permission must also be verbally granted by health care providers who may have become like family members near the end of a long illness.

Table 12-15: Five Important Conversations to Complete for a “Peaceful” Death
• <i>Thank you.</i>
• <i>Please forgive me.</i>
• <i>I forgive you.</i>
• <i>I love you.</i>
• <i>Goodbye.</i>

Forgiveness and reconciliation are spiritual as well as personal issues (Hall, 1998). Depending on the woman's belief system, it may be important to have a priest, a pastor, a rabbi, or other spiritual representative present throughout the last month of life. In societies where large numbers of women are dying, there may be insufficient care givers because this is a role often assumed by women. It is important to find someone to sit with the dying woman to provide comfort and security in her last hours. Simple presence without conversation represents real support and caring.

Puchalski defines spirituality as “whomever or whatever gives one a transcendent meaning in life.” She suggests doing a spiritual assessment of the woman at the same time that other historical information is gathered. The mnemonic FICA is useful for remembering what questions to ask (Table 12-16).

Table 12-16: Spiritual Assessment – FICA	
F – Faith or beliefs	Do you consider yourself spiritual or religious? What things do you believe in that give meaning to your life?
I – Importance and Influence	What influence does it have on how you take care of yourself? What role do your beliefs play in regaining your health?
C – Community	Is there a person or group who are really important to you? Are you part of a religious community?
A – Address	How would you like your health care providers to address these issues?

Adapted from Puchalski, 2000.

D. TIME OF DEATH

At the time of death it is important to be familiar with the woman's customs. Friends and family present may want to hold hands or stand in a circle around the bed. A prayer or song may be said or sung together. In many cultures, the women (or men, depending upon the belief system) will want to wash the body, perhaps apply oils, and to wrap the body in appropriate garments. Staff should be aware of these practices and allow the family as much time as is needed to complete these rituals. It may be necessary to wait for other friends or family members to arrive to say their own goodbyes. Children should not be kept from participating and will understand the death within their own age-related construct.

E. GRIEF AND BEREAVEMENT

Grief is the process and work of adjusting to the irrevocable loss of persons, objects, relationships, and dreams. The grieving period often begins before death (anticipatory grieving) but may appropriately extend for two years or more after death depending upon the nature of the relationship. Grief is a normal response to loss and includes such symptoms as sadness, crying, withdrawal from other friends and family, loss of drive or ability to concentrate, and fears of "losing one's mind" or experiencing physical symptoms similar those of the person who died. The grieving person requires significant support such as brief visits, phone calls, or invitations to simple social events. Many community hospice programs can provide this type of support.

One role of the palliative care team is to assure that care is given to those left behind, the bereaved. Because of the concentration of activity near the time of death, the bereaved may not feel the full impact of the death for at least two weeks after the actual event. Contact at this time is helpful as is remembering the person on important anniversaries such as one month after the death, holidays, and days particular to the individual who died such as a birthday or wedding anniversary. The first and tenth year anniversaries of the death are often a difficult time for families and friends. Many cultures have rituals related to the date of death that continue to comfort those surviving. Coping strategies that have been useful throughout the disease can also be applied after the death of a loved one.

MULTIPLE LOSS

Having to mourn a second or third person soon after the death of the first is generally more than any individual is able to cope with alone. Dean (1995) found a direct relationship between the number of bereavement episodes suffered by one person and the development of "stress response" symptoms or, as Rando says, "psychic numbing" (Rando, 1993). Although the phenomenon of "multiple loss" has been acknowledged in association with natural disasters and concentration camp survivors, there has been little published about how to cope with and resolve the issues raised by multiple loss.

Many survivors of multiple loss are afraid to openly grieve for fear of losing control of their emotions. Holding onto this grief produces a syndrome similar to that seen with "burn-out" (Bennett, 1995; Price, 1984). Emotional numbing, withdrawal from others, misdirected anger, a lack of pleasure in anything, and resorting to use of drugs or alcohol are all common elements of this syndrome. Kastenbaum (1969) called this series of consecutive losses "bereavement overload." More recently Nord (1996) has delineated four stages of response to multiple AIDS-related loss. These are not mutually exclusive stages and may occur at random rather than in a linear fashion. These stages are: 1) shock and denial, 2) overload and confusion, 3) facing reality, and 4) reinvestment and recovery.

The traditional bereavement model is inadequate for grieving the multiple losses experienced by survivors of AIDS-related loss. Care of persons with AIDS is complicated by the fact that the care giver may himself or herself be infected and facing death. It is important to be able to refer the care giver for appropriate

medical care and counseling. Depression is not unusual and, particularly in those who are also infected, should be treated appropriately and aggressively, even at the time of death of the loved one.

Not only members of the gay and hemophilic communities (which have been hit particularly hard by the epidemic), but mothers of inner city minority youth who may have experienced the death of more than one child and are often alone in trying to resolve their grief are at risk for complicated mourning. "When multiple deaths occur, the people to whom the mourner would ordinarily go for support are gone" (Rando, 1993). Therefore, new models for dealing with these losses need to be developed. Survivors of multiple loss might be helped by a referral for professional counseling.

A time-honored hospice technique has been to attempt to make the sufferer aware of the many manifestations of grief by verbalizing that thoughts of "going crazy" are not unusual and by reassuring those grieving that they, as survivors, are and will be OK (Table 12-17). According to Nord (1996), "social support, community involvement, and fostering a sense of purpose are useful" toward achieving the goal of empowerment, which helps reduce the role of victim. Achieving a sense of balance in life and pursuing a "life outside of AIDS" give survivors a necessary source of detachment. Physical exercise, meditation, and trips away from the usual environment are acceptable methods used to care for the care provider (Table 12-18). An active sense of humor is also helpful.

Table 12-17: Methods for Coping with Multiple Loss

• Acknowledge the loss
• Normalize feeling of "going crazy"
• Physical exercise; adequate sleep
• Community service; foster "sense of purpose"
• Keep the memory alive
• Perform rituals, e.g., quilt panel, memorial service

"Bearing witness" means keeping the memory alive; the AIDS quilt is a good example. The quilt is also an example of the power and importance of ritual. Making a quilt panel is a shared experience that provides support for the makers and for the viewers. Memorial services on a regular basis can be comforting and assist the survivor in bringing closure for an individual death.

GUIDELINES FOR AFTER THE DEATH

Mallinson (1997) has outlined guidelines for addressing grief that might be useful in working with those who are surviving loss from HIV disease. Simply rehearsing words or phrases ahead of time makes it easier for the health care team to interact with survivors during a time many find awkward.

- Acknowledge the death: "I understand that your [partner; spouse] died last week. How is this going for you?"

- Validate the importance to the survivor: "You knew her for a long time, and the two of you were very close. What was she like?"
- Speak of the deceased when appropriate: "I remember when Tommy was first born. This would have been his second birthday this week. How are you feeling?"
- Note the existence of multiple losses: "Since you have been coming to clinic, you have lost your partner, your best friend, and now, your daughter. I can't imagine what it is like. How do you handle the grief?"
- Learn about grief and loss: Take courses, attend workshops, read research, and acquire therapeutic communication skills.

Table 12-18: Facilitating the Grieving Process
1. Share your thoughts
2. Make time for enjoyable activities
3. Exercise regularly
4. Treat yourself to little extras
5. Work through your grief gradually

Source: Leash, 1994.

VIII. CARE OF THE CARE PROVIDER

Palliative care is difficult work because it requires that team members suspend personal needs or beliefs in deference to the desires of the patient and family. It requires a degree of emotional maturity and insight regarding personal feelings or beliefs that might interfere with the work. One must develop coping skills for both external and internal stressors (Bennett, 1995). "Debriefing" is important and must be a recognized part of this care.

Although "support groups" often seem like a useful mechanism, they can be burdensome themselves and are not helpful for everyone. Staff must have a recognized way to "take a time-out" and be flexible enough to "cover" for a colleague who needs a bit of time to "regroup" (Puckett, 1996). Many who do hospice work have learned to take breaks or minivacations, to develop outside interests, or to do community service of another type. Without conscious support of all members of the team the burn-out rate would undoubtedly be high (Price, 1984).

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XIII: OCCUPATIONAL EXPOSURE

Rani Lewis, MD

I. INTRODUCTION

The risk of HIV transmission to medical personnel has been recognized since 1984, with the first reported case of HIV transmitted to a health care worker (HCW) following needlestick injury (Anonymous, 1984). Since that time, information regarding occupational exposure and outcomes has been collected. As of December 2001, there were 57 confirmed cases and 138 possible cases of occupationally-acquired HIV infection among U.S. health care workers reported to the Centers for Disease Control and Prevention (CDC) (Gerberding, 2003). Among the confirmed cases, the most common occupations were nurses (23), laboratory technicians (20), and physicians (6). A HCW is defined as any person whose activities involve contact with patients or with blood and/or body fluid from patients in a health care, laboratory, or public safety setting. An exposure is defined as a percutaneous injury (needlestick or other cut with a sharp object), mucous membrane or nonintact skin (e.g., chapped or abraded skin, dermatitis), or prolonged contact and/or contact involving an extensive area with blood, tissue, or certain other body fluids. Table 13-1 lists types of exposure that yield a significant health care risk for HIV transmission. Table 13-2 lists body fluids with their relative relationship to risk to exposure. When possible, biomolecular assays, including nucleic acid sequencing, have been used to determine the similarity in viral strain between the infected HCW and the possible source (Diaz, 1999).

Table 13-1: Types of Exposure Associated with Transmission

Percutaneous	<ul style="list-style-type: none"> • Needlestick • Cut with sharp object • Human bite
Mucocutaneous	<ul style="list-style-type: none"> • Nonintact skin <ul style="list-style-type: none"> - <i>Abraded</i> - <i>Chapped</i> - <i>Dermatitis</i> • Mucous membrane • Other‡
<p>‡Any contact without barrier protection to concentrated virus in a research laboratory or production facility requires clinical evaluation. There is a theoretical but undocumented risk to HCW from exposures to intact skin.</p>	

High Risk of Transmission	Poorly Defined Risk of Transmission	Low Risk*
<ul style="list-style-type: none"> • Blood, serum • Semen • Vaginal secretions • Other body fluids visibly contaminated with blood 	<ul style="list-style-type: none"> • Amniotic fluid • Cerebrospinal fluid • Pleural fluid • Peritoneal fluid • Pericardial fluid • Synovial fluid 	<ul style="list-style-type: none"> • Cervical mucus • Emesis • Feces • Saliva • Sweat • Tears • Urine • Sputum • Nasal secretions
<p>* Unless visibly contaminated with blood. Source: CDC, 2001.</p>		

Infection Status of Sources					
Exposure Type	HIV-Positive (Asx or HIV-RNA < 1500 c/mL)	HIV-Positive (Sx HIV/AIDS, acute HIV, or HIV-RNA > 1500 c/mL)	Source of unknown HIV status	Unknown source^Ø	HIV-Negative
Lower Risk [¶]	Basic 2-drug PEP recommended	Expanded 3-drug PEP recommended	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors§	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely	No PEP warranted
Higher Risk [†]	Expanded 3-drug PEP recommended	Expanded 3-drug PEP recommended	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors§	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely	No PEP warranted
<p>[¶] Less severe (e.g., solid needle and superficial injury). ^{**} The designation , "consider PEP," indicates that PEP is optional and should be based on an individualized decision between the exposed person and the treating clinician. [§] If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued. [†] More severe (e.g., large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient's artery or vein). ^Ø Unknown source (e.g., a needle from a sharps disposal container) Adapted CDC, 2001.</p>					

In 1995, the Centers for Disease Control and Prevention (CDC) published a report of known cases of occupational exposure in France, the United Kingdom, and the United States (CDC, 1995). An important finding from this retrospective case-control study was that postexposure prophylaxis (PEP) with zidovudine (ZDV) was associated with a significant reduction in seroconversion. This prompted the formation of a U.S. Public Health Service interagency working group, composed of members from the CDC, the Food and Drug Administration, the Health Resources and Services Administration, the National Institutes of Health, and other expert consultants, who developed guidelines for the use of PEP for HCWs after occupational HIV exposure; these recommendations were updated in 2001 and expanded to include recommendations for management of occupational exposure to hepatitis B and hepatitis C viruses (CDC, 2001) (Table 13-3, 13-4).

This chapter will review risk factors for transmission and the magnitude of risk for HIV transmission from an occupational exposure, prevention of exposures, and postexposure management, including PEP with antiretroviral medications.

Table 13-4: Recommendations for HIV Postexposure Prophylaxis after Mucous Membrane and Nonintact Skin[∞] Exposures

<i>Infection Status of Sources</i>					
<i>Exposure Type</i>	<i>HIV-Positive (Asx or HIV-RNA <1500 c/mL)</i>	<i>HIV-Positive (Sx HIV/AIDS, acute HIV, or HIV-RNA >1500 c/mL)</i>	<i>Source of unknown HIV status</i>	<i>Unknown source[∅]</i>	<i>HIV-Negative</i>
Small Volume ^{††}	Consider basic 2-drug PEP	Basic 2-drug PEP recommended	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors [§]	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely	No PEP warranted
Large Volume [†]	Basic 2-drug PEP recommended	Expanded 3-drug PEP recommended	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors [§]	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings where exposure to HIV-infected persons is likely	No PEP warranted

[∞] For skin exposures, follow-up is indicated only if there is evidence of compromised skin integrity (e.g., dermatitis, abrasion, or open wound).

[∅] Unknown source (e.g. splash from inappropriately disposed blood).

^{††} Small volume (i.e., a few drops).

^{**} The designation, "consider PEP," indicates that PEP is optional and should be based on an individualized decision between the exposed person and the treating clinician.

[§] If PEP is offered and taken and the source is later determined to be HIV-negative, PEP should be discontinued.

[†] Large volume (i.e., major blood splash).

II. MAGNITUDE OF RISK

Correct estimation of the likelihood of transmission following occupational exposure is limited by the relative infrequency with which HIV transmission to HCWs is reported. In addition, the retrospective nature of this reporting leads to an increased potential for invalid analysis of the risks. There have been prospective and retrospective reviews of all published cases that implicate occupational exposure. The most complete prospective study performed on data from the United States estimates that the risk of HIV transmission following occupational exposure via single needlestick injury is 0.3% (Bell, 1997). This is compared to a risk of 1–6% for clinical hepatitis (serologic evidence of HBV 23–27%) after percutaneous exposure to HBsAg-positive blood; 22–31% for clinical hepatitis (serologic evidence of HBV 37–62%) (Werner, 1982) after similar exposure to HBeAg-positive blood in unvaccinated health-care workers; and an average incidence of 1.8% infection with hepatitis C virus (HCV) after accidental percutaneous exposure to an HCV-positive source (Alter, 1994; Mitsui, 1992; Puro, 1995). Ippolito and coworkers reviewed the world literature on occupational exposure from an HIV-seropositive source and determined risk to be approximately 0.09% following a mucocutaneous exposure (Ippolito, 1993). As noted in Table 13-2, the risk from skin exposure or exposure to body fluids/tissues other than blood has not been clearly defined. Risk of HIV transmission increases with multiple exposures and with presence of risk factors listed below.

III. RISK FACTORS FOR OCCUPATIONAL HIV TRANSMISSION

The likelihood of HIV infection following exposure is affected by the presence of certain risk factors. Cardo and coworkers (1997) performed a case-control study of internationally gathered cases of percutaneous exposure of HCWs to HIV-infected blood in an attempt to determine factors that increased or decreased the risk of transmission (see Table 13-5). Their data indicate that HCWs who took ZDV after potential exposure had an 81% lower risk of becoming infected (95% confidence interval, 48–94%) than those who did not take this medication.

In general, risk factors include:

- **Type of contact or exposure.** Exposure has been classified into several risk categories (Table 13-1), including percutaneous, mucocutaneous, and intact skin contact, with different risks of transmission.
- **Type of body fluid.** The risk for transmission after exposure to fluids or tissues other than HIV-infected blood has not been quantified but is thought to be significantly lower than for blood exposure (Table 13-2) (Henderson, 1990).
- **Quantity of blood.** Exposure to larger quantities of blood from an HIV source, as indicated by a deep needlestick, exposure to a needle placed directly into a vessel, or visible blood on the injuring device is associated with an increased risk of transmission. Hollow-bore needles transfer more blood than solid needles and account for most exposures resulting in occupational transmission of HIV (Gerberding, 2003; Mast, 1993).

- Disease status of source patient. Exposure to blood from patients with terminal illness increases risk. This likely reflects risk associated with exposure to higher levels of virus in blood (higher viral loads). HIV-RNA level has been shown to be a significant factor in the risk of perinatal transmission. Individuals with acute HIV infection also have very high HIV-RNA levels and probably represent an increased risk of transmission if occupational exposure occurs. HCW seroconversion has been reported after exposure to an HIV-infected patient with undetectable viral load (CDC, 1998b). Other factors often present in late-stage disease, such as more virulent syncytia-inducing HIV strains, may also increase risk.
- Host defenses. There is some limited evidence that the immune response of the HCW may affect the risk of transmission (Pinto, 1997). Pinto et al. demonstrated an HIV-specific cytotoxic T-lymphocyte response among HIV-exposed but uninfected HCWs when the peripheral blood mononuclear cells were stimulated in vitro by HIV mitogens. Along with similar responses seen in other groups with repeated exposure without infection, this suggests the possibility that the host immune response may prevent HIV infection after exposure.
- Postexposure prophylaxis. The data of Cardo et al. (1997) confirm the efficacy of PEP in limiting the risk of HIV transmission to HCWs. Several case reports of transmission in the setting of prompt initiation of PEP, however, indicate that this therapy is not 100% effective. There are at least 21 cases worldwide of PEP failure, including prophylaxis with 2 or more antiretroviral drugs in some cases, following HCW exposure (Gerberding, 2003). HIV resistance to the antiretroviral drugs used or delay in initiation of medication has been hypothesized to play a role in these (and other, non-HCW) prophylaxis failures.

Table 13-5: Logistic-Regression Analysis of Risk Factors for HIV Transmission after Percutaneous Exposure to HIV-infected Blood

Risk Factor	U.S. Cases*	All Cases +
	Adjusted Odds Ratio (95% CI)*	
Deep injury	13.0 (4.4–42)	15.0 (6.0–41)
Visible blood on device	4.5 (1.4–16)	6.2 (2.2–21)
Procedure involving needle in artery or vein	3.6 (1.3–11)	4.3 (1.7–12)
Terminal illness in source patient [§]	8.5 (2.8–28)	5.6 (2.0–16)
Postexposure use of zidovudine	0.14 (0.03–0.47)	0.19 (0.06–0.52)

* All risk factors were significant ($p < .02$)

* All risk factors were significant ($p < .01$)

† CI denotes confidence interval. Odds ratios are for the odds of seroconversion after exposure in workers with the risk factor as compared with those without it.

§ Terminal illness was defined as disease leading to death of the source patient from AIDS within 2 months after the health care worker's exposure.

Source: Cardo, 1997.

IV. PREVENTING OCCUPATIONAL EXPOSURE

Limiting HCWs' exposure to potentially infectious materials is the key to reducing the risks of occupational exposure. Universal precautions, as recommended by the Occupational Safety and Health Administration (OSHA), reflect the concept that all blood and body fluids are potentially infectious and must be handled accordingly. Personal protective equipment (Table 13-6) should be used to prevent blood and other potentially infectious material from reaching a HCW's clothing, skin, eyes, mouth, or mucous membranes (CDC, 1987).

• Gloves
• Gowns
• Laboratory coats
• Face shields
• Eye protection
• Mouthpieces
• Resuscitation bags

Handwashing should be done after touching blood, body fluids or secretions, or contaminated items, whether or not gloves are worn. Hands should also be washed after removing gloves and between patient contacts. Gloves should be worn when in contact with blood or body fluids (including blood drawing), mucous membranes or nonintact skin, or items contaminated with possibly infectious material; it is strongly recommended that gloves be worn when performing any invasive procedure. Clinicians performing surgery, deliveries, or other invasive procedures likely to generate splashes of blood or other body fluids should wear a mask and eye protection or face shield. The use of double-gloving in surgical procedures has been shown to reduce the risk of direct blood contact for operating room personnel (Greco, 1995; Konig, 1992). Needles and other sharp instruments should be handled with great care and disposed of in approved sharps containers. As a rule, do not recap, bend, or break used needles. During surgery hand-to-hand passage of sharp instruments (e.g., needles, scalpels) should be minimized—consider passing these instruments first onto a surgical tray or pan.

Risk of occupational exposure and need for universal precautions applies not only to physicians, nurses, and laboratory workers, but also to medical, nursing, or dental students, and to dentists. Since reports of patient-to-dentist and dentist-to-patient HIV transmission seen in the late 1980s (CDC, 1991a), both the CDC and the American Dental Association have included recommendations regarding the use of barrier precautions in dental settings and sterile technique in the preparation of dental equipment (American Dental Association, 1988).

Another group at increased but less well defined risk are emergency medical technicians, paramedics, and law enforcement agents. These individuals are frequently in contact with patients of unknown or noncommunicated HIV status, in emergency situations. OSHA regulations requiring the availability of

face masks, mouth shields, and ventilation masks are designed to reduce the risk to emergency technicians and other public safety workers. Given the highly unpredictable nature of their risk for exposure, general infection control measures are recommended, even when the risk appears low (International Association of Fire Fighters, 1988). Given the prevalence of HIV infection within prison populations, correctional officers are also at increased risk for occupational exposure and should use universal precautions (Hammett, 1991). Intentional human bites are more common in correctional facilities and may present a risk of infection transmission and should be evaluated appropriately.

V. HIV INFECTION FOLLOWING OCCUPATIONAL EXPOSURE

There is limited information regarding the symptomatology seen in HCWs experiencing seroconversion from occupational exposure. Approximately four fifths of cases were associated with symptoms consistent with primary HIV infection, usually 2–6 weeks after exposure (CDC, 1998b). The mean time to seroconversion is 65 days, and of infected HCWs who seroconvert, 95% have done so within 6 mo after exposure (Busch, 1997). There are rare reported cases of HCWs who remain negative for HIV antibody at 6 mo, but seroconvert by 12 mo after exposure (Ciesielski, 1997; Konig, 1992). Delayed seroconversion has been associated with simultaneous exposure to hepatitis C in two cases, one of which resulted in fulminant and fatal HCV (Ridzon, 1997). Further information regarding the effect of coinfection with other viral illnesses remains to be determined.

HCWs presenting for HIV exposure PEP need to be counseled regarding risks of other viral illnesses to which they may have been exposed, especially hepatitis B and hepatitis C viruses. HCWs at risk for occupational exposure to hepatitis B should have appropriate vaccination.

Hepatitis C virus is the most common chronic blood-borne infection in the United States. The Third National Health and Nutrition Examination Survey (NHANES III) data estimate 3.9 million Americans have been infected with HCV, with 36,000 new infections reported per year (CDC, 1998c). HCV seroconversion most often occurs after percutaneous exposure in the health care setting. Infection via mucous membrane exposure, although extremely rare, has been reported (Sartori, 1993). There is no vaccine or immunoglobulin available for HCV PEP.

VI. POSTEXPOSURE MANAGEMENT

Health care organizations are required to have exposure-control plans, including postexposure management and follow-up for employees at risk. OSHA mandates reporting of exposure incidents.

A. EXPOSURE SITE MANAGEMENT

Wounds and puncture sites should be washed with soap and water; mucous membranes exposed should be flushed with water. The application of bleach to skin or mucosal surfaces is not recommended.

B. EXPOSURE EVALUATION

The type of body fluid involved, type of exposure (percutaneous, mucosal, nonintact skin, etc.), and the severity of the exposure (quantity of blood, duration of contact, etc.) should be evaluated and will affect decisions about PEP (see Tables 13-1, 13-2).

C. SOURCE PATIENT EVALUATION

The source individual of the exposure should be evaluated for possible HIV infection and, if status is unknown, should be tested, after appropriate consent (see Table 13-7). In the absence of risk factors and clinical findings consistent with acute HIV infection, a negative result with use of a sensitive enzyme immunoassay for HIV screening implies a transmission risk of zero. (Gerberding 2003). Medical information such as previous HIV test results; HBV, HCV testing; clinical signs, symptoms, or diagnoses; and history of risk exposures (e.g., injection drug use) may be relevant in making initial decisions regarding PEP. Rapid HIV testing, if available, may be particularly useful in the setting of occupational exposure and can decrease unnecessary antiretroviral exposure, save money, and decrease anxiety. Confirmation of reactive results with screening assay or rapid test is not necessary to start PEP, but should be done before the source patient is informed. If the source patient has signs/symptoms consistent with possible acute HIV infection, testing should include plasma HIV-RNA levels. Initiation of PEP, if indicated, should not be delayed while awaiting test results. If the source is known to be HIV-infected, information about clinical stage of infection, recent CD4 counts, viral load testing, antiretroviral treatment history, and antiretroviral resistance testing, if available, are important in choosing an appropriate PEP regimen; however, initiation of PEP should not be delayed if this information is not immediately available.

Table 13-7: Evaluation of Occupational Exposure Sources

Known Sources
<ul style="list-style-type: none"> • Test known sources for HBsAg, anti-HCV, and HIV antibody <ul style="list-style-type: none"> - Direct virus assays for routine screening of source patients are not recommended - Consider using a rapid HIV-antibody test - If the source person is not infected with a bloodborne pathogen, baseline testing or further follow-up of the exposed person is not necessary • For sources whose infection status remains unknown (e.g., the source person refuses testing), consider medical diagnoses, clinical symptoms, and history of risk behaviors • Do not test discarded needles for bloodborne pathogens
Unknown Sources
<ul style="list-style-type: none"> • For unknown sources, evaluate the likelihood of exposure to a source at high risk for infection <ul style="list-style-type: none"> - Consider likelihood of bloodborne pathogen infection among patients in the exposure setting
CDC, 2001.

The source patient should also be tested for anti-HCV and HBsAg to assess the HCW's risk for hepatitis B and C. Confidentiality of the source patient should be maintained at all times.

D. BASELINE AND FOLLOW-UP TESTING

Baseline testing for HIV antibody should be performed to establish serostatus at the time of exposure and should be repeated at 6 wk, 12 wk, and 6 mo postexposure, regardless of the use of PEP. An extended duration of follow-up may be considered with simultaneous exposure to HCV or use of highly active antiretroviral therapy regimens for PEP because of theoretical concerns about delay in HIV seroconversion in these situations. Pregnancy testing should be offered to HCWs of reproductive age if pregnancy status is unknown.

In addition to HIV, hepatitis B and C are significant concerns. For the HCW exposed to an HCV-positive source, baseline and follow-up testing (at 4–6 mo) for anti-HCV and serum alanine aminotransferase is recommended. Confirmation by a supplemental assay (such as recombinant immunoblot assay or HCV PCR) is recommended for all positive anti-HCV results by enzyme immunoassay (CDC, 2001).

If the HCW has previously received the hepatitis B virus (HBV) vaccine and anti-HBsAg level, which reflects vaccine-induced protection, is unknown, this should be tested; if inadequate, hepatitis B immune globulin is recommended, as well as a booster dose of vaccine. Recommendations for PEP for hepatitis B exposures are outlined in Table 13-8.

<i>Vaccination and antibody response status of exposed person****</i>	<i>Source HBsAg* positive</i>	<i>Source HBsAg* negative</i>	<i>Source unknown or not available for testing</i>
Unvaccinated	HBIG# x 1 and initiate HB vaccine series##	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated			
- known responder**	No treatment	No treatment	No treatment
- known nonresponder@@	HBIG x 1 and initiate revaccination or HBIG x 2***	No treatment	If known high risk source, treat as if source were HBsAg positive
- antibody response unknown	Test exposed person for anti-HBs### 1. If adequate**, no treatment necessary 2. If inadequate@@, administer HBIG x 1 and vaccine booster	No treatment	Test exposed person for anti-HBs 1. If adequate**, no treatment necessary 2. If inadequate@@, administer vaccine booster and recheck titer in 1-2 months
<p><i>Adapted CDC 2001</i></p> <p>**** persons who have previously been infected with HBV are immune to reinfection and do not require postexposure prophylaxis</p> <p>* Hepatitis B surface antigen</p> <p># Hepatitis B immune globulin (dose: 0.06 mL/kg intramuscularly)</p> <p>## Hepatitis B vaccine</p> <p>** A responder is a person with adequate levels of serum antibody to HBsAg (> or = 10 mIU/mL)</p> <p>@@ A nonresponder is a person with inadequate levels of serum antibody to HBsAg (<10 mIU/mL)</p> <p>*** The option of giving one dose of HBIG and reinitiating the vaccine series is preferred for nonresponders who have not completed a second 3-dose vaccine series. Two doses of HBIG are preferred for persons who have previously completed a second vaccine series but failed to respond</p> <p>### Antibody to HBsAg</p>			

E. COUNSELING THE HCW

- Decisions regarding appropriate postexposure management should be individualized; the HCW should be counseled about their personal risk based on considerations outlined above, and recommendations made about initiating PEP.
- The HCW should be informed that knowledge about the effectiveness and the toxicity of the antiretroviral drugs used for PEP is limited and failures of PEP have occurred. The addition of antiretroviral drugs other than ZDV to a PEP regimen is based on the superiority of combination antiretroviral regimens over monotherapy in the treatment of HIV-infected individuals and the theoretical considerations regarding possible resistance concerns and the utility of using drugs having activity at different stages in the viral replication cycle.
- The medical history of the HCW, including medications, presence or possibility of pregnancy, or other medical conditions, should be obtained and may influence decisions or recommendations about PEP, including choice of regimen.
- A specific PEP regimen should be recommended, when indicated, and the rationale for its selection should be discussed. Information should be given about how to take the medications, potential side effects and measures to minimize these, possible drug-drug interactions with recommended regimen and any medications that should not be taken while taking PEP, clinical monitoring for toxicity, and symptoms that should prompt immediate evaluation. Emphasize the importance of adherence.
- PEP may be declined by the HCW.
- The HCW should be urged to seek medical evaluation with the development of any acute illness during the follow-up period. The differential diagnosis in this situation must include acute HIV infection, drug reaction, toxicity from the PEP regimen, or other medical illness.
- Measures to reduce the risk of possible secondary transmission during follow-up (especially in the 6–12 wk after exposure) should be discussed and recommended. These include use of condoms or abstinence to prevent sexual transmission and pregnancy; not donating blood, plasma, tissue, or organs; and, in lactating mothers, discontinuing breastfeeding or pumping breasts and discarding breastmilk during this period.
- There is no need to modify clinical responsibilities based on HIV exposure.
- Each HCW should be given a contact name and/or number to call for concerns or questions.

F. POSTEXPOSURE PROPHYLAXIS FOR HIV

The decision regarding which and how many antiretroviral agents to use is largely empiric and should try to balance the risk for infection against the potential toxicity of the PEP regimen. Current recommendations are to use a two- or three-drug regimen based on level of HIV transmission risk and possibility of drug resistance (see Table 13-4). PEP should be initiated as soon as possible following exposure, preferably within 1–2 hours, and continued for 4 wk. Specific drug recommendations are outlined in

Table 13-9. Standard dosing should be used. The FDA has reports of 22 HCW receiving nevirapine-containing PEP regimens with serious reactions, including 12 cases of hepatotoxicity and 14 with skin reactions (including Stevens Johnson syndrome). Nevirapine should be avoided in PEP regimens (Johnson, 2000; CDC 2001).

Table 13-9: Potential Antiretroviral Regimens For Post-exposure Prophylaxis	
<i>Regimen</i>	<i>Comment</i>
Basic	
zidovudine (ZDV) + lamivudine (3TC)	ZDV only drug with established efficacy; has high rates of GI intolerance, fatigue, headache-monitor CBC 3TC well tolerated and can be given qd; ZDV/3TC available as co-formulation
stavudine (d4T) + lamivudine (3TC)	d4T with good short-term tolerance; 3TC as above
didanosine (ddI) + lamivudine (3TC)	Both can be given with qd dosing; ddI must be taken on empty stomach; peripheral neuropathy with ddI in 5-12%, pancreatitis in 1-9% (fatal in 6% of those who develop pancreatitis)
tenofovir (TDF) + lamivudine (3TC)	TDF well tolerated, effective for PEP in primate model, can be given with qd dosing; 3TC as above
Expanded (Basic regimen plus one of the following)	
lopinavir/ritonavir (LPV/r)	Potent; should be taken with food; monitor liver enzymes
atazanavir (ATV) +/- ritonavir (RTV)	Potent, well tolerated, can be given with qd dosing; boosted well with RTV; should be taken with food; monitor liver enzymes
nelfinavir (NFV)	Well tolerated except for diarrhea; should be taken with dose; monitor liver enzymes
fosamprenavir/ritonavir (fAPV/r)	Low pill burden, can be given qd; no food effect; monitor liver enzymes
indinavir (IDV)	Risk of renal stones; requires tid dosing; must be taken on empty stomach
efavirenz (EFV)	Potent, concern for short-term central nervous system side effects in health care workers; qd dosing
abacavir (ABC) (should not be combined with TDF/3TC because of high rate of early virologic nonresponse)	Rare but potentially fatal hypersensitivity reaction; less potent in combination with basic regimens; available as coformulation with ZDV/3TC

Adapted: Bartlett 2004

These regimens include those recommended in USPHS 2001 guidelines except for d4T/ddI, which is no longer recommended as part of antiretroviral treatment regimens because of high incidence of toxicity. Additional possible regimens are included with agents not available at the time the 2001 guidelines were developed.

Of the HCWs receiving PEP (ZDV or a combination of agents), almost 50% report subjective side effects and these have led to discontinuation of therapy in approximately one third of cases (CDC, 2001). Gastrointestinal side effects are common but are not serious and can generally be managed, as is the case with most adverse effects seen with PEP. Serious side effects, including renal stones and pancytopenia, have been reported but are rare. For more details about side effects with different antiretroviral agents, see Chapter XIV on Pharmacology. Laboratory monitoring should include a complete blood count and renal and hepatic function tests at baseline and 2 wk after initiation of PEP; more in-depth testing may be indicated based on underlying medical conditions or specific toxicity associated with drugs in the PEP regimen (e.g., glucose testing if on a protease inhibitor). Table 13-10 outlines situations for which expert consultation is advised (see Chapter 15 for resources on PEP consultation).

Table 13-10: Situations for which expert consultation regarding PEP is advised

- | |
|--|
| <ul style="list-style-type: none"> • Delayed (i.e., later than 24–36 hours) exposure report
- <i>the interval after which there is no benefit from postexposure prophylaxis (PEP) is undefined</i> |
| <ul style="list-style-type: none"> • Unknown source (e.g., needle in sharps disposal container or laundry) |
| <ul style="list-style-type: none"> • Known or suspected pregnancy in the exposed person |
| <ul style="list-style-type: none"> • Resistance of the source virus to antiretroviral agents known or suspected |
| <ul style="list-style-type: none"> • Toxicity of the initial PEP regimen <ul style="list-style-type: none"> - <i>adverse symptoms, such as nausea and diarrhea are common with PEP</i> - <i>symptoms often can be managed without changing the PEP regimen by prescribing antimotility and/or antiemetic agents</i> - <i>modification of dose intervals (i.e., administering a lower dose of drug more frequently throughout the day, as recommended by the manufacturer), in other situations, might help alleviate symptoms</i> |

Adapted CDC, 2001.

VII. SPECIAL CONSIDERATIONS

A. ANTIRETROVIRAL RESISTANCE

It is unclear how antiretroviral resistance influences risk of HIV transmission. Occupational transmission of drug-resistant strains has been reported despite use of PEP with combination drug regimens (Perdue, 1999; Beltrami, 2000a). In a study of occupational exposures 39% of 41 source patients had resistance mutations to reverse transcriptase inhibitors and 10% to protease inhibitors (Beltrami, 2000b). If resistance of the source patient's virus to one or more of the drugs in the PEP regimen is known or suspected (based on drug history, virologic response to treatment, or prior resistance testing), drugs should be selected to include agents to which the virus is likely to be sensitive. Clinical consultation with an expert in HIV treatment should be obtained for guidance in this situation. However, it is important not to delay starting PEP because of resistance concerns; if resistance is known or suspected, a third or fourth drug may be included in the regimen until consultation is obtained.

B. THE PREGNANT HCW

In addition to the counseling issues noted above, the pregnant HCW should be informed about what is known and not known about potential risks, benefits, and side effects for the fetus and herself related to the antiretroviral agents used in PEP. (Issues relating to the use of antiretroviral drugs in pregnancy are discussed in Chapter VII: HIV and Reproduction and in Chapter XIV: Pharmacology.) PEP should not be denied on the basis of pregnancy and pregnancy should not prevent the use of an optimal PEP regimen. However, regimens containing efavirenz or a combination of ddI and d4T should generally be avoided. For breastfeeding HCWs, temporary discontinuation of breastfeeding should be considered while on PEP to avoid infant exposure to these drugs.

VIII. THE HIV-SEROPOSITIVE HCW

There has been great controversy about HCWs who are infected with HIV and continue to work. The infection of several patients by an HIV-seropositive dentist is well known although poorly understood. In a retrospective evaluation of over 22,000 patients treated by 51 health care workers infected with HIV (over three quarters in surgical or dental disciplines) no cases of transmission of HIV from HCW to patient were documented (Laurie, 1995). Health care workers with HIV may also themselves be at risk for contracting a communicable disease; appropriate precautions should be taken and appropriate immunizations given.

All clinicians with exudative or transudative skin lesions should refrain from direct patient care until these lesions have healed. It is believed that HIV-positive HCWs who follow universal precautions and do not perform invasive procedures pose no risk to their patients. Furthermore, there are no current data suggesting that HIV-positive HCWs performing nonexposure-prone invasive procedures should have their practice restricted, assuming they use universal precautions, appropriate technique, and adequate sterilization and disinfection of instruments.

“Exposure-prone” procedures require more consideration. Exposure-prone characteristics include digital palpation of a needle point in a body cavity or the simultaneous presence of the HCW’s fingers and a needle or sharp instrument in a poorly visualized or highly confined anatomic space. These procedures are associated with increased risk for percutaneous injury to the HCW and potential increased risk to the patient. It is recommended that all HCWs who perform these procedures know their HIV status. HIV-positive HCWs performing exposure-prone procedures should seek counsel from an expert review panel on a case-by-case basis. Mandatory testing of HCWs is not recommended. The ethics of patient notification of exposure to an HIV-infected HCW continues to be argued (Blatchford, 2000; Donnelly, 1999).

It is imperative that institutions have a standard policy on the management of HIV-infected HCWs, as well as policies on the management of a HCW potentially infected by a patient (CDC, 1991c).

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XIV: PHARMACOLOGIC CONSIDERATIONS IN HIV-INFECTED PREGNANT PATIENTS

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II. INTRODUCTION

The decision to administer drugs to a pregnant woman is largely based on the therapeutic benefit to the mother and/or fetus vs. the potential risk to the mother and the developing fetus. Clinicians are often advised to avoid prescribing drugs for pregnant patients because human safety data in pregnancy are lacking for many, if not most medications. However, in some clinical situations the benefits of treatment far outweigh the risks. These are important considerations when selecting agents to treat patients with human immunodeficiency virus (HIV), to prevent mother-to-child HIV transmission, and to prevent or treat opportunistic infections.

There is limited information concerning the safety of many antiretrovirals in pregnancy. Mutagenicity, carcinogenicity, and teratogenicity studies in animals are the basis for most data on safety in pregnancy. However, generally animals are administered doses 5 to 20 times higher than those given to humans; clinical applicability to human treatment is not always clear.

It is now standard care to treat HIV-infected patients with an “antiretroviral cocktail” or a combination of antiretroviral agents, making it difficult to assess the safety of a single antiretroviral agent. More prospective

clinical data are needed. Clinicians are encouraged to report all in utero exposures to the Antiretroviral Pregnancy Registry (telephone 1-800-258-4263; Fax 1-800-800-1052; Internet access www.APRegistry.com), a collaborative effort of pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners. Observational data on antiretroviral exposure during pregnancy are collected and are used to assess potential teratogenicity of these drugs.

The tables contained in this chapter include detailed information about pharmacologic agents commonly used in the treatment of HIV-infected women and drugs often used in pregnancy or as complementary therapies, with particular emphasis on issues related to their use in pregnancy.

III. PHARMACOKINETICS OF DRUGS IN PREGNANCY

Although many physiologic changes occur during pregnancy, few trials have been conducted to evaluate their clinical significance on the pharmacokinetics of commonly used drugs. Physiologic changes that may affect drug pharmacokinetics include delayed gastric emptying, decreased intestinal motility, increased volume of distribution (an average increase of 8L), increased renal blood flow (by 25–50%), and increased glomerular filtration rate (by 50%) (Davidson, 1974; Dunnihoo, 1992; Parry, 1970). Pharmacokinetics parameters of nevirapine given as a single dose of 200 mg at the onset of labor were similar but more variable than in nonpregnant adults, possibly due to incomplete absorption associated with altered gastrointestinal function during labor (Mirochnick, 1998). Recent data suggests that NVP levels may be detectable as long as 3 weeks after a single dose given at onset of labor (Jourdain, 2004). Pregnancy does not change the pharmacokinetics of ZDV, 3TC, d4T, and ddI (Moodley, 1998; Schuman, 1990; Wang, 1999). Serum concentrations of the PIs that have been studied in pregnancy (indinavir [IDV], ritonavir [RTV], and saquinavir [SQV]) appear to be lower in pregnancy when given as single PIs (without boosting) (Perinatal Guidelines Working Group, 2004). SQV achieves adequate drug levels when boosted with RTV (Acosta, 2001) and nelfinavir (NFV) achieves adequate levels when given as 1250 mg twice daily (Bryson, 2002). A recent pharmacokinetic study including 4 women on an IDV-containing regimen with or without ritonavir (RTV) found a decrease in plasma concentrations of IDV during pregnancy with spontaneous increase postpartum in two women on IDV alone, consistent with metabolic induction of cytochrome P450 activity in pregnancy; this induction was offset by the concomitant use of RTV (Kosel, 2003). The clinical significance of these differences in pregnancy is unclear.

Table 14-1: Abbreviations

Drug Abbreviations	
ABC: Abacavir (Ziagen)	INV: Inivrase (saquinavir, HGC)
APV: Amprenavir (Agenerase)	IVIG: Intravenous immune globulin
ATV: Atazanavir (Reyataz)	LPV/r: Lopinavir/Ritonavir (Kaletra)
AZT: Zidovudine (Retrovir)	NFV: Nelfinavir (Viracept)
CBV: Combivir (AZT+3TC)	NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor
ddI: Didanosine (Videx)	NRTI: Nucleoside Reverse Transcriptase Inhibitor
d4T: Stavudine (Zerit)	NVP: Nevirapine (Viramune)
ddC: Zalcitabine (Hivid)	PI: Protease Inhibitor
DLV: Delavirdine (Rescriptor)	RBT: Rifabutin (Mycobutin)
EFV: Efavirenz (Sustiva)	RTV: Ritonavir (Norvir)
FTC: Emtricitabine (Emtriva)	SQV: Saquinavir (Inivrase, Fortovase)
ENF: Enfuvirtide (Fuzeon, T-20)	3TC: Lamivudine (Epivir)
FTV: Fortovase (saquinavir, SGC)	TDF: Tenofovir (Viread)
fAPV: Fosamprenavir (Lexiva)	TMP-SMX: Trimethoprim sulfamethoxazole (Bactrim, etc.)
HU: Hydroxyurea	TZV: Trizivir (ABC+AZT+3TC)
IDV: Indinavir (Crixivan)	VZIG: Varicella zoster immune globulin
INH: Isoniazid	ZDV: Zidovudine (Retrovir)
Miscellaneous Abbreviations	
ART: Antiretroviral Therapy	pk: pharmacokinetics
ARV: antiretroviral	po: by mouth
AUC: area under the concentration time curve (i.e. total drug exposure)	qd: daily
Cmax: peak serum concentration	qid: four times per day
Cmin: trough serum concentration	qm: monthly
EC: Enteric Coated	qod: every other day
HAART: Highly Active Antiretroviral Therapy	qw: every week
IV: Intravenous	soln: solution
IM: Intramuscular	tid: three times per day
VL: Viral Load	tiw: three times per week
bid: twice per day	TAM: thymidine analogue mutation
biw: twice per week	TDM: Therapeutic drug monitoring
hs: bedtime (hour of sleep)	ULN: upper limit of normal
mo: month	

A	Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters).
B	Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of pregnant women have not been conducted.
C	Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
D	Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
X	Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

Table 14-3: Antiretrovirals

Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
Abacavir (Ziagen®, ABC)	300 mg bid or 600 mg qd Available as 300 mg tablets; 10 mg/ml oral solution; Trizivir: ZDV 300 mg/ 3TC 150 mg/ ABC 300 mg Epzicom: 3TC 300 mg ABC 600 mg	Hypersensitivity reaction—fever, rash, fatigue, malaise, GI symptoms, and arthralgias (noted in 2–3% of patients). Mandatory and permanent discontinuation with hypersensitivity reaction. Deaths reported upon rechallenge; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	C	Rodent studies demonstrated placental passage, anasarca, skeletal malformation at 1000 mg/kg dose (35 times human therapeutic levels) during organogenesis. However rabbits receiving 8.5 times human therapeutic levels did not have fetal malformation.	Based on ex vivo data, placental transfer was 32–66% (Bawdon, 1998).	No data on use for prevention of perinatal transmission.
Zidovudine (Retrovir®, AZT, ZDV)	300 mg po bid. PACTG protocol dosing: Prenatal: 100 mg 5x per day (alternatively 300 mg bid) beginning at weeks 14–34; Intrapartum 2 mg/kg IV for first hour then 1 mg/kg IV until birth. Infant received 2 mg/kg po q 6 h for the first 6 wk of life beginning 8–12 hr after birth Available as 100 mg capsules; 300 mg tablets; 10 mg/ml IV solutions; 10 mg/mL oral solution; 300 mg Combivir (ZDV 300 mg/3TC 150 mg). Trizivir (ZDV 300 mg/3TC 150 mg/ABC 200 mg)	GI intolerance, malaise; headache (in 5–10%); bone marrow suppression (anemia and neutropenia seen more commonly with late stage AIDS); myalgia; myopathy; transaminase elevation; fingernail discoloration; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	C	Prolonged high dose ZDV exposure associated with nonmetastasizing vaginal squamous tumors in 13% of adult rodents; possibly due to concentration of unmetabolized ZDV in rodent urine (but not in humans). Transplacental carcinogenicity studies in mice with differing results: (1) doses 2.5–50 times human dose given in late gestation resulted in increase in lung, liver, female reproductive tract tumors in offspring exposed to highest dose level; (2) doses approximately 3 times human therapeutic exposure in pregnancy associated with no increase in tumor incidence in offspring. No evidence of fetal malformations or developmental toxicity with doses up to 500–600 mg/kg/day in pregnant rats, mice, rabbits	Human studies demonstrated 85% placental passage. No excess maternal toxicities or fetal defects noted with AZT during pregnancy. Long-term toxicity data (up to 6 yrs.) for infants exposed to AZT in utero and postpartum did not show an increased risk of tumors or abnormal developmental parameters.	The nucleoside analogue with the most extensive clinical data on safety and efficacy during pregnancy. When feasible all antiretroviral regimens for the prevention of perinatal transmission should include AZT.

Table 14-3: Antiretrovirals (continued)

Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Stavudine (Zerit [®] , d4T)	Wt >60 kg dose: 40 mg po bid. Wt <60 kg dose: 30 mg po bid XR: wt >60kg 100 mg po qd. Wt <60 kg 75 mg po qd. Available as 15, 20, 30, 40 mg capsules; 1mg/mL for oral solution. New 100 mg extended release capsule (Zerit XR) Released early 2003.	Peripheral neuropathy (in 5–15% of patients); transaminase elevation (in 8% of patients); rare cases of lactic acidosis and severe hepatomegaly with steatosis, lipodystrophy, pancreatitis; rare cases of rapidly progressive ascending neuromuscular weakness	C	Studies in rhesus monkeys demonstrated 76% placental passage. Not teratogenic in rodents, but decreased sternal bone calcium. Carcinogenic studies not completed.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving combination of d4T and ddI as component of ARV therapy. No increase in birth defects noted in Antiretroviral Pregnancy Registry	Combination of d4T and ddI should be prescribed in pregnancy with caution, generally only when other NRTI drug combinations have failed or caused unacceptable toxicity/ side effects. Due to the antagonism between AZT and d4T, they should never be used together as a part of a HAART regimen.

Didanosine (Videx®, ddi)	<p>Wt >60 kg dose: 200 mg po bid or 400 mg po qd (tabs); 400 mg po qd (EC); 250 mg po bid or 500 mg po qd (powder).</p> <p>Wt <60 kg dose: 125 mg po bid or 250 mg po qd (tabs); 250 mg po qd (EC); or 167 mg po bid or 334 mg po qd (powder).</p> <p>Available as 25, 50, 100, 150 200 mg chewable buffered tablets; 100, 167, 250 mg buffered powder for oral solution; 125, 200, 250, or 400 mg enteric coated capsules</p> <p>Take 1/2 hr. before or 2 hr. after meals.</p>	GI intolerance (diarrhea, mouth sores), peripheral neuropathy in (5–12% of patients); pancreatitis (in 1–9% of patients with 6% of cases fatal); transaminase elevation; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	B	Not teratogenic or carcinogenic in rodent studies.	Placental passage approximately 50% PACTG 249 Phase I study showed that ddi was well tolerated by mother and fetus when started at weeks 26–36. (Wang, 1999).	GI side effects may limit use. The pediatric powder and EC tablet formulations are better tolerated (for every 4 g of ddi, mix with 200 cc of Maalox®).
Lamivudine (Epivir®, 3TC)	<p>150 mg po bid or 300 mg po qd</p> <p>Available as 150 mg, 300 mg tablets; 10 mg/mL oral solution; Combivir (ZDV 300 mg/3TC 150 mg); Trizivir (ZDV 300 mg/3TC 150 mg/ABC 300 mg); Epzicom: 3TC 300 mg/ABC 600 mg</p>	Generally very well tolerated; occasional headache; nausea; diarrhea; abdominal pain; and insomnia; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	C	Not teratogenic or carcinogenic in rodent studies.	Human studies demonstrated 100% placental passage. No increase in birth defects noted in Antiretroviral Pregnancy Registry.	Associated with reduction in perinatal transmission when combined with ZDV (PETRA clinical trial) in later pregnancy or labor plus 1 wk post partum to mother and newborn (see chapter VII Reproduction).
Emtricitabine (Emtriva®, FTC)	<p>200 mg po qd</p> <p>Available as 200 mg capsules</p> <p>Truvada: FTC 200 mg/ TDF 300 mg</p>	Occasional headache, diarrhea, nausea, rash, generally of mild to moderate severity; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	B	No increase in fetal malformations in mice and rabbits. Unknown if placental passage.	No data Placental passage unknown	Similar to 3TC. FTC is active against hepatitis B. Resistance profile is identical to 3TC. Little experience in pregnancy. Not indicated for treatment of chronic HBV infection and safety and efficacy not established in patients with HBV/HIV coinfection.

Table 14-3: Antiretrovirals (continued)						
Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Zalcitabine, (Hivid®), Didoxycytidine, ddC	0.75 mg po tid Available as 0.375, 0.75 mg tablets.	High incidence of peripheral neuropathy (17–31% of patients); stomatitis; aphthous ulcers; hepatitis; rare cases of pancreatitis reported; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	C	Studies in rhesus monkey demonstrated 30–50% placental passage. Carcinogenic in rodent studies resulting in thymic lymphoma. Teratogenic in rodent studies resulting in hydrocephalus at high dose (see Table 14-6 Drug-Drug Interactions).	Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses.	ddC is not a component in currently recommended ARV regimens; should not be used with ddI or d4T due to additive peripheral neuropathy and other toxicity.
Nucleotide Reverse Transcriptase Inhibitors (N-RTIs)						
Tenofovir DF (Viread®, TDF)	300 mg po qd Available as 300 mg capsules. Tuvada: TDF 300 mg/FTC 200 mg	Generally well tolerated. Most common side effects: Headache, diarrhea, nausea and vomiting. Asymptomatic elevation of CPK and transaminase levels in 10%. Neutropenia in 7% and increased amylase in 6%. Rare reports of renal insufficiency. Rare lactic acidosis with hepatic steatosis	B	Gravid Rhesus monkeys study showed no fetal malformations; however reduction in body weight, insulin-like growth factor, and fetal bone porosity was observed (25 times AUC with human therapeutic dosing) (Tarantal, 2004). Placental passage demonstrated in rats and monkeys.	No data Placental passage unknown	Should be taken with food. Data from monkeys support the use of tenofovir DF for post-exposure prophylaxis.
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)						
Efavirenz (Sustiva®, EFV)	600 mg po q hs Available as 50, 100, 200 mg capsules or 600 mg tablets Take on empty stomach.	Morbiliform rash in 15–27% of patients with 1–2% requiring discontinuation; one case of Stevens-Johnson syndrome reported; CNS effects (confusion, depersonalization, abnormal dreams) usually seen in up to 52% of patients and resolve in 2–4 wk; transaminase elevation in 2–3% of patients, hyperlipidemia.	D	Placental passage of 100% seen in cynomolgus monkeys, rats, and rabbits. Teratogenicity demonstrated in cynomolgus monkeys resulting in anencephaly, anophthalmia, microphthalmia. Increase in hepatocellular adenomas and carcinomas and pulmonary alveolar bronchiolar adenomas in female mice at exposures 1.7 times human therapeutic doses.	4 cases of central nervous system defects with 1st trimester exposure; birth defects observed in 3 of 88 live births with 1st trimester exposure and 0 of 11 births with exposure later in pregnancy (Antiretroviral Pregnancy Registry)	Efavirenz should be avoided during pregnancy (particularly early pregnancy) and in women trying to conceive or not using effective contraception.

<p>Nevirapine (Viramune[®], NV/P)</p>	<p>200 mg po qd for 14 days then 200 mg po bid Available as 200 mg tablets or 50 mg/5mL oral suspension.</p>	<p>Rash in 17% of patients (7% discontinued due to rash, many patients require hospitalization) Stevens-Johnson syndrome reported; transaminase elevation; severe hepatitis; fever, nausea; headache. Women may be at increased risk of rash and liver toxicity, especially with CD4 >250 cells/mm³ (Mazhude, 2002; Bersoff-Matdra, 2001; Stern, 2002)</p>	<p>C</p>	<p>Not teratogenic in rodent studies. No data on carcinogenicity.</p>	<p>Nevirapine-associated hepatotoxicity (including hepatic failure) reported in pregnancy (Knutdson, 2003; Lyons, 2003; Langlet, 2000). These toxicities have not been reported in women or infants receiving HIVNET 012 two-dose regimen for prevention of perinatal transmission.</p>	<p>In HIVNET 012 administration of single-dose nevirapine given to mother during labor and to infants within 72 hr of delivery was compared with administration of AZT during labor and AZT for 7 days to infants. The 18 mo data showed that 26% of infants in the AZT and 16% of infants in the nevirapine arm were infected, a 41% reduction with nevirapine (Jackson, 2003). Monitor LFTs q 2wk x 1st 4 wk, then q mo x 4 mo; then q 1-3 mo. Use with caution as part of combination regimen in pregnant women for purpose of prevention of perinatal transmission. Contraindicated in women with CD4 counts > 250/mm³.</p>
<p>Delavirdine (Rescriptor[®], DLV)</p>	<p>400 mg po tid Available as 100 mg or 200 mg tablets</p>	<p>Rash in 18% of patients (4.3% discontinued due to rash, usually does not require discontinuation unless mucous membrane involvement); rare erythema multiforme or Stevens Johnson syndrome; headache; increased transaminase levels (see Table 14-6 Drug-Drug Interactions)</p>	<p>C</p>	<p>Placental passage of 4-15% in late-term rodent studies. Teratogenic in rodent studies resulting in ventricular septal defects; Maternal toxicity, embryotoxicity and decreased pup survival seen with doses five times the human dose. No data on carcinogenicity.</p>	<p>Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses.</p>	<p>Due to the availability of more potent NNRITIs (e.g., nevirapine) use of delavirdine is generally not recommended.</p>

Table 14-3: Antiretrovirals (continued)						
Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Protease Inhibitors (PIs)						
Lopinavir/Ritonavir (LPV/r) (Kaletra®)	Lopinavir 400 mg/ritonavir 100 mg (3 capsules or 5 mL) twice daily with food Available as 133.33 mg lopinavir/33.3 mg ritonavir capsules; 80 mg lopinavir/20 mg ritonavir per mL oral solution.	Diarrhea in 13.8–23.8% of patients; nausea, vomiting, abdominal pain, asthenia, headache and rash reported. Class adverse events such as hyperlipidemia, fat redistribution and hyperglycemia are possible.	C	No treatment-related malformations in animal studies. No embryonic or fetal development toxicities seen in rabbits. Delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses.	No human data available. Preliminary data indicate minimal placental passage of ritonavir; unknown for lopinavir	
Ritonavir (Norvir®, RTV)	600 mg po bid (when used as sole PI), but Ritonavir now used at lower doses with other PIs as pharmacologic enhancer or booster. (See Table 14-6) Available as 100 mg capsules; 600 mg/7.5 mL oral solution. Take with food, if possible (may improve tolerability)	Severe GI intolerance (nausea, vomiting, diarrhea; abdominal pain, common with 600 mg bid dosing); taste perversion; asthenia; circumoral and peripheral paresthesias; pancreatitis; lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation (increased incidence seen with hepatitis B and C coinfection); elevated CPK and uric acid.	B	Not teratogenic but slight increase in cryptorchidism reported in rodent studies. Increase in liver adenomas and carcinomas in male mice (4 times human therapeutic dose). No carcinogenic effects in rats.	Minimal transplacental passage.	Use may be limited by GI intolerance at full dose. Better tolerated when used as booster with another PI (RTV 100 mg bid and 2nd PI).
Saquinavir, SQV (Invirase®, INV, hard gel capsules; Fortovase®, FTV soft gel capsules)	INV or FTV 400 mg po bid with ritonavir 400 mg po bid. Invirase not recommended as sole PI; Fortovase 1200 mg po tid when used alone (see Table 14-6) Available as: Invirase 200 mg capsules; Invirase 500 mg tablets; Fortovase 200 mg capsules; take Fortovase with large meal.	GI intolerance (nausea, diarrhea, abdominal pain); lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation.	B	Placental passage in rat and rabbit is minimal. No teratogenicity reported in rodent studies. No data on carcinogenicity.	Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses. Minimal transplacental passage.	Invirase 1,000 mg RTV/100 mg bid is the preferred dosing regimen due to better pharmacokinetics and tolerance.

<p>Indinavir, IDV (Crixivan®)</p>	<p>800 mg po tid (see Table 14-6) 400/400 mg or 800/100 mg or 800/200 mg IDV/RTV bid + EFV 600 mg Available as 200, 333, 400 mg capsules. Take 1 hr before or 2 hr after meals; may take with low fat meals</p>	<p>Nephrotoxicity +/- hematuria in 5-15% of patients (48 oz of fluid recommended to decrease incidence); indirect hyperbilirubinemia (\geq 2.5 mg/dL in 10-15% of patients); lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation.</p>	<p>C</p>	<p>Placental passage is significant in rats, but low in rabbits. Not teratogenic in rodent studies (but extra ribs have been reported). Incidence of hyperbilirubinemia in neonatal Rhesus monkeys increased with neonatal but not in utero exposure. No data on carcinogenicity.</p>	<p>Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses. Minimal transplacental passage.</p>	<p>Due to theoretical concerns of hyperbilirubinemia and nephrotoxicity in newborns, indinavir should be avoided during late pregnancy.</p>
<p>Nelfinavir, NFV (Viracept®)</p>	<p>750 mg po tid or 1250 mg po bid Available as 250 mg tablets; 625 mg tablets; FDA-approved 50 mg/g oral powder. Take with increased fat meal</p>	<p>Diarrhea (treatable with Imodium or pancrealipase); lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation.</p>	<p>B</p>	<p>No increase in birth defects noted in Antiretroviral Pregnancy Registry. Minimal transplacental passage.</p>	<p>The combination of AZT, 3TC, and nelfinavir is widely used and has been well tolerated during pregnancy.</p>	<p>Use with caution in patient with sulfa allergy</p>
<p>Fosamprenavir, fos APV (Lexiva®) (prodrug of amprenavir)</p>	<p>1400 mg po bid with RTV: 1400 mg Lexiva/200 mg RTV po qd (not recommended for PI-experienced patients) or 700 mg Lexiva/100 mg RTV po bid Available as 700 mg tablets</p>	<p>GI intolerance most common (nausea, vomiting, diarrhea); headache; rash (in 19% of patients), usually mild-moderate but Stevens Johnson syndrome reported; lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation.</p>	<p>C</p>	<p>Increased abortions in rabbits, reduction in pup survival and body weight in rats. Placental passage unknown</p>	<p>No data</p>	<p>Use with caution in patient with sulfa allergy</p>

Table 14-3: Antiretrovirals (continued)						
Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Amprenavir, APV (Agenerase®)	1400 mg bid (oral solution); <50 kg: APV 20 mg/kg bid (max 2800 mg/day oral solution). APV and RTV oral solutions should not be co-administered due to competition of metabolic pathway of the two vehicles. Available as 15 mg/mL oral solution; also as 50 mg capsules, but capsules and solution NOT interchangeable on mg-per-mg basis. Capsules rarely used because of high pill burden—APV largely replaced by fAPV.	GI intolerance most common (nausea, vomiting, diarrhea); rash (in 20–27% of patients). Stevens Johnson syndrome (in approximately 1%); paresthesias; headache; lipodystrophy syndrome; hyperlipidemia; transaminase elevation	C	Increased incidence benign and malignant liver tumors in male rodents at exposures 2- to 4-fold higher than human dosing. Increased abortions in rabbits and increased incidence of deficient bone ossification in rabbits and rats at exposures lower than recommended human dosing. Reduced body weight in rodent offspring at exposures 2-fold higher than human dosing.	Placental passage unknown. No data in use of APV in pregnant women	Use of oral solution contraindicated in pregnant women, patients with renal or hepatic failure, or those treated with disulfiram or metronidazole because of inability to adequately metabolize propylene glycol base. Use with caution in patients with sulfa allergy.
Atazanavir, ATV (Reyataz®)	400 mg qd with food. With RTV: 300 mg qd/RTV 100 mg qd Available as 100 mg, 150 mg, 200 mg capsules.	Common: Reversible benign hyperbilirubinemia (grade 3–4 occurring in 35–47% of patients), jaundice, and scleral icterus. Occ: nausea, vomiting, abdominal pain, lipodystrophy, rash, headache, and mild transaminase elevation minimal impact on serum lipids.	B	No teratogenic effects in rats or rabbits	No data Placental passage unknown	Avoid near term due to the potential exacerbation of physiologic hyperbilirubinemia in the neonate.

Fusion Inhibitors	<p>Enfuvirtide (Fuzeon® , T-20)</p>	<p>90 mg (1ml) SQ q12h into upper arm, anterior thigh or abdomen with each injection given at a site different from the preceding injection site</p> <p>Each single-use vial contains 108 mg of enfuvirtide to be reconstituted with 1.1 mL of sterile water for injection with delivery of approx. 90 mg/1ml</p>	<p>Common ADR: local site reaction (grade 3 or 4) including pain (9%), erythema (32%), pruritus (4%), induration (57%), and nodules or cysts (26%) (with 3% requiring d/c).</p> <p>Occ: Bacterial pneumonia (reported in 4.68 events vs. 0.61 events per 100 pts-years).</p> <p>Hypersensitivity reaction (<1%): symptoms may include rash, fever, nausea, vomiting, chills, hypotension, elevated transaminases – may recur on rechallenge.</p>	<p>B</p>	<p>Not teratogenic in animal studies</p>	<p>No data Placental passage unknown</p>	<p>A clear advantage of enfuvirtide is the lack of cross-resistance with currently available antiretrovirals, however, as with other antiretrovirals and as seen in clinical trials, salvage therapy with enfuvirtide is only as good as the background regimen with which it is combined.</p>
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Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients						
Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Trimethoprim-sulfamethoxazole, TMP-SMX (Bactrim [®] , Septra [®] , Cotrim [®] , Sulfatrim [®])	PCP prophylaxis: 1 DS po qd, 1 SS po qd, 1 DS po tid PCP treatment: 5 mg/kg (based on the trimethoprim component) po or IV q 8 h	Fever, leukopenia; rash and/or GI intolerance (in 25–50% of HIV-infected persons, most patients tolerate readministration of lower dose after 2 wk of discontinuation); megaloblastic anemia, neutropenia, thrombocytopenia. Hematologic toxicity increased with folate depletion and high doses—treat with leucovorin 3–15 mg qd x 3 days. Reversible hyperkalemia (with high doses); photosensitivity; renal failure; hemolytic anemia with G6PD deficiency; hepatitis including cholestatic jaundice; thrush; erythema multiforme; Stevens Johnson syndrome.	C	Cleft palate has been observed in some animals.	In a surveillance study of Michigan Medicaid recipients, 2296 exposures to trimethoprim/sulfamethoxazole in the first trimester resulted in a 5.5% incidence of birth defects. This incidence suggests an association between the drug and congenital defects (cardiovascular); however, other factors such as mother's disease, concurrent drug use, and chance may be involved (Briggs, 1998).	Most authorities consider sulfonamides safe in pregnancy. Theoretical risk of kernicterus in the neonate if administered near term.
Azithromycin (Zithromax [®])	MAC prophylaxis: 1200 mg po q week; MAC treatment: 500 mg or 600 mg po qd (in combination with ethambutol +/- rifabutin)	GI intolerance (4%); diarrhea; nausea; abdominal pain; vaginitis; reversible hearing loss (more common with 500 mg x 30–90 days); increased transaminases	B	Animal studies show no harm to the fetus.	Azithromycin and erythromycin were compared for the treatment of chlamydia in pregnancy. The authors recommended using azithromycin due to efficacy and better tolerability. Effect on the fetus was not evaluated (Adair, 1998).	The benefit of azithromycin administration for MAC prophylaxis or treatment outweighs potential risk of congenital malformations.

Clarithromycin (Biaxin®)	MAC prophylaxis: 500 mg po bid MAC treatment: 500 mg po bid (in combination with ethambutol and/or rifabutin.)	GI intolerance (4%); diarrhea; headache; reversible dose-related hearing loss; taste disturbances	C	Studies in monkeys show growth retardation, cleft palate, and embryonic loss	The Teratogen Information Service in Philadelphia reported that the outcome of 34 first or second trimester exposures were similar to those expected in the nonexposed population. The 122 pregnancies exposed to clarithromycin in the 1st trimester did not have increased major or minor malformations when compared with matched controls. Incidence of spontaneous abortion was higher in clarithromycin-exposed group compared with controls (14% vs 7%) (p=.04) (Schick, 1996).	Should be used with caution during pregnancy because of teratogenicity in animals.
Pyrazinamide	15 mg/kg/day for latent TB (2.0 g max); 20-25 mg/kg/day for active TB (2.0 g max); 30-50 mg/kg 2-3 times/wk (3.0-4.0 g max) for intermittent therapy	Nongouty polyarthralgia; asymptomatic hyperurcemia; hepatitis (dose related, frequency not increased when given with INH or rifampin, rarely serious); GI intolerance; gout	C	No animal data available.	No human data available.	Due to insufficient data pyrazinamide should generally be avoided in pregnancy. INH, rifampin, and ethambutol are recommended as first-line agents for treatment of drug-sensitive TB during pregnancy.

Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients (continued)						
Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Isoniazid (INH, Tubizid [®] , Nydrazid [®])	300 mg po qd	Age-related hepatitis: <20 yr old-11/35 yr old-6%/45 yr old-11 %/ 55 yr old-18%; drug should be discontinued if transaminase levels are >3-5 x normal limits; allergic reactions; fever; peripheral neuropathy (especially with preexisting alcoholism, diabetes, pregnancy, malnutrition); glossitis	C	Animal studies show embryocidal effect, but not teratogenic.	Retrospective analysis of more than 4900 exposures to INH did not show increased fetal malformations. (Snider, 1980).	The American Academy of Pediatrics and the American Thoracic Society recommend that pregnant women with a positive PPD should receive INH if HIV-positive, have had recent TB contact, or have an X-ray showing old TB; start after 1st trimester if possible.
Rifampin (Rifadin)	10 mg/kg/day (600 mg/day max) for TB prophylaxis or active TB; 600 mg 2-3x/wk with DOT	Orange discoloration of urine, tears, sweat; hepatitis—usually cholestatic changes during first month (frequency not increased when given with INH); jaundice (usually reversible with dose reduction and/or continued use); GI intolerance; hypersensitivity reactions; flu-like syndrome with intermittent use characterized by dyspnea, wheezing	C	Animal data show congenital malformations—cleft palate, spina bifida, and embryotoxicity.	Several reviews have evaluated treatment of TB in pregnancy. All concluded that rifampin was not teratogenic and recommended use of the drug with INH and ethambutol if necessary (American Thoracic Society, 1986).	The American Thoracic Society recommends rifampin in combination with INH and ethambutol if treatment for drug-sensitive TB is needed during pregnancy. Many drug interactions. Because of potential increased risk of hemorrhagic disease in neonates, prophylactic vitamin K 10 mg should be administered to the neonate.
Rifabutin (Mycobutin [®])	300 mg po qd (dose is decreased to 150 mg qd or 300 mg 3x/wk when used with indinavir, nelfinavir, amprenavir; 150 qod with RTV or LPV/r; 450 mg qd or 600 mg 3x/wk with EFV; 300 mg 3x/wk with NVP; 150 mg 3x/wk with SQV/RTV. Not recommended with DLV or SQV alone (Fortovase).	Orange discoloration of urine, tears, sweat; uveitis with eye pain, photophobia, redness and blurred vision—usually seen with high doses (600 mg/day or concurrent use of fluconazole or clarithromycin); hepatitis; GI intolerance; allergic reactions	B	Animal data showed skeletal abnormalities.	No human data available.	Experience with rifabutin in pregnancy is limited. Many drug interactions with dose modifications recommended. (See Drug Interactions Table 14-6)

Ethambutol (Myambutol®)	15-25 mg/kg po qd (1.6 g max); 35-50 mg/kg 2x/wk (4.0 g max); 25-30 mg/kg 3x/wk (2.4 g max)	Optic neuritis (decreased acuity, reduced color discrimination, constricted fields, scotomata— dose related and infrequent with 15 mg/kg); GI intolerance; confusion; precipitation of acute gout.	C	Teratogenic in animal studies.	No congenital defects have been reported. In 38 patients exposed to ethambutol during pregnancy, no increased risk of birth defects observed (including embryonic optic nerve toxicity). (Brobowitz, 1974).	The CDC considers ethambutol safe in pregnancy.
Atovaquone (Mepron®)	750 mg po bid for PCP treatment or prophylaxis; 1500 mg po qd for PCP prophylaxis; 1500 mg po bid for toxoplasmosis treatment (with pyrimethamine or sulfadiazine)	GI intolerance (nausea, vomiting, diarrhea); headache; rash. 7-9% required discontinuation due to side effects	C	Not teratogenic in rat studies. Maternal and fetal toxicities (decreased fetal weight, early fetal resorption and post- implantation fetal loss) reported in rabbits.	No human data available.	Alternative regimen for PCP prophylaxis and treatment due to high cost, poor GI tolerance, and lack of safety data in pregnancy. Preferred regimens for PCP prophylaxis and treatment include trimethoprim/ sulfamethoxazole and dapsone. Third-line treatment and prophylaxis for toxoplasmosis
Hydroxyurea (Hydrea®, Droxia®)	500 mg po bid	Dose-dependent leukopenia, anemia and thrombocytopenia; GI intolerance (N/V/D, constipation), stomatitis; rash; alopecia	D	Hydroxyurea is teratogenic in several animal studies; anomalies include nervous system, palate, skeleton, neural tube and cardiac defects.	Eight case reports of hydroxyurea exposure during pregnancy did not demonstrate teratogenicity, however, the data are too limited to draw any conclusions (Briggs, 1998).	Contraindicated due to high incidence of teratogenicity in animal studies and limited human experience. No longer recommended as part of HAART.

Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Amphotericin B (Fungizone®)	0.5–1.2 mg/kg IV qd depending on specific condition. 0.7 mg/kg for cryptococcal meningitis	40–50% incidence of fever and chills; 30–40% incidence of renal tubular acidosis—dose dependent and reversible in absence of prior renal damage and dose <3 g (reduced with hydration and sodium loading); 20% incidence of hypokalemia; hypomagnesemia; anemia; phlebitis and pain at infusion site; hypotension; nausea; vomiting; metallic taste; headache	B	Animal studies demonstrated amphotericin to be harmless in pregnancy.	The Collaborative Perinatal Project identified 9 1st trimester exposures to amphotericin and found no adverse fetal effect (Briggs, 1998).	Can be used in pregnancy for the treatment of serious fungal infections.
Flucytosine (Ancobon®)	25 mg/kg q 6 h (monitor levels – goal 50–100 mcg/mL at steady state)	GI intolerance (N/V/D); marrow suppression with leukopenia or thrombocytopenia (dose related with renal failure, serum concentration >100 mg/mL or concurrent amphotericin); confusion; rash; hepatitis (dose related); enterocolitis; headache; photosensitivity reaction; peripheral neuropathy	C	Teratogenicity reported in animal studies.	Three case reports of second and third trimester exposure resulted in no defects in the newborns, however, no conclusion can be drawn (Briggs, 1998).	4% of administered dose converts to 5FU in the fungal organism. 5FU has been associated with congenital malformations. Use with amphotericin for the treatment of cryptococcal meningitis may reduce relapse rates but does not reduce mortality or speed recovery (van der Horst, 1997). Use in pregnancy only if benefits outweigh potential risks.
Nystatin	500,000 units 5x/day (oral thrush)	GI intolerance (N/V/D)	B	No animal data	489 first trimester exposures to nystatin were observed in a Michigan Medicaid recipients surveillance study. No association between nystatin and congenital defects was observed (Briggs, 1998).	Due to low systemic absorption nystatin may be used in the management of thrush during pregnancy.

Clotrimazole	10 mg troches 5x/day (oral thrush); 100 mg intravaginal tablets bid x 3 day or qd x 7 day; 1 applicator (5g) vaginal cream q hs x 7-14 day (Candida vaginitis)	GI intolerance (NAV); transaminase elevation. Topical treatment (rare): burning, erythema, pruritus	C	Embryotoxic in rats and mice. Not teratogenic in mice, rabbits, and rats.	2624 exposures to clotrimazole (vaginal use) were observed in the first trimester in a Michigan Medicaid recipients surveillance study. No association between clotrimazole and congenital defects were observed (Briggs, 1998)	Due to minimal systemic absorption nystatin is preferred over clotrimazole in the management of thrush during pregnancy. Vaginal use in 1st trimester should be on risk/benefit basis
Fluconazole (Diflucan®)	C. esophagitis: 200-800 mg/day; 150 mg po x 1 for Candida vaginitis; 150 mg po q wk for multiple recurrences Cryptococcal infection: 200-400 mg/day.	Dose-related GI intolerance including bloating, nausea, vomiting, pain, anorexia, weight loss (8-11% with dose <400 mg/day; 30% with dose >400 mg/day); reversible alopecia in 10-20% of patients receiving 400 mg/day for 3 months; transaminase elevation to >8 x normal; rare cases of fatal hepatitis and Stevens Johnson syndrome	C	Teratogenic in animal studies.	Craniofacial, limb and cardiac defects have been reported in 4 infants with 1st trimester exposure to high-dose fluconazole (Pursley, 1996; Aleck, 1997). Anomalies do not appear to be increased among infants born after exposure to single dose fluconazole in the 1st trimester (Mastroiacovo, 1996; Sorenson, 1999).	Contraindicated in the 1st trimester due to potential for teratogenicity. Use topical agents in treatment of C. vaginitis in pregnancy.
Itraconazole (Sporanox®)	100-400 mg po qd, depending on specific condition	Headache; GI intolerance—nausea (10%) and vomiting; rash (8%); hypokalemia reported with high doses (600 mg per day); adrenal insufficiency; impotence; gynecomastia; leg edema; transaminase elevation, rare cases of fatal hepatitis	C	Teratogenic in rats and mice (encephaloceles, macroglossia, and skeletal malformation).	FDA has received 14 case reports of malformations following use of itraconazole, 4 were limb defects. However in another report of 80 exposures to single-dose itraconazole or fluconazole no malformations were reported (Rosa, 1996).	Contraindicated in the 1st trimester due to potential for teratogenicity.

Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients (continued)						
Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Voriconazole (Vfend®)	IV: 6 mg/kg IV q12h x 2 doses (load), then 3-4 mg/kg IV q12h infused over 1-2 hours. PO: (>40 kg) 200 mg po tid x 1 da (load), then 200-300 mg po bid; (<40 kg) 100 mg po q12h, may be increased to 150 mg po q12h (administer on an empty stomach, avoid high fat food!)	Common: Visual disturbances ("abnormal vision" described as blurriness, color changes, and enhanced vision) seen in 20.6% of pts but less than <1% required discontinuation. Occ: Inc.LFTs (13%) and alk phos required d/c in 4-8%, hallucination (4.3%), rash (6%), nausea/vomiting.	D	Teratogenic in animal studies	No data	Avoid in pregnancy. Do not use with EFV or RTV (400 mg bid)
Pyrimethamine (Daraprim®)	Acute treatment of toxoplasmosis: Pyrimethamine 100-200 mg loading dose, then 50-75 mg po qd, in combination with sulfadiazine 4-6 g po per day in four divided doses for at least 6 wk, plus leucovorin 10-20 mg po qd; Toxoplasmosis maintenance dose: After acute treatment, pyrimethamine 25-50 mg po qd, plus sulfadiazine 2-4 g po per day in four divided doses, plus leucovorin 10-25 mg po qd Toxoplasmosis prophylaxis: Pyrimethamine 50-75 mg po q wk, in combination with dapsone, plus leucovorin 25 mg po q wk	Folic acid deficiency with megaloblastic anemia and pancytopenia (dose-related and reversed with leucovorin); allergic reactions; GI intolerance (nausea, anorexia, vomiting)	C	Teratogenic in animal studies.	No adverse fetal effects were reported in two reviews of treatment of toxoplasmosis in pregnancy (Matsui, 1994; Wong, 1994).	If pyrimethamine is used during pregnancy, concomitant leucovorin (folic acid) supplementation (25 mg/day) is recommended, especially during the 1st trimester, to prevent hematologic toxicity.

Sulfadiazine	<p>Acute treatment of toxoplasmosis: Sulfadiazine 4–6 g po per day in four divided doses, in combination with pyrimethamine 50–75 mg po qd for at least 6 wk, plus leucovorin 10–20 mg po qd</p> <p>Toxoplasmosis maintenance dose: After acute treatment, sulfadiazine 2–4 g po qd in four divided doses, plus-pyrimethamine 25–50 mg po qd, plus leucovorin 10–25 mg po qd</p>	<p>Allergic reactions—rash, pruritus; crystalluria with renal damage, urolithiasis and oliguria; GI intolerance; photosensitivity; hepatitis; fever; periarthritis nodosum; Stevens Johnson syndrome; serum sickness</p>	C	<p>At high doses, animals developed cleft palate and bone abnormalities.</p>	<p>Extensive use in humans without complication except one case of agranulocytosis that was possibly associated (Briggs, 1998).</p>	<p>Theoretical risk of kernicterus in the neonate if administered near term.</p>
Aerosolized pentamidine	<p>PCP prophylaxis—300 mg nebulized q mo</p>	<p>Asthma reaction reported in 2–5% of patients; cough seen in 30% of patients</p>	C	<p>Systemic pentamidine is embryotoxic but not teratogenic in rats and rabbits</p>	<p>Aerosolized pentamidine given to 15 women during the 2nd and 3rd trimesters did not alter pregnancy outcome or cause fetal harm (Nanda, 1992).</p>	<p>CDC and manufacturer advise against the use of pentamidine during pregnancy due to the lack of data; however, aerosolized pentamidine may be considered safe due to minimal systemic absorption (Kaplan, 1995). Concerns have been raised about adequate drug distribution during pregnancy due to restrictive changes with an enlarged uterus.</p>

Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients (continued)						
Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Intravenous pentamidine	PCP treatment—3–4 mg/kg IV qd	Nephrotoxicity—seen in 25% (usually reversible with discontinuation); hypotension (administer IV over 60 min to decrease risk); hypoglycemia—seen in 5–10% (usually occurs after 5 days of treatment including past treatment, may last days or weeks) may lead to insulin-dependent diabetes; marrow suppression (leukopenia; thrombocytopenia); GI intolerance with nausea, vomiting, abdominal pain, anorexia, and bad taste; transaminase elevation; pancreatitis; toxic epidermal necrolysis; fever	C	Not teratogenic in rat and rabbit studies, however, has been shown to be embryocidal.	Spontaneous abortion reported, but causal relationship has not been established.	Use in pregnancy only if benefits outweigh potential risks. Due to the toxicity profile Bactrim or clindamycin/primaquine is preferred
Primaquine	15–30 mg (base) po qd (in combination with clindamycin for the treatment of PCP)	Hemolytic anemia (G6PD deficiency); methemoglobinemia; GI intolerance; neutropenia	C	No animal studies available.	No human data available.	Theoretical concern is hemolytic anemia in G6PD-deficient fetus. Should screen for G6PD deficiency in mother before use.
Albendazole (Albenza®)	400 mg po bid x 3 weeks for microsporidiosis	Diarrhea; abdominal pain; transaminase elevation; hepatotoxicity; reversible pancytopenia and neutropenia	C	Teratogenic and embryotoxic in rodent and rabbit studies.	No human data available.	Contraindicated in pregnancy.

Dapsone	100 mg po qd (PCP prophylaxis). 100 mg po qd plus trimethoprim x 3 wk (PCP treatment). 50 mg po qd or 200 mg q wk plus leucovorin and pyrimethamine (PCP + toxoplasmosis prophylaxis).	Rash; blood dyscrasias including methemoglobinemia and sulfhemoglobinemia and hemolytic anemia (with or without G6PD deficiency); nephrotic syndrome; fever, nausea, anorexia; blurred vision; photosensitivity; tinnitus; insomnia; irritability; headache (transient); rare "sulfone syndrome"—fever, exfoliative dermatitis, jaundice, adenopathy, methemoglobinemia and anemia	C	No animal teratogenicity studies conducted. Carcinogenic risk in rats.	No adverse effects reported. (Luzzi, 1993).	Dapsone has been used extensively in the treatment of malaria and for chemoprophylaxis of leprosy without producing major fetotoxicity or causing birth defects. Recommend screening for G6PD deficiency in mother before use.
Acyclovir (Zovirax®)	5–10 mg/kg IV q 8 h; 200–800 mg po x 3–5 times per day	GI intolerance (nausea and vomiting; diarrhea); renal toxicity (especially with rapid IV infusion); dizziness; transaminase elevation; itching, headache. Toxicities are infrequent.	C	Not teratogenic but potential to cause chromosomal damage at high doses.	Birth defects reported in 23 of 1002 exposures; however, this was not statistically different from the expected rate. (Glaxo Wellcome, 1996)	Acyclovir is 1st choice for therapy of HSV infections in pregnancy and should be used for VZV if parenteral therapy indicated.
Valacyclovir (Valtrex®)	1000 mg po tid (for zoster); 500 mg po bid (for recurrent HSV); 500–1000 mg po qd (for HSV suppression)	GI intolerance—nausea, vomiting, diarrhea; headache; constipation	B	Not teratogenic in animal studies.	No human data available but likely to be similar to acyclovir.	Recommendation similar to acyclovir since valacyclovir is converted to acyclovir. Valacyclovir is preferred treatment for chicken pox in pregnancy.
Famciclovir (Famvir®)	500 mg po q 8 h (for zoster); 125–250 mg q 12 h (recurrent HSV and HSV suppression)	Headache; nausea; fatigue	B	Carcinogenic, but not embryotoxic or teratogenic in animal studies.	No human data.	Until more data are available, acyclovir is 1st choice in pregnancy.

Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients (continued)						
Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Ganciclovir (Cytovene®)	CMV retinitis: Induction: 5 mg/kg IV q12h x 2 wk then Maintenance: 5 mg/kg IV qd	Neutropenia (ANC <500 in 15–20%; usually early in treatment and responds within 3–7 days to drug holiday or to G-CSF); thrombocytopenia (platelet count <20,000 in 10%, reversible); Monitor CBC 2–3 times/wk and discontinue if ANC <500-750 or platelet count <25,000; anemia; fever; rash; CNS—headache, seizures, confusion, changes in mental status; abnormal liver function tests (2–3%)	C	Teratogenic (in concentrations comparable to those achieved in humans) and embryotoxic: cleft palate, anophthalmia, hydrocephalus, aplastic kidney and pancreas (rabbits); growth retardation.	No human data.	Based on limited data and weighing toxicity of the various drugs, ganciclovir is 1st choice for treatment during pregnancy; for retinal disease intraocular implants or intravitreal injections should be considered to limit fetal exposure to systemically administered drugs. Monitor fetus with fetal movement counts in 3rd trimester and periodic ultrasound after 20 wk gestation for evidence of significant anemia, manifest as hydrops fetalis. Evaluate newborn for bone marrow suppression.
Valganciclovir (Valcyte®)	Induction: 900 mg po bid w/ food x 3 weeks; Maintenance: 900 mg po qd.	Diarrhea; nausea; fever; bone marrow suppression; LFT elevation.	C	Teratogenic (in concentrations comparable to those achieved in humans) and embryotoxic: cleft palate, anophthalmia, hydrocephalus, aplastic kidney and pancreas (rabbits); growth retardation.	No data	Concerns expected to be same as with ganciclovir. Monitor fetus with fetal movement counts in 3rd trimester and periodic ultrasounds after 20 wk gestation for evidence of significant anemia, manifest as hydrop fetalis. Evaluate newborn for bone marrow suppression.

<p>Cidofovir (Vistae®)</p>	<p>CMV retinitis Induction: 5 mg/kg q week x 2 weeks then q2 weeks (give concurrently with probenecid and hydration). Probenecid Regimen: 2 g given 3 hours prior to cidofovir and 1 g given at 2 and 8 hours after infusion (total 4 g); >1L normal saline 1 or 2 hrs immediately before cidofovir infusion.</p>	<p>Nephrotoxicity—dose dependent, reduced with hydration and probenecid. (Side effect of probenecid includes chills, fever, headache, rash and nausea in 30–50% of patients); uveitis; GI intolerance; neutropenia; metabolic acidosis</p>	<p>C</p>	<p>Embryotoxic and teratogenic (meningoencephalic, skeletal abnormalities) in rats and rabbits.</p>	<p>No human data available.</p>	<p>Ganciclovir is 1st choice for treatment during pregnancy. Use only if benefits appear to outweigh potential risks.</p>
<p>Foscarnet (Foscavir®)</p>	<p>CMV retinitis Induction: 60 mg/kg IV q 8 hr or 90 mg/kg IV q12hr x 14 day. Maintenance: 90–120 mg/kg IV qd. Acyclovir-resistant HSV or VZV: 40 mg/kg IV q 8 h or 60 mg/kg IV q 12 h x 3 wk</p>	<p>Renal failure (usually reversible; 30% get serum creatine (Cr) >2 mg/dL; (monitor Cr 1–3 times/wk and discontinue if Cr >2.9 mg/dL); mineral and electrolyte changes—reduced magnesium, phosphorus, ionized calcium, potassium (monitor serum electrolytes 1–2 times/wk and monitor for symptoms of paresthesias); seizures (10%); fever, GI intolerance; anemia; genital ulceration; neuropathy</p>	<p>C</p>	<p>Skeletal malformation or variation in animal studies.</p>	<p>No human data available.</p>	<p>Due to high incidence of nephrotoxicity, monitoring of aminioic fluid volume by ultrasound weekly after 20 wk gestation to detect oligohydramnios is recommended. Electrolyte and renal function should be evaluated in neonate if therapy given near delivery.</p>
<p>Ribavirin (Rebetrol®)</p>	<p>Treatment of hepatitis C (in combination with interferon): <75 kg—400 mg q am and 600 mg q pm. >75 kg—600 mg bid</p>	<p>Hemolytic anemia (mean hgb decrease is 3 g/dL); leukopenia; hyperbilirubinemia; increased uric acid.</p>	<p>X</p>	<p>Ribavirin has been demonstrated teratogenic in low doses in multiple animal species (limb abnormalities, craniofacial defects, exencephaly, anophthalmia) in rodents (and in all animals tested), but not in primates when given during the first trimester.</p>	<p>No data available.</p>	<p>Use of ribavirin contraindicated during pregnancy and in male partners of pregnant women.</p>

Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients (continued)						
Drug Name	Dosing	Adverse Effects	FDA Class	Animal Data	Human Experience in Pregnancy	Comments
Interferon (Roferon [®] , Intron [®])	Treatment of hepatitis C (in combination with ribavirin): 3 million units 3 x/week. IM or SQ. Also used at higher doses for treatment of hepatitis B and Kaposi's sarcoma	Flu-like syndrome; GI intolerance (NV/D, anorexia); CNS toxicity (delirium; obtundation and depression); neutropenia, anemia, thrombocytopenia, increased transaminase, rash; alopecia; proteinuria	C	Abortifacient in rhesus monkeys when given 20-500 times the human dose.	Limited case reports of interferon exposure during pregnancy do not suggest an association with birth defects; however, data are too limited to draw a conclusion.	Since goal of treatment of HCV is to prevent long-term sequelae, treatment in pregnancy rarely indicated and generally not recommended.
Peg-interferon (Peg-Intron [®] [alfa-2B]/ Pegasys [®] [alfa-2A])	Peg-Intron: 1mcg/kg SC q week (with ribavirin). [Dose reduced to 0.5 mcg/kg recommended for ANC <750 or plt <50k and DIC if ANC <500 or plt <25K]. Pegasys: 180mcg SC qweek (with ribavirin) [dose reduce with heme toxicity]. Peg-interferon alfa-2A or alfa-2B and ribavirin is treatment of choice for HCV.	Common: Flu-like symptoms, headache, dizziness, fatigue, fever, rigor, injection site inflammation, depression (29%), insomnia, alopecia, GI (abd. pain, anorexia, NV/D). Occasional: Thrombocytopenia, neutropenia, hypo and hyperthyroidism, LFTs elevation.	C	Abortifacient in rhesus monkeys.	No data	Since goal of treatment of HCV is to prevent long-term sequelae, treatment in pregnancy rarely indicated and generally not recommended.
Caspofungin	70 mg IV load on day 1, then 50 mg IV qd (infuse over 1 hour)	Generally well tolerated. Histamine-mediated symptoms including rash, facial swelling, pruritus and sensation of warmth have been reported. Rare: Fever, phlebitis, nausea, vomiting, headache, eosinophilia, proteinuria, increased alk phos and hypokalemia	C	Animal data with exposure similar to a 70 mg dose in human resulted in incomplete ossification of skull, torso, cervical ribs and talus/calcaneus.	No data	Avoid in pregnancy until more data becomes available.

Thalidomide (Thalomid®)	50–200 mg/da po—used for treatment of aphthous ulcers, wasting	Sedations, rash, neuropathy, constipation, neutropenia found in up to 50%	X	–	High potential for birth defects, including absent or abnormal limbs; cleft lip; absent ears; heart, renal or genital abnormalities. Single dose can be associated with teratogenic effects.	Contraindicated in pregnancy and in women at risk for pregnancy (not using effective contraception or trying to conceive).
ANC, absolute neutrophil count; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; G-CSF, granulocyte-colony stimulating factor; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; INH, isoniazid; MAC, <i>Mycobacterium avium</i> complex; N/V/D, nausea/vomiting, diarrhea; PCP, <i>Pneumocystis carinii</i> pneumonia.						

Table 14-5: Safety of Commonly Used Antimicrobials

<i>Drug Name</i>	<i>FDA Class</i>	<i>Animal Data</i>	<i>Human Experience in Pregnancy</i>	<i>Comments</i>
Metronidazole	B	Animal (rodents) data show risk of carcinogenicity.	2 meta-analyses, a population-based case-control study, and a prospective controlled cohort study have not found increased risk in birth defects (Diav-Citrin, 2001; Czeizel, 1998; Caro-Paton, 1997; Burtin 1995)	Most authorities feel metronidazole is safe in the 2nd and 3rd trimester. Use with caution in 1st trimester.
Clindamycin	B	No fetal harm demonstrated in rat studies. Cleft palate observed in one mouse strain.	In a surveillance study of Michigan Medicaid recipients, 647 exposures to clindamycin during the first trimester resulted in a 4.8% incidence of birth defects. Patterns of anomalies do not support an association between clindamycin and congenital effects (Briggs, 1998).	Clindamycin is usually considered safe to use during pregnancy.
Penicillins	B	Carcinogenicity demonstrated in rats after prolonged subcutaneous administration of penicillin in peanut oil.	Several collaborative perinatal project reports involving over 12,000 exposures to penicillin derivatives during the 1st trimester indicated no association between penicillin derivative drugs and birth defects (Briggs, 1998).	Penicillins are usually considered safe to use during pregnancy.
Cephalosporins	B	Not teratogenic or fetotoxic.	Extensive pregnancy exposure was not associated with birth defects.	Cephalosporins are usually considered safe to use during pregnancy.
Erythromycin	B	No teratogenic effect in rat studies.	In a surveillance study of Michigan Medicaid recipients, 6972 patients exposed to erythromycin during the first trimester resulted in a 4.6% incidence of birth defects. Patterns of anomalies do not support an association between erythromycin and congenital malformations.	Avoid estolate salt (due to hepatotoxicity in 10% of patients). Other forms are usually considered safe to use during pregnancy.
Tetracyclines	D	Teratogenic in animal studies resulting in retardation of skeletal development and embryotoxicity.	Tetracyclines are contraindicated in pregnancy due to retardation of skeletal development and bone growth, enamel hypoplasia, and discoloration of teeth of fetus. Maternal liver toxicity has also been reported.	Contraindicated.

Fluoroquinolones	C	Animal data demonstrated arthropathy in immature animals resulting in erosions in joint cartilage.	In a prospective follow-up study conducted by the European Network of Teratology Information Services (ENTIS), 666 cases of fluoroquinolone exposure (the majority during the 1st trimester) showed a congenital malformation rate of 4.8%. From previous epidemiologic data, this rate did not exceed the background rate (Schaefer, 1996).	Based on animal data and the availability of alternative antimicrobial agents, the use of fluoroquinolones during pregnancy is contraindicated.
Aminoglycosides	D	Fetotoxicity reported in rodent studies.	Eighth cranial nerve toxicity in the fetus is well documented with exposure to kanamycin and streptomycin and can potentially occur with other aminoglycosides.	Gentamicin is classified by the FDA as "C" (although it has the same potential adverse effects). Use as preferred aminoglycoside if treatment indicated.
Imipenem	C	Animal studies (monkeys) show increased embryogenic loss.	No data in humans.	Due to the lack of human data, use only in life-threatening infections.
Meropenem	B	No risk.	No data in humans.	Due to the lack of human data, use only in life-threatening infections.
Chloramphenicol	C	No animal data.	A collaborative perinatal project monitored 98 exposures during the first trimester and 348 exposures anytime during pregnancy. No relationship between chloramphenicol and malformations were found (Briggs, 1998).	Although apparently nontoxic to the fetus, chloramphenicol should not be used near term due to the potential of cardiovascular collapse (gray baby syndrome).
Aztreonam	B	Animal studies show no harm to the fetus.	No human data available.	Likely to be safe in pregnancy, but due to the lack of data, use only if absolutely needed.
Methenamine	C	No animal data.	In a surveillance study of Michigan Medicaid recipients, 209 exposures to methenamine during the first trimester resulted in a 3.8% incidence of birth defects. This data did not support an association between methenamine and congenital defects.	The benefit of methenamine therapy is not likely to be worth the potential risk of use during pregnancy.
Nitrofurantoin	B	Not teratogenic or fetotoxic in rat and rabbit studies.	In a surveillance study of Michigan Medicaid recipients, 1292 exposures to nitrofurantoin resulted in a 4.0% incidence of birth defects. These data did not support an association between nitrofurantoin and congenital defects (Briggs, 1998).	Most authorities feel that use of nitrofurantoin is safe during pregnancy.
Vancomycin	C	No animal data.	The manufacturer has received reports of vancomycin use during pregnancy without adverse fetal effects.	Consider use only when the benefit outweighs the risk of drug administration.

Table 14-6 Drug Interactions of Antiretrovirals						
Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
Drug Interactions with Nucleoside Reverse Transcriptase Inhibitors						
AZT (Zidovudine) (Retrovir [®])	Ganciclovir/ Valganciclovir	Pharmacodynamic interaction/Additive toxicity	Enhanced bone marrow toxicity	Delayed	Moderate	Monitor CBC frequently. May require switch to alternative antiretroviral or use concomitant G-CSF.
AZT	Acetaminophen	Competitive inhibition of glucuronidation	May rarely result in granulocytopenia and hepatotoxicity	Delayed	Minor	Intermittent use of acetaminophen is considered safe. Adverse effects not consistently reported.
AZT	Stavudine	In vitro and in vivo antagonism	Decreased antiviral efficacy	Immediate	Major	Concomitant administration not recommended.
AZT	Rifampin	Enzymatic induction resulting in increased glucuronidation of AZT	Increased clearance of AZT	Delayed	Moderate	Clinical significance unknown.
AZT	Ribavirin	In vitro ribavirin inhibits phosphorylation of AZT Pharmacodynamic interaction	Antagonism in vitro but not in vivo Additive anemia	Immediate Delayed	Moderate/ Severe	Avoid combination if possible or closely monitor virologic response. Anemia may be severe. May require treatment or change in drugs.
AZT	Doxorubicin	Pharmacodynamic interaction	Additive bone marrow suppression	Delayed	Moderate	Additive bone marrow suppression. Consider alternative to AZT or support with G-CSF.
AZT	Zalcitabine	Low potency combination	Non-responsive regimen	Delayed	Moderate	Avoid combination.
AZT	Myelosuppressive drugs (e.g., interferon, pyrimethamine)	Pharmacodynamic interaction	Additive bone marrow suppression	Delayed	Moderate	Use with caution. Monitor for bone marrow suppression.
AZT	Atovaquone	Inhibition of AZT glucuronidation	AZT: AUC increased 31% decreased clearance	Immediate	Moderate	Clinical significance unknown. Use standard dose.

ddl (Didanosine) (Videx®)	Ganciclovir/ Valganciclovir	Unknown	ddl AUC increased by >100% with concomitant dosing (or when oral ganciclovir is administered 2 hours after ddl); ganciclovir AUC decreased 21%	Delayed	Moderate	Monitor for ddl toxicity (i.e. peripheral neuropathy, pancreatitis). Appropriate doses for combination of ddl and ganciclovir not established. Dose adjustment may be required.
ddl	Tenofovir	Unknown	ddl increased by 40–60%. Suboptimal response in 91% of patients with ddl/TDF/3TC only	Delayed	Major	May increase rate of peripheral neuropathy and pancreatitis. Lower dose of ddl EC to 250 mg qd with TDF co-administration for pts >60kg. Dose for pts <60kg 200 mg qd.
ddl	Indinavir Ritonavir Delavirdine	Increase in gastric pH due to the buffer in ddl formulation	Decreased absorption of indinavir, ritonavir, and delavirdine	Immediate	Moderate	Separate administration time by at least 2 hours or use ddl EC formulation.
ddl	Dapsone	Increase in gastric pH due to the buffer in ddl formulation	No significant interaction	Immediate	Mild	Use standard dose.
ddl	Itraconazole Ketoconazole	Increase in gastric pH due to the buffer in ddl formulation	Decreased absorption of antifungal agent	Immediate	Major	Separate administration time by at least 2 hours or use ddl EC formulation. Fluconazole may be preferred as an alternative azole antifungal.
ddl	Fluoroquinolones, tetracyclines	Chelation of fluoroquinolones and tetracyclines by the divalent cation in DDI formulation	Significant decrease in antibiotic absorption resulting in sub-therapeutic levels	Immediate	Major	Administer quinolones or tetracyclines 2 hours before or 6 hours after DDI administration or use ddl EC formulation.
ddl	Pentamidine IV Ethambutol	Pharmacodynamic interaction / additive toxicity	May increase the risk of pancreatitis	Delayed	Moderate	Should avoid in patients with current alcohol use. Use caution when administering to patients with a history of alcoholism.
ddl	Atazanavir	Decreased absorption of ATV due to buffer in ddl formulation	ATV AUC decreased 87% with buffered ddl given simultaneously; no significant interaction expected with ddl EC	Immediate	Severe	buffered ddl: Take ATV with food 2 hr before or 1 hr after ddl (if this timing of dosing not followed, 90% reduction in ATV level); ddl EC: take at different times (ATV with food and ddl on empty stomach).

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
ddl	ddC, hydroxyurea, INH, cisplatin, disulfiram, thalidomide, vincristine, gold, hyalalazine, and long-term metronidazole.	Pharmacodynamic interaction/ Additive toxicity	May increase the risk of peripheral neuropathy.	Delayed	Moderate	Avoid co-administration or give with careful monitoring for symptoms of peripheral neuropathy. Incidence of peripheral neuropathy increases with low CD4 count.
ddl	64T	Pharmacodynamic interaction/ Additive toxicity	Increased risk lactic acidosis in pregnant women. Peripheral neuropathy and pancreatitis also reported with this combination.	Delayed	Major	Avoid co-administration especially during pregnancy, unless no other antiretroviral options are available and potential benefits outweigh risks.
ddl	Methadone	Unknown	buffered ddl AUC decreased by 63%, methadone levels remains unchanged. No interaction with ddl EC	Delayed	Moderate	Consider using ddl EC. May consider buffered ddl increase.
ddl	Allopurinol	Unknown	ddl levels increased by 120%	Immediate	Moderate	Avoid co-administration.
ddl	Ribavirin	Inhibition of mitochondrial DNA polymerase gamma	ddl intracellular triphosphate levels increased	Delayed	Major	Increased of risk of pancreatitis and lactic acidosis. Avoid co-administration.
ddC (Zalcitabine) (Hivid®)	ddl, d4T, INH, cisplatin, disulfiram, thalidomide, vincristine, gold, hyalalazine, pyridoxine, and long-term metronidazole.	Pharmacodynamic interaction/ Additive toxicity	May increase the risk of peripheral neuropathy.	Delayed	Moderate	Avoid or give with careful monitoring of symptoms of peripheral neuropathy. Risk of peripheral neuropathy increases with total exposure and low CD4 count.
ddC	Lamivudine	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Moderate	To be avoided.
ddC	AI or mg containing antacid	Interference with absorption	ddC absorption decreased by 25%	Immediate	Moderate	Do not take simultaneously.

ddC	Pentamidine I.V.	Pharmacodynamic interaction	Additive toxicity	Delayed	Moderate	May increase the risk of development of fulminant pancreatitis. Monitor signs of toxicity.
ddC	Probenecid	Inhibition of tubular secretion	May decrease elimination of ddC. ddC AUC increased by 54%	Delayed	Moderate	
d4T (Stavudine) (Zerit®)	ddC, INH, cisplatin, disulfiram, thalidomide, vincristine, gold, hydralazine, pyridoxine, and long-term metronidazole.	Pharmacodynamic interaction/Additive toxicity	May increase the risk of peripheral neuropathy	Delayed	Moderate	Avoid or give with careful monitoring of symptoms of peripheral neuropathy. Peripheral neuropathy increases with total exposure and low CD4 count.
d4T	ddl	Pharmacodynamic interaction/ Additive toxicity	Increased risk lactic acidosis in pregnant women. Peripheral neuropathy and pancreatitis also reported with this combination.	Delayed	Major	Avoid coadministration use during pregnancy, unless no other antiretroviral options are available and potential benefits outweigh risks.
d4T	Methadone	Unknown	d4T drug levels decreased by 23%. Methadone levels unchanged	Delayed	Mild	Clinical significance unknown, no dose adjustment needed (unlikely to be significant).
d4T	Zidovudine	In vitro and in vivo antagonism	Decreased efficacy of the combination therapy	Immediate	Major	Concomitant administration not recommended due to antagonism.
d4T	Ribavirin	In vitro ribavirin interacts with thymidine-phosphorylated nucleoside analogs	Antagonism in vitro but not in vivo	Immediate	Minor	Not clinically significant.
3TC (Lamivudine) (Epivir®)	Bactrim	Trimethoprim competitively inhibits renal tubular secretion.	AUC of lamivudine increased by 44%	Immediate	Minor	No dosage adjustment required due to the safety profile of 3TC (not clinically significant).
3TC	Abacavir + tenofovir	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Major	Avoid use of this combination without an NNRTI or a PI.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
3TC	Emtricitabine	Overlapping resistance profile	Non-suppressive regimen	Delayed	Major	Avoid use together.
3TC	Tenofovir + didanosine	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Major	Avoid use of this combination without an NNRTI or a PI.
3TC	Zalcitabine	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Moderate	Consider alternative combination.
FTC (Emtricitabine) (Emtriva®)	-					In vitro data suggest potential for CYP450-mediated interactions involving emtricitabine with other agents is low; in human studies, no significant PK changes in either drug with tenofovir, indinavir, famciclovir, or stavudine.
FTC	Lamivudine	Overlapping resistance profile	Non-suppressive regimen	Delayed	Major	Avoid.
Abacavir (Ziagen®)	Alcohol	Unknown	Alcohol increases ABC levels by 41%. No effect on alcohol levels	Immediate	Minor	Clinical significance unknown. No dose adjustment recommended.
Abacavir	Tenofovir + didanosine	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Major	Avoid us of this combination without an NNRTI or a PI.
Drug Interactions with Nucleotide Reverse Transcriptase Inhibitors						
Tenofovir (Viread®)	Atazanavir	Possible interference with absorption	Atazanavir AUC decreased by 25%; decreased C _{min} by 23%	Immediate	Moderate	Clinical significance unknown. Consider dosing tenofovir 2 hours before atazanavir or "boosting" with RTV dose: (ATV 300 mg + RTV 100 mg).
Tenofovir	ddl	Unknown Low potency combination	ddl AUC increased by 40-60%.	Delayed	Major	May increase rate of peripheral neuropathy and pancreatitis. Lower dose of ddl to 250 mg qd with TDF co-administration for pts >60kg. Dose adjustments for pts <60kg 200 mg qd. Preliminary data shows low potency.

Tenofovir	Cidofovir, ganciclovir, valganciclovir	Possible competition for active tubular secretion	May increase concentration of TDF or these drugs	Immediate	Moderate	Monitor for dose-related toxicities.
Tenofovir	Lamivudine + Abacavir	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Major	Avoid use of this combination without an NNRTI or a PI.
Tenofovir	Lamivudine + didanosine	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Major	Avoid use of this combination without an NNRTI or a PI.
Tenofovir	Didanosine	Increased ddl serum level	ddl AUC increased by 44% may result in increased toxicity	Immediate	Major	Monitor for ddl associated toxicities for patients \geq 60 kg, decrease ddl EC dose 250 mg qd for patients < 60 kg.
Drug Interactions with Non-Nucleoside Reverse Transcriptase Inhibitors						
Nevirapine (Viramune®)	Ethinyl estradiol (Oral contraceptives)	Induction of hepatic metabolism	Ethinyl estradiol AUC decreased by 23%	Delayed	Major	Patients should be aware of the potential interaction. Alternative or additional birth control method should be recommended.
NVP	Methadone	Induction of hepatic metabolism	Substantially decreased methadone AUC by 46%	Delayed	Moderate	Opiate withdrawal may occur. May need to increase dose of methadone by 15–25% (some patients may require doses of greater than 150 mg per day).
NVP	Ketoconazole	Induction of hepatic metabolism by nevirapine. Inhibition of hepatic metabolism by ketoconazole	Ketoconazole levels decreased by 72%. Nevirapine levels increased by 15–30%	Delayed	Moderate	Co-administration not recommended. Ketoconazole dose may need to be increased. Fluconazole may be preferred as alternative azole agent.
NVP	Rifampin/ Rifabutin	Induction of hepatic metabolism	Nevirapine levels decreased by 37% with rifampin and 16% with rifabutin	Delayed	Major	Co-administration not recommended with rifampin. Rifabutin is the preferred alternative agent.

Table 14-6 Drug Interactions of Antiretrovirals (continued)

Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
NVP	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism by both NVP and anticonvulsants.	May decrease serum levels of NVP and anticonvulsants	Delayed	Moderate	Consider alternative anticonvulsants (i.e. valproic acid, levetiracetam, or topiramate).
NVP	Clarithromycin	Induction of hepatic metabolism by nevirapine	Clarithromycin AUC decreased by 30%, but active hydroxy-metabolite is increased	Delayed	Minor	No dose modification needed. Use standard doses of nevirapine and clarithromycin.
NVP		Inhibition of hepatic metabolism by clarithromycin	Nevirapine AUC increased by 26%	Immediate	Minor	
NVP	St. John's wort	Induction of hepatic metabolism by St. John's wort	NVP clearance increased by 35%	Delayed	Major	Co-administration is contraindicated.
NVP	Saquinavir	Induction of hepatic metabolism	Saquinavir AUC decreased by 38%. NVP level not affected.	Delayed	Moderate	Avoid concurrent use unless saquinavir is "boosted" with ritonavir (SQV 1000 mg/RTV 100 mg bid).
NVP	Ritonavir	Induction of hepatic metabolism	Ritonavir AUC decreased by 11%. NVP level not affected	Delayed	Minor	Use standard doses.
NVP	Indinavir	Induction of hepatic metabolism	Indinavir AUC decreased by 28%. NVP level not affected	Delayed	Minor	Clinical trials demonstrated good efficacy with standard dose. Consider increasing IDV to 1000 mg q8h (or IDV 800 mg/RTV 100 mg q12h) with NVP coadministration.
NVP	Nelfinavir	Induction of hepatic metabolism	Nelfinavir levels increase by 10%. NVP level not affected	Delayed	Minor	Use standard doses.

NVP	Lopinavir/r	Induction of hepatic metabolism	LPV/r AUC decreased by 22%. C_{min} decreased by 55%. NVP level not affected	Delayed	Major	Dose: LPV/r 533 mg/133 mg (4 caps) bid with food (NVP standard dose). Though pharmacokinetic data exist, co-administration is not recommended due to overlapping resistance.
NVP	Efavirenz	Induction of hepatic metabolism	EFV AUC decreased by 22%. NVP AUC not affected	Delayed	Moderate	Consider using ATV 300 mg/RTV 100 mg qd. Monitor NVP-associated side effects.
NVP	Atazanavir	No data				
NVP	Fluconazole	Inhibition of NVP metabolism	May increase NVP serum level	Immediate	Moderate	Monitor NVP-associated side effects.
NVP	Voriconazole	Potential for bi-directional inhibition	May significantly decrease voriconazole serum level	Delayed	Moderate/Severe	Monitor frequently for toxicities and voriconazole efficacy. Dose adjustment may be needed.
NVP	Norethindrone	Induction of norethindrone metabolism	May decrease norethindrone	Delayed	Major	Use additional method of contraception.
NVP	Rifampentine	Induction of NVP metabolism	May significantly decrease NVP serum level	Delayed	Major	Avoid use together; consider rifabutin.
Delavirdine (Rescriptor®) (DLV)	Indinavir	Induction of hepatic metabolism	Indinavir AUC increased by 40%. DLV no change	Immediate	Moderate	May reduce indinavir dose to 600 mg q8h. DLV standard dose.
DLV	Nelfinavir	Inhibition of hepatic metabolism by delavirdine; Induction of hepatic metabolism by nelfinavir	NFV AUC increased by 72%. DLV AUC decreased by 42% C_{min} decreased by 52%.	Immediate; delayed	Moderate	Do not co-administer.
DLV	Ritonavir	Inhibition of hepatic metabolism	Ritonavir AUC increased by 61%. DLV no change	Immediate	Minor	Standard doses likely (no data).
DLV	Saquinavir	Inhibition of hepatic metabolism	Invirase® C_{min} increased by 500%; DLV AUC decreased by 15%.	Delayed	Minor	A beneficial interaction. No dose adjustment necessary. Monitor transaminase levels.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
DLV	Amprrenavir	Inhibition of hepatic metabolism by DLV. Induction of hepatic metabolism by APV	Amprrenavir AUC increased by 125%. DLV AUC decreased by 60%	Delayed	Major	Co-administration not recommended.
DLV	Lopinavir/r	Inhibition of hepatic metabolism	LPV AUC increased by 8–134%. DLV no change	Immediate	Minor	Limited data. No dose adjustment.
DLV	ddl and antacid	Decreased delavirdine absorption due to antacid content in DDI	Delavirdine AUC decreased by 41%	Immediate	Moderate	Separate administration by at least 1 hour or use ddl EC.
DLV	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism	Increased serum levels of simvastatin and lovastatin	Immediate	Moderate	Avoid concurrent administration. Consider alternatives such as atorvastatin, pravastatin, fluvastatin. Monitor for adverse effects due to limited clinical data.
DLV	H2 blockers, Proton pump inhibitors (i.e. omeprazole)	Decreased delavirdine absorption due to antacid content in DDI	May decrease delavirdine concentration	Immediate	Moderate	Concurrent administration contraindicated.
DLV	Terfenadine, Astemizole, Cisapride	Inhibition of hepatic metabolism	Increased levels of terfenadine, astemizole, cisapride	Immediate	Major	Concurrent administration contraindicated due to potential for serious cardiac arrhythmias.
DLV	Midazolam, Triazolam	Inhibition of hepatic metabolism	Midazolam and triazolam AUCs increased	Immediate	Major	Concurrent administration contraindicated due to potential for prolonged sedation. Lorazepam and temazepam may be safe alternatives.
DLV	Ergot alkaloid	Inhibition of hepatic metabolism	Possible acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.

DLV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease serum level of delavirdine	Delayed	Major	Co-administration is contraindicated.
DLV	Clarithromycin	Inhibition of hepatic metabolism	Clarithromycin levels increased by 100% and delavirdine levels increased by 44%	Immediate	Minor	May require clarithromycin dose adjustment, based upon CrCl.
DLV	Ethinyl estradiol	Unknown	Ethinyl estradiol levels decreased by 20%	Delayed	Major	Patients should be aware of the potential interaction. Alternative or additional birth control method should be recommended.
DLV	Quinidine	Inhibition of hepatic metabolism	May increase quinidine serum concentration	Immediate	Major	No data. Use with caution with close EKG monitoring and serum levels of quinidine.
DLV	Ketoconazole	Inhibition of hepatic metabolism by delavirdine	Ketoconazole AUC increased by 50%	Immediate	Minor	Consider dose reduction of ketoconazole. DLV 200-400 mg tid.
DLV	Rifampin	Inhibition of hepatic metabolism	Delavirdine C_{min} decreased below the level of detection AUC decreased by 96%	Delayed	Major	Concurrent administration contraindicated due to sub-therapeutic level of delavirdine.
DLV	Rifabutin	Inhibition of hepatic metabolism by delavirdine	Rifabutin AUC increased by 100%	Immediate	Moderate	Concurrent administration contraindicated due to sub-therapeutic level of delavirdine.
DLV	Rifabutin	Induction of hepatic metabolism by rifabutin	Delavirdine AUC decreased by 80%	Delayed	Major	Concurrent administration contraindicated.
DLV	Warfarin	Potential inhibition of warfarin metabolism	May increase warfarin	Immediate	Moderate	Monitor INR.
DLV	Voriconazole	Potential for bi-directional inhibition	May increase voriconazole and DLV serum level	Immediate	Moderate	Monitor frequently for toxicities.
DLV	Bepridil	Potential inhibition of bepridil metabolism	May increase bepridil serum level	Immediate	Moderate	Use with caution; monitor for cardiac arrhythmias.

Table 14-6 Drug Interactions of Antiretrovirals (continued)

Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
DLV	Tadalafil	Potential inhibition of tadalafil metabolism	May substantially increase in tadalafil AUC and half life	Immediate	Moderate	Start tadalafil 5 mg dose; do not exceed a single 10 mg dose of tadalafil in 72 hours.
DLV	Vardenafil	Potential inhibition of vardenafil metabolism	May substantially increase vardenafil AUC	Delayed	Moderate	Start with a 2.5 mg dose; do not exceed a single 2.5 mg dose of vardenafil in 72 hours. Avoid using SOV as sole protease inhibitor with efavirenz. If RTV/SQV/efavirenz regimen used: dose SQV 1000 mg/RTV 100-200 mg bid plus EFV 600 mg qhs or RTV/SQV 400 mg/400 mg bid plus EFV 600 mg qhs.
EFV	Nelfinavir	Inhibition of hepatic metabolism	Invirase® AUC decreased by 60%. Efavirenz AUC decreased by 12%	Immediate	Minor	A beneficial pharmacokinetic interaction. No dose adjustment needed.
EFV	Amprenavir	Induction of hepatic metabolism	Nelfinavir AUC increased by 21%	Delayed	Moderate	Dose: APV 600 mg/ RTV 100 mg q12h + EFV 600 mg qhs.
EFV	Indinavir	Induction of hepatic metabolism	Amprenavir AUC decreased by 36%	Delayed	Moderate	May need to increase indinavir dose to 1000 mg q8h or consider IDV "boosted" with 200 mg RTV.
EFV	Ritonavir	Dual inhibition of hepatic metabolism	Indinavir AUC decreased by 31%	Immediate	Minor	No adjustment needed.
EFV	Lopinavir	Induction of hepatic metabolism	Efavirenz AUC increased by 21%. Ritonavir AUC increased by 17%	Delayed	Major	Dose: LPV/r 533 mg/r133 mg (4 caps)/bid + EFV 600 mg qhs.
EFV	Ergot alkaloid	Induction of hepatic metabolism	LPV AUC decreased by 19%. C _{min} decreased by 39%	Immediate	Major	Concurrent administration contraindicated.

EFV	Midazolam, Triazolam	Induction of hepatic metabolism	AUCs of midazolam and triazolam increased	Immediate	Major	Concurrent administration contraindicated due to potential for prolonged sedation. Lorazepam and temazepam may be safe alternatives.
EFV	Terfenadine, Astemizole, Cisapride	Induction of hepatic metabolism	Levels of terfenadine, astemizole, cisapride increased	Immediate	Major	Concurrent administration contraindicated due to potential for serious cardiac arrhythmia.
EFV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease efavirenz serum level	Delayed	Major	Co-administration is contraindicated.
EFV	Clarithromycin	Induction of hepatic metabolism	Clarithromycin AUC decreased by 39%	Immediate	Moderate	Incidence of rash increased to 46% with concurrent administration. No interaction with azithromycin, a better alternative.
EFV	Ethinyl estradiol	Inhibition of hepatic metabolism	Ethinyl estradiol AUC increased by 37%	Immediate	Minor	No dose changes recommended. Clinical significance of interaction unknown. No data on progestin component of oral contraceptive available. Alternative or additional form of birth control recommended.
EFV	Rifabutin	Inhibition of hepatic metabolism	Rifabutin AUC decreased by 35%. No effect on Efavirenz AUC	Delayed	Moderate	If concurrent administration required, increase dose of rifabutin to 450 mg or 600 mg po qd.
EFV	Rifampin	Inhibition of hepatic metabolism	Efavirenz AUC decreased by 26%. No change in rifampin levels	Delayed	Moderate	Consider increasing EFV to 800 mg qhs with rifampin co-administration. An alternative is to use rifabutin dose adjusted to 450-600 mg qd (or 600 mg 3x/week) with standard dose EFV.
EFV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism by both EFV and anticonvulsants.	May decrease serum levels of EFV and anticonvulsants	Delayed	Moderate	Consider alternative anticonvulsants (i.e valproic acid, levetiracetam, or topiramate). Consider increasing EFV to 800 mg po qd with co-administration. Monitor anticonvulsant level.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
<i>Primary drug</i>	<i>Interacting drug</i>	<i>Mechanism of interaction</i>	<i>Effect</i>	<i>Time course</i>	<i>Severity</i>	<i>Comments/ management recommendation</i>
EFV	Nevirapine	Induction of hepatic metabolism	EFV AUC decreased by 22%. NVP AUC not affected	Delayed	Moderate	Though pharmacokinetic data exist, co-administration is not recommended due to overlapping resistance.
EFV	Methadone	Induction of hepatic metabolism	Decrease methadone AUC by 57%	Delayed	Moderate	Opiate withdrawal may occur. May need to increase dose of methadone.
EFV	Atazanavir	Induction of hepatic metabolism	ATV decreases AUC by 74%	Delayed	Major	Use ATV 300 mg + RTV 100 mg qd with food. Standard EFV dose.
EFV	Fosamprenavir	Induction of hepatic metabolism	fAPV C _{min} decreases 36% when dosed at fAPV 1400 mg + RTV 250 mg qd	Delayed	Major	Use fAPV 700 mg + RTV 100 mg bid, OR fAPV 1400 mg + RTV 300 mg with EFV co-administration.
EFV	Indinavir	Induction of hepatic metabolism	IDV decreases 31%	Delayed	Major	Increase IDV dose to 1000 mg q8h or consider IDV 800 mg + RTV 200 mg q12h.
EFV	Warfarin	Unknown	Potential increase or decrease in warfarin levels	Delayed	Moderate	Monitor INR.
Drug Interactions with Protease Inhibitors						
Indinavir (Crixivan®) (IDV)	ddi	Impairment of indinavir absorption by DDI buffer	Decreases absorption of indinavir	Immediate	Moderate	Separate indinavir and ddi dosing by at least 2h or use ddi EC formulation.
	Simvastatin/Lovastatin	Inhibition of hepatic metabolism	Increased serum levels of simvastatin and lovastatin	Immediate	Moderate	Avoid concurrent administration. Possible alternative include atorvastatin, pravastatin, fluvastatin. Monitor for adverse effect due to limited clinical data with these agents.
IDV	Rifabutin	Inhibition of hepatic metabolism by indinavir	Rifabutin AUC increased by 2 fold.	Immediate	Moderate	Decrease rifabutin dose by half (150 mg once a day) or 300 mg 3x/week.

IDV	Rifabutin	Induction of hepatic metabolism by rifabutin	Indinavir AUC decreased by 32%	Delayed	Moderate	May need to increase indinavir dose to 1000 mg tid. When IDV "boosted" with RTV, adjust rifabutin 150 mg qod. Concurrent administration contraindicated.
IDV	Rifampin	Induction of hepatic metabolism	Indinavir AUC decreased by 90%	Immediate	Major	Concurrent administration contraindicated.
IDV	Terfenadine, Astemizole, Cisapride	Inhibition of hepatic metabolism	Drug levels increased by 3-fold or greater	Immediate	Major	Concurrent administration contraindicated due to potential for cardiac arrhythmias. Alternative antihistamines include loratadine, fexofenadine, or cetirizine. Alternative pro-kinetic agent includes metoclopramide.
IDV	Ergot alkaloid	Inhibition of hepatic metabolism	Potential acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.
IDV	Ketoconazole, Itraconazole	Inhibition of hepatic metabolism	Indinavir AUC increased by 70%	Immediate	Moderate	Dose Indinavir at 600 mg Q8h. No dose adjustment when "boosted" with RTV.
IDV	Midazolam, Triazolam	Inhibition of hepatic metabolism	AUCs of midazolam and triazolam are increased	Immediate	Major	Concurrent administration contraindicated due to potential for prolonged sedation.
IDV	St. John's wort	Induction of hepatic metabolism by St. John's wort	Indinavir AUC decreased by 57%.	Delayed	Major	Co-administration is contraindicated.
IDV	Clarithromycin	Inhibition of hepatic metabolism	Clarithromycin AUC increased by 53%	Immediate	Minor	No dose adjustment.
IDV	Oral contraceptives	Inhibition of hepatic metabolism	Ethinyl estradiol AUC increased by 24% and norethindrone AUC increased by 26%.	Immediate	Minor	No dose adjustment.

Table 14-6 Drug Interactions of Antiretrovirals (continued)

Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
IDV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism	May decrease serum levels of IDV. IDV may increase anticonvulsant serum level.	Delayed	Moderate	Consider alternative anticonvulsants (i.e. valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level.
IDV	Sildenafil	Inhibition of hepatic metabolism	Sildenafil AUC increased 3-fold.	Immediate	Moderate	The maximum dose of sildenafil is 25 mg/48h.
IDV	Nelfinavir	Inhibition of hepatic metabolism.	Indinavir AUC increased by 50% Nelfinavir AUC increased by 80%	Immediate	Minor	Limited dosing data using IDV 1200 mg bid + NFV 1250 mg bid.
IDV	Ampronavir	Inhibition of hepatic metabolism	Ampronavir AUC increased by 26%. Indinavir AUC increased by 38%.	Immediate	Minor	No dose adjustment recommended. Dose APV 800 mg tid /IDV 800 mg tid.
IDV	Ritonavir	Inhibition of hepatic metabolism	Indinavir AUC increased by 2 to 5-fold.	Immediate	Minor	Interaction allows indinavir to be dosed twice a day. Dose: IDV 400 mg/RTV 400 mg or IDV 800 mg bid/RTV100 bid. IDV 1200 mg/RTV 400 mg qd (limited data).
IDV	Lopinavir/r	Inhibition of hepatic metabolism	Indinavir AUC increased by 3-fold	Immediate	Moderate	Dose: IDV 600 mg or 666 mg bid plus LPV/r 400 mg/100 mg bid.
IDV	Saquinavir	Inhibition of hepatic metabolism	Saquinavir AUC increased 4 to 7 fold. No effect on Indinavir level	Immediate	Moderate	In vitro antagonism. Avoid co-administration.
IDV	Nevirapine	Induction of hepatic metabolism	Indinavir AUC decreased by 28%. NVP level not affected.	Delayed	Minor	Clinical trials demonstrated good efficacy with standard doses. Some experts recommend increasing the dose of IDV to 1000 mg q8h. When using "boosted" IDV consider RTV dose 200 mg bid.
IDV	Efavirenz	Induction of hepatic metabolism	Indinavir AUC decreased by 31%	Delayed	Moderate	May need to increase indinavir dose to 1000 mg q8h or IDV 800/ RTV 100 q12h.
IDV	Delavirdine	Inhibition of hepatic metabolism	Indinavir AUC increased by 40%. DLV no change.	Immediate	Moderate	May reduce indinavir dose to 600 mg q8h. DLV standard dose.

IDV	Methadone			No change in serum level	Delayed	Moderate	No interaction. Use standard dose
IDV	Voriconazole	When IDV is boosted with RTV, potential for bi-directional interaction		Voriconazole levels may be decreased with IDV/RTV	Delayed	Moderate	No interaction with IDV but voriconazole may be decreased with RTV co-administration. Monitor for toxicities and therapeutic efficacy.
IDV	Tadalafil	Inhibition of hepatic metabolism		May substantially increase tadalafil AUC	Immediate	Moderate	Start with 5 mg dose and do not exceed a single dose of 10 mg in 72 hrs.
IDV	Vardenafil	Inhibition of hepatic metabolism		Vardenafil increases 16-fold IDV unboosted decreases 30%	Immediate	Moderate	For unboosted IDV, consider using sildenafil instead; for IDV + RTV, do not exceed 2.5 mg vardenafil in 72 hrs.
IDV	Atorvastatin	Inhibition of hepatic metabolism		Potential for atorvastatin AUC increase	Immediate	Moderate	Use lowest possible starting dose of atorvastatin with careful monitoring or avoid use together.
Saquinavir (Invirase®) (Fortovase®) (SQV)	Ritonavir	Inhibition of hepatic metabolism		Saquinavir AUC increased by 20-fold.	Immediate	Minor	Dual protease inhibitor combination with the most clinical experience. Recommended doses: RTV 400 mg bid plus SQV 400 mg bid. RTV 100 mg bid plus SQV 1000 mg bid. RTV 100 mg plus SQV 1600 mg qd.
SQV	Indinavir	Inhibition of hepatic metabolism		Saquinavir AUC increased 4 to 7- fold No effect on Indinavir	Immediate	Moderate	In vitro antagonist. Avoid co-administration.
SQV	Nelfinavir	Inhibition of hepatic metabolism		Fortovase®AUC increased by 3 to 5-fold. Nelfinavir AUC increased by 20%	Immediate	Minor	Recommended doses are nelfinavir 750 mg tid and Fortovase® 800 mg tid or 1200 mg bid.
SQV	Amprenavir	Induction of hepatic metabolism		Saquinavir level decreased by 18%. Amprenavir level decreased by 36%.	Delayed	Moderate	Limited data: SQV (FTV) 800 mg tid plus APV 800 mg tid.
SQV	Lopinavir/r	Inhibition of hepatic metabolism		Saquinavir C _{min} increased by 3..6-fold	Immediate	Minor	Dose: SQV 800–1000 mg bid plus LPV/r 400/100 mg bid.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
SQV	Ketoconazole	Inhibition of hepatic metabolism	Saquinavir level increased by 3-fold.	Immediate	Minor	Beneficial pharmacokinetic interaction. Use standard doses. If ketoconazole dose is >200 mg/da, monitor for GI side effects and adjust doses accordingly.
SQV	Midazolam, Triazolam	Inhibition of hepatic metabolism	Midazolam and triazolam AUCs increased	Immediate	Major	Concurrent administration contraindicated due to potential for prolonged sedation.
SQV	Terfenadine, Astemizole, Cisapride	Inhibition of hepatic metabolism	Drug levels increased by 3-fold or greater.	Immediate	Major	Concurrent administration contraindicated due to potential for cardiac arrhythmias. Alternative antihistamines include loratadine, fexofenadine, or cetirizine. Alternative pro-kinetic agent includes metoclopramide.
SQV	Dexamethasone	Induction of hepatic metabolism	May decrease SQV serum levels	Delayed	Moderate	Clinical significance unknown.
SQV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism	May decrease serum levels of SQV	Delayed	Moderate	Consider alternative anticonvulsants (i.e valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level.
SQV	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.
SQV	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism.	Simvastatin and lovastatin serum level increased	Immediate	Moderate	Avoid co-administration. Recommended alternatives include atorvastatin, pravastatin (but pravastatin AUC decreased by 50% with SQV/r), fluvastatin. Monitor for adverse effects due to limited clinical data with these agents.

SQV	Clarithromycin	Inhibition of hepatic metabolism	Clarithromycin increases SQV AUC 177% and SQV increases clarithromycin AUC 45%	Immediate	Minor	Beneficial pharmacokinetic interaction. Use standard doses.
SQV	Rifabutin/ Rifampin	Induction of hepatic metabolism	Rifabutin and rifampin decrease AUC of saquinavir by 40% and 80% respectively.	Delayed	Major	Concurrent administration contraindicated unless using RTV/SQV. Consider RTV/SQV 400 mg/400 mg with rifabutin 150 mg 3x/week or rifampin 600 mg qd or 3x/week.
SQV	Sildenafil	Inhibition of hepatic metabolism.	Sildenafil AUC increased by 2-fold.	Immediate	Moderate	Caution with concurrent use. Do not exceed 25 mg of sildenafil in a 48-hour period.
SQV	Oral contraceptives					No data.
SQV	Methadone	Induction of hepatic metabolism	8-10% reduction in methadone level.	Delayed	Minor	Insignificant interaction. No dose adjustment needed.
SQV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease SQV serum level	Delayed	Major	Co-administration is contraindicated.
SQV	Garlic supplement (3.5 mg bid)	Unknown	SQV C _{min} decreased by 49%	Delayed	Moderate	Avoid concurrent administration.
SQV	Delavirdine	Inhibition of hepatic metabolism	SQV increases 5-fold	Immediate	Minor	Decrease SQV-sgc dose to 800 mg tid, and monitor transaminase levels.
SQV	Efavirenz	Induction of hepatic metabolism	SQV decreases 62%, EFV decreases 12%	Delayed	Moderate	Use SQV-sgc 400 mg + RTV 400 mg.
SQV	Nevirapine	Inhibition of hepatic metabolism	SQV decreases 25%	Delayed	Moderate	SQV-sgc 400 + RTV 400 mg or SQV-sgc 1000 mg + RTV 100 mg bid or SQV-hgc 1000 mg + RTV 100 mg bid.
SQV	Warfarin	Unknown	Increases or decreases warfarin	Delayed	Moderate	Monitor INR.
SQV	Amirypiline Imipramine	Inhibition of hepatic metabolism	May increase tricyclics	Immediate	Minor	Monitor tricyclic antidepressant concentration.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
SQV	Voriconazole	Potential for bi-directional inhibition	With SQV/RTV voriconazole serum level may be decreased	Delayed	Moderate	Monitor for toxicities and therapeutic efficacy.
SQV	Tadalafil	Inhibition of hepatic metabolism	May substantially increase tadalafil AUC	Immediate	Moderate	Start with a 5 mg dose and do not exceed a single 10 mg dose of tadalafil in 72 hrs.
SQV	Vardenafil	Inhibition of hepatic metabolism	Vardenafil AUC may increase substantially	Immediate	Moderate	Start with a 2.5 mg dose, and do not exceed a single 2.5 mg dose in 72 hrs.
SQV	Atorvastatin	Inhibition of hepatic metabolism	Atorvastatin increases 450% when combined with SQV/RTV	Immediate	Moderate	Use lowest possible starting dose of atorvastatin with careful monitoring.
Ritonavir (Norvir®) (RTV)	Metronidazole	Alcohol in ritonavir liquid may precipitate a disulfiram-like reaction.	Unexpected nausea	Immediate	Moderate	Warn patient of the alcohol content in ritonavir liquid.
RTV	Voriconazole	Hepatic induction	Decreased voriconazole by 82% when administered with RTV 400 mg bid	Delayed	Major	Do not co-administer with standard dose RTV 400 bid; no data with boosting doses of RTV.
RTV	Oral contraceptives	Induction and increase in glucuronosyl transferase activity.	Ethinyl estradiol level decreased by 40%	Delayed	Major	Warn patient of interaction. Use alternative or additional method of contraception.
RTV	Sildenafil	Inhibition of hepatic metabolism.	Sildenafil AUC increased by 2 to 11-fold.	Immediate	Major	Caution with concurrent use. Do not exceed 25 mg of sildenafil in a 48-hour period.
RTV	Theophylline	Induction of glucuronosyl transferase activity.	Theophylline AUC decreased by 43%	Delayed	Moderate	Monitor theophylline levels; dose may need to be increased if subtherapeutic.
RTV	Ketoconazole	Inhibition of hepatic metabolism	Ketoconazole AUC increased by greater than 3-fold.	Immediate	Moderate	May need to decrease ketoconazole dose.

RTV	Rifabutin	Inhibition of hepatic metabolism	Rifabutin AUC increased 4-fold	Immediate	Moderate	Dose rifabutin 150 mg qod or 150 mg 3x/week with standard ritonavir.
RTV	Rifampin	Induction of hepatic metabolism	Ritonavir AUC decreased by 35%	Delayed	Moderate	There may be an increased risk of liver toxicity. Dose RTV 400 mg/ SQV 400 mg bid with rifampin 600 mg qd.
RTV	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.
RTV	Terfenadine, Astemizole, Cisapride	Inhibition of hepatic metabolism	Drug level increased by 3-fold or greater.	Immediate	Major	Concurrent administration contraindicated due to potential for cardiac arrhythmias. Alternative antihistamines include loratadine, fexofenadine, or cetirizine. Alternative prokinetic agent includes metoclopramide.
RTV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease RTV serum level	Delayed	Major	Co-administration is contraindicated.
RTV	Benzodiazepines	Inhibition of hepatic metabolism	Prolonged sedation due to accumulation of benzodiazepine	Delayed	Major	Concurrent administration of midazolam and triazolam are contraindicated. Alternative benzodiazepines that can be used: Temazepam, oxazepam, and lorazepam.
RTV	Antiarrhythmics	Inhibition of hepatic metabolism	AUC of antiarrhythmics increased	Immediate	Major	Concurrent administration of propafenone, quinidine, flecainide, encainide, amiodarone, and bepridil are contraindicated.
RTV	Methadone	Induction of hepatic metabolism	Methadone levels decreased by 37%.	Delayed	Moderate	Clinical significance unknown.
RTV	Ketoconazole	Inhibition of hepatic metabolism	Ketoconazole levels increased by 3-fold.	Immediate	Moderate	Use with caution; do not exceed 200 mg ketoconazole per day.
RTV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism	May decrease serum levels of RTV. RTV may increase serum level of anticonvulsants	Delayed	Moderate	Consider alternative anticonvulsants (i.e valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level. Carbamazepine toxicity has been reported.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
RTV	Antidepressant (TCAs: desipramine, amitriptyline.) SSRIs, Bupropion	Inhibition of hepatic metabolism	Desipramine AUC increased by 145%. Increased serum levels of SSRIs, bupropion	Immediate	Major	Monitor desipramine levels. Consider citalopram, sertraline, or fluoxetine. Monitor for increased effects from SSRIs, bupropion. Doses of RTV used in boosted PI regimens may have minimal effects.
RTV	Antipsychotic (Olanzapine)	Induction of hepatic metabolism	Olanzapine AUC decreased by 50%.	Delayed	Moderate	Olanzapine dose may need to be increased.
RTV	Antipsychotic (Pimozide)	Inhibition of hepatic metabolism	May significantly increase pimozide serum level resulting in QTc prolongation	Immediate	Major	Concurrent administration of pimozide is contraindicated.
RTV	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism.	Serum levels of simvastatin and lovastatin are increased.	Immediate	Moderate	Avoid co-administration, alternatives that may be used include atorvastatin, pravastatin, fluvastatin. Monitor for adverse effects due to limited clinical data.
RTV	Opioid analgesic	Inhibition of hepatic metabolism.	Prolonged sedation and possible respiratory depression	Immediate	Major	Avoid concurrent administration of meperidine, propoxyphene, and fentanyl. Morphine may be a safer alternative.
RTV	Clarithromycin	Inhibition of hepatic metabolism.	Clarithromycin AUC increased by 77%	Immediate	Minor	Reduce clarithromycin dose for renal failure. Consider using azithromycin.
RTV	Didanosine (buffered)	Interference with absorption	Decreased ritonavir absorption.	Immediate	Major	Consider using ddI EC or separate administration by >2 hours.
RTV	Saquinavir	Inhibition of hepatic metabolism.	Saquinavir AUC increased by 20-fold.	Immediate	Minor	Dual protease inhibitor with the most clinical experience. Recommended doses: ritonavir 400 mg bid and SQV (Fortovase® or Invirase®) 400 mg bid or SQV 1000 mg + RTV 100 mg bid or SQV 1600 mg + RTV 100 mg qd.

RTV	Indinavir	Inhibition of hepatic metabolism.	Indinavir AUC increased by 2 to 5-fold.	Immediate	Minor	Interaction allows indinavir to be dosed twice a day, which may reduce renal stones associated with higher dose indinavir. Dose: IDV 400 mg bid and RTV 400 mg bid or IDV 800 mg bid + RTV 100 bid.
RTV	Nelfinavir	Inhibition of hepatic metabolism.	Nelfinavir AUC increased by 2.5-fold.	Immediate	Minor	Only marginal PK benefit. Clinical trials have used ritonavir 400 mg bid and nelfinavir 500 mg or 750 mg bid.
RTV	Amprenavir	Inhibition of hepatic metabolism.	Amprenavir AUC increased by 2.5-fold.	Immediate	Minor	Dose: APV 600 mg bid plus RTV 100 mg bid or APV 1200 mg qd plus RTV 200 mg qd.
RTV	Atazanavir	Inhibition of hepatic metabolism	ATV increases AUC by 238%	Immediate	Minor	A beneficial PK interaction, use ATV 300 mg + RTV 100 mg qd.
RTV	Fosamprenavir	Inhibition of hepatic metabolism	fAPV increases AUC by 100%, C _{min} by 400% when combined with 200 mg RTV	Immediate	Minor	A beneficial PK interaction, use RTV-boosted regimen (fAPV 700 mg + RTV 100 mg bid) in ARV-experienced patients.
Nelfinavir (Viracept®)	Ketoconazole	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 35%	Immediate	Minor	No dose adjustment needed.
NFV	Fluconazole	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 30%	Immediate	Minor	May be beneficial. No dose adjustment needed.
NFV	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism.	Increased serum level of simvastatin and lovastatin	Immediate	Moderate	Avoid co-administration: Alternatives includes pravastatin (but pravastatin AUC decreased by 47%), and fluvastatin. Monitor for adverse effects due to limited clinical data. Atorvastatin levels increased by 74%.
NFV	Methadone	Induction of hepatic metabolism	Decreased serum level of inactive methadone (S)-isomer. No change in active methadone (R)-isomer	Delayed	Minor	Use standard dose. No withdrawal symptoms observed.
NFV	Rifampin	Induction of hepatic metabolism	Nelfinavir AUC decreased by 82%	Delayed	Major	Concurrent administration contraindicated.

Table 14-6 Drug Interactions of Antiretrovirals (continued)

<i>Primary drug</i>	<i>Interacting drug</i>	<i>Mechanism of interaction</i>	<i>Effect</i>	<i>Time course</i>	<i>Severity</i>	<i>Comments/ management recommendation</i>
NFV	Rifabutin	Induction of hepatic metabolism by rifabutin	Nelfinavir AUC decreased by 32%	Delayed	Moderate	If co-administration required, increase nelfinavir to 1000 mg po tid.
NFV		Inhibition of hepatic metabolism by nelfinavir	Rifabutin levels increased by 2-fold	Immediate	Moderate	If co-administration required, decrease rifabutin to 150 mg po qd or 300 mg 3x/week.
NFV	Benzodiazepines	Inhibition of hepatic metabolism	Prolonged sedation due to accumulation of benzodiazepine	Immediate	Major	Midazolam and triazolam are contraindicated. Alternative benzodiazepines include temazepam and lorazepam.
NFV	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.
NFV	Terfenadine, Astemizole, Cisapride	Inhibition of hepatic metabolism	Drug levels increased by 3-fold or greater.	Immediate	Major	Concurrent administration contraindicated due to potential cardiac arrhythmia. Recommended alternative antihistamine: loratidine, fexofenadine, or cetirizine. Alternative pro-kinetic agent: metoclopramide.
NFV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease NFV serum level	Delayed	Major	Co-administration is contraindicated.
NFV	Oral contraceptives	Induction of hepatic metabolism	Ethinyl estradiol AUC decreased by 47%	Delayed	Major	Advise patient to use alternative or additional method of contraception.
NFV	Sildenafil	Inhibition of hepatic metabolism.	Sildenafil AUC increased by 2-11 fold.	Immediate	Major	Caution with concurrent use. Do not exceed 25 mg of sildenafil in a 48-hour period.

NFV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism	May decrease serum levels of NFV. NFV may increase serum levels of anticonvulsants	Delayed	Moderate	Consider alternative anticonvulsants (i.e valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level.
NFV	Indinavir	Inhibition of hepatic metabolism.	Indinavir AUC increased by 50% Nelfinavir AUC increased by 80%	Immediate	Minor	Limited data for dosing IDV 1200 mg bid + NFV 1250 mg bid.
NFV	Saquinavir	Inhibition of hepatic metabolism	Fortovase® AUC increased by 3-5 fold. Nelfinavir AUC increased by 20%	Immediate	Moderate	Dose nelfinavir 750 mg tid and Fortovase 800 mg tid or 1200 mg bid.
NFV	Amprenavir	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 15%. Amprenavir AUC increased by 50%.	Immediate	Minor	Limited data: NFV 1250 mg bid plus APV 1200 mg bid.
NFV	Ritonavir	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 1.5 fold. Increase in Nelfinavir metabolite.	Immediate	Moderate	Limited data: ritonavir 400 mg bid and nelfinavir 500 mg or 750 mg bid. Boosting with ritonavir will yield only minimal pharmacokinetic enhancement of nelfinavir serum concentration.
NFV	Lopinavir/r	Induction of hepatic metabolism by NFV. Inhibition of hepatic metabolism by LPV/r.	LPV decreased by 33%. NFV increased 25%	Delayed	Moderate	Consider increasing LPV/r dose to 4 caps bid with NFV co-administration.
NFV	Nevirapine					No significant drug interaction. Use standard dose.
NFV	Delavirdine	Induction of hepatic metabolism	Delavirdine AUC decreased by 50%. NFV AUC increased by 2-fold.	Immediate	Minor	Consider increasing DVV dose to 600 mg tid with standard dose NFV 1250 mg bid (limited data).
NFV	Efavirenz	Inhibition of hepatic metabolism	NFV AUC increased by 20%. EFV levels unchanged.	Immediate	Minor	No significant drug interaction. Use standard dose.
NFV	Voriconazole	Potential for bi-directional interaction	NFV and voriconazole may be increased	Immediate	Moderate	Monitor for toxicities.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
Amprénavir (Agenerase®) (APV)	Rifampin	Induction of hepatic metabolism	Amprénavir AUC decreased by 80%	Delayed	Major	Concurrent administration contraindicated.
APV	Rifabutin	Induction of hepatic metabolism	Amprénavir AUC decreased by 14%. Rifabutin AUC increased by 204%	Delayed	Moderate	Dose rifabutin 150 mg qd or 300 mg 3x/week. No change in amprénavir dose.
APV	Ketoconazole	Inhibition of hepatic metabolism	Amprénavir AUC increased by 32%. Ketoconazole AUC increased by 44%	Immediate	Minor	May be beneficial. No dose adjustment needed.
APV	Clarithromycin	Inhibition of hepatic metabolism	Amprénavir AUC increased by 18%	Immediate	Minor	No dose adjustment needed.
APV	Oral contraceptives	Induction of hepatic metabolism	Potential decreases in ethinyl estradiol level.	Delayed	Major	Advise patient of potential risk and the use of an alternative or additional method of contraception.
APV	Sildenafil	Inhibition of hepatic metabolism.	Sildenafil AUC increased by 2-11 fold.	Immediate	Major	Caution with concurrent use. Do not exceed 25 mg of sildenafil in a 48-hour period.
APV	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism.	Simvastatin and lovastatin levels increased.	Immediate	Moderate	Avoid concurrent administration. Alternative agents include atorvastatin, pravastatin, fluvastatin. Monitor for adverse effects due to limited clinical data.
APV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease APV serum level	Delayed	Major	Co-administration is contraindicated.

APV	Saquinavir	Induction of hepatic metabolism	Saquinavir level decreased by 18%. Ampronavir level decreased by 36%.	Delayed	Minor	No dose adjustment. Insufficient data for dose recommendation.
APV	Indinavir	Inhibition of hepatic metabolism	Ampronavir AUC increased by 33%. Indinavir AUC decreased by 38%.	Immediate	Minor	No dose adjustment. IDV 800 mg tid plus APV 800 mg tid.
APV	Nelfinavir	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 15%. Ampronavir AUC increased by 50%.	Immediate	Minor	No dose adjustment. NFV 750 mg tid plus APV 800 mg tid.
APV	Ritonavir	Inhibition of hepatic metabolism	Ampronavir AUC increased by 2.5-fold.	Immediate	Minor	Dose: APV 600 bid/RTV 100 bid or APV 1200 mg qd/RTV 200 mg qd.
APV	Lopinavir/r	Induction of hepatic metabolism by APV. Inhibition of hepatic metabolism by LPV/r	APV C _{min} increased 5-fold. LPV AUC decreased 30–50%.	Delayed	Moderate	Dose: LPV/r 533 mg/133 mg (4 caps) + APV 750 mg bid (+/- EFV).
APV	Efavirenz	Induction of hepatic metabolism	Ampronavir AUC decreased by 36%. Efavirenz AUC increased by 15%.	Delayed	Moderate	Dose: APV 600 mg/RTV 100 mg bid + EFV 600 mg qHS.
APV	Nevirapine	Induction of hepatic metabolism	APV level may be significantly decreased			No data.
APV	Delavirdine	Induction of hepatic metabolism by APV. Inhibition of hepatic metabolism by DLV	DLV AUC decreased by 60% and trough decreased by 90%. APV AUC increased by 25%.	Delayed	Major	Co-administration not recommended.
APV	Methadone	Induction of hepatic metabolism	Decreased serum level of inactive methadone (S)-isomer. No change in active methadone (R)-isomer	Delayed	Minor	Use standard dose. No withdrawal symptoms observed.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
<i>Primary drug</i>	<i>Interacting drug</i>	<i>Mechanism of interaction</i>	<i>Effect</i>	<i>Time course</i>	<i>Severity</i>	<i>Comments/ management recommendation</i>
APV	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated
APV	Midazolam, Triazolam	Inhibition of hepatic metabolism	AUC of midazolam and triazolam are increased.	Immediate	Major	Concurrent administration contraindicated due to potential for prolonged sedation. Lorazepam and temazepam may be safe alternatives.
APV	Terfenadine Astemizole Cisapride	Inhibition of hepatic metabolism	Cardiotoxic drug level increased by 3-fold or greater.	Immediate	Major	Concurrent administration contraindicated due to potential for cardiac arrhythmias. Alternatives include loratidine, fexofenadine, or cetirizine. Alternative prokinetic agent includes metoclopramide.
APV	Amiodarone, lidocaine (systemic), quinidine, and bepridil		May increase serum level of antiarrhythmics.	Immediate	Moderate	Use with caution. Monitor antiarrhythmic serum level.
APV	Pimozide		May increase serum level of pimozide.	Immediate	Major	Contraindicated. Potential for life-threatening cardiac arrhythmia.
APV	Calcium channel blocker		May increase serum level of calcium channel blocker	Immediate	Moderate	Use with caution. Close monitoring recommended.
APV	Dexamethasone		May decrease APV serum level.	Delayed	Moderate	Use with caution.
APV	Cyclosporine, tacrolimus, rapamycin		May increase immunosuppressant serum level.	Immediate	Moderate	Therapeutic drug monitoring of immunosuppressant highly recommended.
APV	Amitriptyline, imipramine, and desipramine		May increase TCA serum level.	Immediate	Moderate	Consider therapeutic drug monitoring or use SSRI (i.e. citalopram, sertraline, or fluoxetine).

APV	Phenytoin, carbamazepine, and phenobarbital		May significantly decrease APV serum level.	Delayed	Moderate	Consider alternative anticonvulsant (i.e. valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level.
APV	Didanosine	May interfere with absorption	APV serum level may be decreased	Immediate	Moderate	Dosing should be separated by 1 hour.
APV	Warfarin	Unknown	Increase or decrease in warfarin	Immediate	Moderate	INR must be monitored.
APV	Voriconazole	Potential for bi-directional interaction (or induction with RTV co-administration)	Voriconazole may be decreased with RTV co-administration. APV may be increased	Immediate	Moderate	Monitor for toxicities and therapeutic efficacy.
APV	Bepiridil	Inhibition of hepatic metabolism	May increase bepridil	Immediate	Moderate	Use with caution.
APV	Tadalafil	Inhibition of hepatic metabolism	May substantially increase tadalafil AUC and half life	Immediate	Moderate	Start with 5 mg dose; do not exceed a single 10 mg dose of tadalafil in 72 hrs.
APV	Vardenafil	Inhibition of hepatic metabolism	May increase vardenafil AUC	Immediate	Moderate	Start with a 2.5 mg dose; do not exceed a 2.5 mg dose of vardenafil in 72 hrs.
APV	Atorvastatin	Inhibition of hepatic metabolism	May increase atorvastatin substantially	Immediate	Moderate	Use lowest possible starting dose of atorvastatin with careful monitoring.
Fosamprenavir drug-drug interactions						
Since fosamprenavir is converted to amprenavir, all drug interaction data for "unboosted" amprenavir should also apply to "unboosted" fosamprenavir. However, there are some interactions that are more pronounced with fosamprenavir.						
fAPV	LPV/r	Enzyme induction	Significant decrease in levels of both LPV and APV	Delayed	Major	Boosting with RTV still resulted in significant reduction of APV trough at standard dose. Best PK data with fAPV 1400 mg bid and LPV/r 533 mg/133 mg bid.
fAPV/r	EFV	Enzyme induction	APV Cmin decreased by 17% (90% CI 4–29%) with bid vs. 36% (90% CI 8–56%) with qd fAPV dosing	Delayed	Moderate	Recommended Dose: fAPV 700 mg bid/RTV 100 mg bid or fAPV 1400 mg qd/RTV 300 mg qd.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
<i>Primary drug</i>	<i>Interacting drug</i>	<i>Mechanism of interaction</i>	<i>Effect</i>	<i>Time course</i>	<i>Severity</i>	<i>Comments/ management recommendation</i>
fAPV	Atorvastatin	Enzyme inhibition	Atorvastatin AUC increased by 130% (with fAPV 1400 mg bid) and 150% (with fAPV 700 mg/RTV 100 mg bid). No change in APV AUC.	Immediate	Moderate	Close monitoring recommended. Do not exceed 20 mg per day of atorvastatin.
fAPV/r	Ritonavir	Enzyme inhibition	Ampronavir AUC increased by over 2-fold. C _{min} increased by 4-fold with daily administration and 6-fold with twice daily administration compared to fAPV 1400 mg bid.	Immediate	Minor	Dose: fAPV 700 mg bid/RTV 100 mg bid or fAPV 1400 mg qd/RTV 200 mg qd.
Lopinavir/r	Methadone	Induction of hepatic metabolism	Methadone AUC decreased by 53%	Delayed	Minor	No withdrawal symptoms observed in 2 out of 3 studies. Standard dose recommended. Monitor and increase dose of methadone if needed.
LPV/r	Rifampin	Induction of hepatic metabolism	LPV AUC decreased 75%	Delayed	Major	Concurrent administration contraindicated. Consider using rifabutin with LPV/r.
LPV/r	Rifabutin	Inhibition of hepatic metabolism by LPV/r	Rifabutin serum level increased by 3-fold. LPV serum level not affected	Immediate	Moderate	Dose: LPV/r 3 caps bid plus rifabutin 150 mg qod or 150 mg 3x/week.
LPV/r	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.

LPV/r	Terfenadine Astemizole Cisapride	Inhibition of hepatic metabolism	Drug level increased by 3-fold or greater.	Immediate	Major	Concurrent administration contraindicated due to potential for cardiac arrhythmias. Alternative antihistamines include loratidine, fexofenadine, or cetirizine. Alternative pro-kinetic agent includes metoclopramide.
LPV/r	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease LPV serum level	Delayed	Major	Co-administration is contraindicated.
LPV/r	Benzodiazepines	Inhibition of hepatic metabolism	Prolonged sedation due to accumulation of benzodiazepine	Delayed	Major	Concurrent administration of midazolam and triazolam are contraindicated. Alternative benzodiazepine that can be used: Temazepam, oxazepam, and lorazepam.
LPV/r	Antidepressants (TCA, SSRIs, Bupropion)	See RTV section				
LPV/r	Antiarrhythmics	Inhibition of hepatic metabolism	AUC of antiarrhythmics increased	Immediate	Major	Concurrent administration of propafenone, flecainide, and encainide are contraindicated.
LPV/r	Antipsychotic (Pimozide)	Inhibition of hepatic metabolism	May significantly increase pimozide serum level resulting in QTc prolongation	Immediate	Major	Concurrent administration of pimozide is contraindicated.
LPV/r	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism.	Serum levels of simvastatin and lovastatin are increased.	Immediate	Moderate	Avoid co-administration, alternatives that may be used include pravastatin, fluvastatin. Monitor for adverse effects due to limited clinical data.
LPV/r	Phenytoin (also carbamazepine and phenobarbital).	Induction of hepatic metabolism	LPV decreased by 33%. Phenytoin decreased by 31%.	Delayed	Major	Consider alternative anticonvulsants. Consider TDM. Monitor anticonvulsant levels with co-administration.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
LPV/r	Atorvastatin	Inhibition of hepatic metabolism	Atorvastatin AUC increased by 6-fold.	Immediate	Moderate	Clinical significance unknown. Use with caution. Starting dose atorvastatin 10 mg qd.
LPV/r	Indinavir	Inhibition of hepatic metabolism	Indinavir AUC increased by 3-fold	Immediate	Moderate	Dose: IDV 600 mg or 666 mg bid plus LPV/r 400 mg/100 mg bid.
LPV/r	Amprenavir	Induction of hepatic metabolism by APV. Inhibition of hepatic metabolism by LPV/r	APV C _{min} increased 5-fold. LPV AUC decreased 30–50%.	Delayed	Moderate	Dose: LPV/r 533 mg/133 mg (4 caps) + APV 750 mg bid.
LPV/r	Efavirenz	Induction of hepatic metabolism	LPV AUC decreased by 40%.	Delayed	Major	Dose: LPV/r 533 mg/133 mg (4 caps) bid + EFV 600 mg qhs.
LPV/r	Delavirdine	Inhibition of hepatic metabolism.	LPV AUC increased by 8–134%. DIV no change	Immediate	Minor	Limited data. No dose adjustment.
LPV/r	Nevirapine	Induction of hepatic metabolism	LPV C _{min} decreased by 55%. NVP level not affected.	Delayed	Major	Dose: LPV/r 533 mg/133 mg (4 caps) bid (NVP standard dose).
LPV/r	Saquinavir	Inhibition of hepatic metabolism	Saquinavir C _{min} increased by 3–6-fold	Immediate	Minor	Dose: SQV 1000 mg bid plus LPV/r 400/100 mg bid.
LPV/r	Nelfinavir	Induction of hepatic metabolism by NFV. Inhibition of hepatic metabolism by LPV/r.	LPV decreased by 33%. NFV increased 25%.	Delayed	Moderate	Consider increasing LPV/r dose to 4 caps bid with NFV co-administration.
LPV/r	Itraconazole	Inhibition of hepatic metabolism	May increase itraconazole serum level	Immediate	Moderate	Use with caution; do not exceed 200 mg itraconazole.
LPV/r	Voriconazole	Potential for bi-directional inhibition and/or induction	May decrease voriconazole serum level	Immediate	Moderate	Monitor for toxicities and therapeutic efficacy. Co-administration not recommended by manufacturer.
LPV/r	Vardenafil	Inhibition of hepatic metabolism	May substantially increase vardenafil AUC	Immediate	Moderate	Start with a 2.5 mg dose; do not exceed a 2.5 mg dose of vardenafil in 72 hrs.

LPV/r	Ethinyl estradiol	Induction of hepatic metabolism	EE AUC decreases 42%	Immediate	Major	Use alternative or additional method.
Atazanavir (ATV)	Clarithromycin	Inhibition of hepatic metabolism	ATV AUC increased by 28%. Clarithromycin AUC increased by 94%. Clarithromycin hydroxy-metabolite AUC decreased by 30%	Immediate	Major	QTc prolongation observed with co-administration. 50% of clarithromycin dose recommended.
ATV	ddl (buffered)	Interference with absorption	No effect on ddl serum level. ATV AUC decreased by 87%.	Immediate	Major	Administer ATV 400 mg one hour after ddl (buffered) administration. Consider ddl EC.
ATV	EFV	Induction of hepatic metabolism (inhibition of hepatic metabolism with RTV boosting)	ATV AUC decreased by 74%. EFV not measured (ATV AUC increased by 39% with RTV boosting)	Delayed (Immediate)	Major (Minor)	Co-administration of ATV as a sole PI with EFV is not recommended. Boosting ATV 300 mg with 100 mg RTV recommended with EFV co-administration (doubles total ATV exposure and increases ATV trough by 300%).
ATV	Oral contraceptives	Inhibition of glucuronidation.	Ethinyl estradiol AUC increased by 48%. Norethindrone AUC increased by 110%. ATV not measured.	Delayed	Minor	Clinical significance unknown. Monitor for adverse reactions with oral contraceptive; consider alternative method of contraception.
ATV	Diltiazem	Inhibition of hepatic metabolism	Diltiazem AUC increased by 125%. Desacetyl diltiazem (active metabolite) AUC increased by 165%. ATV not affected.	Immediate	Major	Increase in PR interval observed. Use with caution. Start with 50% of diltiazem dose and titrate slowly. Monitor BP and pulse.
ATV	Atenolol	Inhibition of hepatic metabolism	Atenolol AUC increased by 25%. ATV not affected.	Immediate	Moderate	No effect on PR or QTc interval with co-administration. Monitor BP and pulse.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
ATV	Rifabutin	Inhibition of hepatic metabolism	Rifabutin AUC increased. ATV not affected	Immediate	Moderate	Dose: ATV 400 mg qd plus rifabutin 150 mg 3x/week.
ATV	SQV	Inhibition of hepatic metabolism	SQV AUC increased by 5.5-fold. ATV not affected	Immediate	Minor	Beneficial PK interactions which allows once-a-day administration of SQV 1200 mg. Standard dose AZT/3TC with ATV.
ATV	AZT/3TC	No effect	AZT and 3TC not affected. ATV not measured			
ATV	Ketoconazole	No effect	ATV not affected. Ketoconazole not measured			Standard dose ATV with ketoconazole co-administration.
ATV	Tenofovir	Interference with absorption	ATV AUC decreased by 25%. TDF not measured	Immediate	Moderate	Interaction likely to occur due to interference with absorption. ATV dose 300 mg qd + RTV 100 mg qd with co-administration.
ATV	Rifampin	Induction of hepatic metabolism	ATV may be decreased	Delayed	Moderate	Rifabutin may be a safer alternative. Dose: ATV 400 mg qd plus rifabutin 150 mg 3x/week.
ATV	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities may be observed	Immediate	Major	Concurrent administration contraindicated until more data become available.
ATV	Terfenadine Astemizole Cisapride	Inhibition of hepatic metabolism	Drug level may be increased by 3-fold or greater.	Immediate	Major	Concurrent administration contraindicated until more data become available.
ATV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease ATV serum level	Delayed	Major	Concurrent administration contraindicated until more data become available.

ATV	Benzodiazepines	Inhibition of hepatic metabolism	May prolong sedation due to accumulation of benzodiazepine	Delayed	Major	Concurrent administration of midazolam and triazolam are contraindicated until more data become available. Alternative benzodiazepine that can be used: Temazepam, oxazepam, and lorazepam.
ATV	Antiarrhythmics	Inhibition of hepatic metabolism	AUC of antiarrhythmics increased	Immediate	Major	Concurrent administration of propafenone, quinidine, flecainide, encainide, amiodarone, and bepridil are contraindicated until more data become available.
ATV	Proton-pump inhibitors	Decreased absorption	Significantly decreases ATV levels	Immediate	Major	Avoid concomitant use.
ATV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism	May decrease serum levels of ATV. ATV may increase serum levels of anticonvulsants	Delayed	Moderate	Consider alternative anticonvulsant (i.e. valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level. Carbamazepine toxicity has been reported.
ATV	Methadone	No data				No data.
ATV	Nevirapine	No data				Consider using ATV 300 mg + RTV 100 mg qd.
ATV	Ritonavir	Induction of hepatic metabolism	ATV AUC increases by 238%	Immediate	Minor	Use ATV 300 mg + RTV 100 mg.
ATV	Warfarin	Unknown	May increase in warfarin concentration	Delayed	Moderate	Monitor INR.
ATV	Amriptyline Imipramine	Inhibition of hepatic metabolism	May increase tricyclic concentration	Immediate	Minor	Monitor tricyclic antidepressant concentration.
ATV	Voriconazole	Potential for bi-directional inhibition and/or induction	May decrease voriconazole serum level with RTV co-administration	Delayed	Moderate	Monitor for toxicities and therapeutic efficacy.
ATV	Sildenafil	Inhibition of hepatic metabolism	May increase sildenafil AUC	Immediate	Moderate	Use with caution; start with reduced dose of 25 mg q48h and monitor for adverse affects.

Table 14-6 Drug Interactions of Antiretrovirals (continued)						
Primary drug	Interacting drug	Mechanism of interaction	Effect	Time course	Severity	Comments/ management recommendation
ATV	Tadalafil	Inhibition of hepatic metabolism	May substantially increase tadalafil AUC	Immediate	Moderate	Start with 5 mg dose; do not exceed a single 10 mg dose of tadalafil in 72 hrs.
ATV	Vardenafil	Inhibition of hepatic metabolism	May substantially increase vardenafil AUC	Immediate	Moderate	Start with a 2.5 mg dose; do not exceed a 2.5 mg dose of vardenafil in 72 hrs.
ATV	H2 receptor antagonist	Interference with absorption	May significantly decrease ATV concentration	Immediate	Moderate	Separate ATV concentration by 12 hrs.
ATV	Atorvastatin	Inhibition of hepatic metabolism	May increase atorvastatin substantially	Immediate	Moderate	Use lowest possible starting dose (10 mg) of atorvastatin with careful monitoring.
Tipranavir/ ritonavir (currently in Phase III trials)	Efavirenz		No change in EFV PK, TPV PK (at 500/100 mg dose)			Phase II trials are currently using TPV500/200 mg with the co-administration of EFV (Roszko, 2003).
TPV/r	AZT		AZT AUC decreased by 40%. No change in TPV PK.		Minor	Clinical significance unknown.
TPV/r	ddl EC		No Interactions			Separate administration time by 4 hours due to potential interaction of self emulsifying drug delivery system (SEDDS) of TPV and the ddl EC outer coat.
TPV/r	Tenofovir		TPV AUC decreased by 20% (with TPV 500 mg/100 mg)		Minor	Reduction of TPV may be due to decrease in RTV. TPV 500 mg/200 mg should be considered.
TPV/r	LPV/r		LPV AUC decreased by 49%		Major	Do not co-administer.
TPV/r	APV		APV AUC decreased by 45%		Major	Do not co-administer.
TPV/r	SQV		SQV AUC decreased by 70%		Major	Do not co-administer.

Drug Interactions with Fusion Inhibitors				
Fuseon	No significant drug interactions			
<p>AUC= Area Under the Concentration Time Curve C_{max} = Peak serum concentration C_{min} = Trough serum concentration CrCl = Creatinine clearance TDM = Therapeutic drug monitoring Time course: Delayed = maximal interaction occurring at 14 days Immediate = interaction occurring immediately</p> <p>Severity: Major = Do not co-administer; contraindicated Moderate = Can be co-administered with caution and possible dose adjustment. Minor = Can be co-administered.</p>				

Table 14-7: Clinically Pertinent Food-Drug Interactions

<i>Valganciclovir / Itraconazole Capsule / Ritonavir / Atazanavir:</i> Should be taken with food or within 2 hr of eating.
<i>AZT:</i> Can be taken with food to decrease GI side effects.
<i>Saquinavir¹ (Fortovase® and Invirase®) / Atovaquone / Nelfinavir:</i> Should be administered with a high-fat meal.
<i>Efavirenz / Amprenavir:</i> High-fat meal should be avoided.
<i>Didanosine² / Indinavir³ / Itraconazole Solution / EFV:</i> Should be taken on an empty stomach (1 hr before or 2 hr after meals).
<i>Grapefruit Juice:</i> Increases saquinavir levels 40–100% but decreases indinavir AUC by 26%.

1 No food restriction when saquinavir is co-administered with RTV.

2 No food restriction when ddI is co-administered with TDF.

3 No food restriction when IDV is co-administered with RTV.

Table 14-8: Drugs of Special Consideration in Pregnant Women

<i>Drug Name</i>	<i>FDA Class</i>	<i>Comments</i>
Terbutaline	B	Terbutaline has produced significant increases in birth weights (Briggs et al, 1998). Follow-up studies did not show increased adverse fetal outcomes (Svenningsen, 1982).
Ritodrine	B	The manufacturer reports that ritodrine administration after the 20th wk of gestation has not been associated with an increase in fetal abnormalities.
Methergine	C	Indicated for postpartum uterine bleeding due to atony. According to the manufacturer, oral methylergonovine .2 mg 3–4 times daily may be administered to nursing mothers for a MAXIMUM of 1 wk postpartum to control uterine bleeding. Should not be given during antenatal period. Should not be used in women with hypertension (including pre-eclampsia) or heart disease.
Pain Medication		
Acetaminophen	B	Acetaminophen is considered safe for shortterm use in all stages of pregnancy.
Aspirin	C	Use of aspirin, especially of chronic or intermittent high doses, should be avoided in pregnancy. May increase risk for maternal or newborn hemorrhage. Full dose aspirin in 3rd trimester may result in premature closure of ductus arteriosus and may prolong gestation and labor. Acetaminophen is preferred analgesic/antipyretic during pregnancy.
Nonsteroidal anti-inflammatory drugs (NSAIDs)	C	Avoid in pregnancy. Due to prostaglandin synthesis inhibition, constriction of ductus arteriosus has been reported. Persistent pulmonary hypertension in the newborn has occurred when NSAIDs were used in 3rd trimester or near term. NSAIDs have been shown to inhibit labor and prolong pregnancy and have been associated with decreases in amniotic fluid volume.
Narcotic analgesic	B	Narcotic analgesics can be used short term in pregnancy. Avoid the use of high doses for prolonged periods near term as neonatal withdrawal can occur.

Table 14-9: Alternative/Complimentary Medication to Avoid in Pregnancy

Drug Name	Animal Data	Human Experience in Pregnancy	Comments
Vitamin A	A known teratogen at high doses in animal data.	A double-blind randomized trial of low-dose supplementation with vitamin A or beta-carotene (7000 µg retinol equivalent) in malnourished pregnant women reported a 40% decrease in newborn mortality (West, 1999). In a prospective case-controlled study of 423 exposures to 10,000 IU vitamin A during the first 9 wk an increased risk of major malformations was not reported (Mastroiacovo, 1999).	Until more data are available it is prudent to consume only the recommended dietary allowance of 8000 IU (which can be obtained by a balanced diet).
Vitamin B6 (in doses above 100 mg/day)	None	None	Avoid use of high doses in pregnancy. Possible health hazard: ataxia and peripheral neuropathy.*
Niacin (in doses above 500 mg immediate-release or 750 mg sustained-release)	None	None	Avoid use of high doses in pregnancy. Possible health hazard: GI symptoms (nausea, vomiting, diarrhea, abdominal cramps), liver disease.*
Selenium (in doses of greater than 800–1000 µg per day)	None	None	Avoid use of high doses in pregnancy. Possible health hazard: tissue damage.*
Ma-huang (<i>Ephedra sinica</i>)	None	None	Avoid use in pregnancy. The FDA warns against using Ma-huang (<i>Ephedra sinica</i>) due to possible health hazards including: high blood pressure, irregular heartbeat, nerve damage, injury, insomnia, tremor, headache, seizure, heart attack, stroke, and death.* Over 500 reports of adverse events including 8 fatalities have been reported to the FDA (CDC, 1996).
St. John's wort (<i>Hypericum perforatum</i>)	None	None	Metaanalysis of St. John's wort suggests that it was more effective than placebo and as effective as low-dose tricyclic antidepressants for short-term management of mild to moderately severe depression (Kim, 1999). Due to the lack of data in pregnancy the routine use of St. John's wort cannot be recommended. Major drug interaction: Indinavir trough concentration (C _{mir}) decreases by 81% when co-administered with St. John's wort.

Table 14-9: Alternative/Complimentary Medication to Avoid in Pregnancy (continued)

<i>Drug Name</i>	<i>Animal Data</i>	<i>Human Experience in Pregnancy</i>	<i>Comments</i>
Chaparral herb (traditional American Indian medicine)	None	None	Avoid use in pregnancy. Possible health hazard: liver disease, possibly irreversible.*
Comfrey herb	None	None	Avoid in pregnancy. Possible health hazard: obstruction of blood flow to liver, possibly leading to death.*
Slimming/dieter's tea	None	None	Avoid in pregnancy. Possible health hazard: nausea, diarrhea, vomiting, stomach cramps, chronic constipation, fainting, possibly death.*
Germander herb	None	None	Avoid in pregnancy. Possible health hazard: liver disease, possibly leading to death.*
Lobelia herb (Indian tobacco)	None	None	Avoid in pregnancy. Possible health hazard: respiratory distress, tachycardia, hypotension, and possibly coma and death at higher doses.*
Magnolia-Stephania herb	None	None	Avoid in pregnancy. Possible health hazard: renal failure which may be irreversible.*
Willow bark herb	None	None	Avoid in pregnancy. Possible health hazard: allergic reaction (marketed as aspirin-free product, although it actually contains a precursor of aspirin with subsequent conversion to aspirin).*
Wormwood herb	None	None	Avoid in pregnancy. Possible health hazard: neurological symptoms, paresthesia, delirium and paralysis.*
Germanium mineral	None	None	Avoid in pregnancy. Possible health hazard: kidney damage, possibly death.*
L-tryptophan amino acid	None	None	Avoid in pregnancy. Possible health hazard: eosinophilic myalgia syndrome, a potentially fatal blood dyscrasia. (FDA has limited its import into the US).*

* Note: Folic acid deficiency has been associated with increased risk of neural tube defects in the fetus and megaloblastic anemia in the mother. All pregnant women should receive sufficient dietary or supplementary folic acid to maintain normal maternal folate levels. The CDC recommends daily consumption of 0.4 mg of folic acid from diet and/or supplements for all women of childbearing age before the onset of pregnancy.

Table 14-10: Dosing of Antiretroviral Agents in Renal Insufficiency and/or Hepatic Insufficiency

Drug Name	Usual adult dose	Dosing for GFR > 50 mL/min	Dosing for GFR 10-50 mL/min	Dosing for GFR < 10 mL/min	Dosing in Hemodialysis (HD)	Dosing in Peritoneal dialysis (PD)	Hepatic clearance/ Comments
Zidovudine (Retrovir®, AZT)	300 mg bid, or 200 mg tid	300 mg bid	300 mg bid	300 mg qd	300 mg qd	300 mg qd, a very small amount removed in PD (no supplemental dose needed) (Gallicano, 1992)	Extensive with significant first pass liver metabolism to GAZT. Excreted in urine as 14–18% unchanged drug and 60–74% GAZT. With GFR <20 mL/min half life is increased from 1.1–1.4 hr to 0.9 to 8 hours (with high inter patient variation).
Didanosine (Videx®, Dideoxyinosine, ddi)	Wt >60kg dose: 400 mg qd (tabs) or 500 mg qd (powder). Wt <60kg dose: 250 mg qd (tabs) or 334 mg qd (powder). Dose can also be taken in two divided doses	Usual dose	50% of usual dose	25% of usual dose	25% of usual dose qd, on days of dialysis give post dialysis: 30% removal after a 3-hours session (Knupp, 1996)	25% of usual dose qd. Not removed with PD (Knupp, 1996)	Metabolism not fully evaluated. 20–40% excreted unchanged in the urine.
Stavudine (Zerit®, d4T)	Wt >60kg dose: 40 mg bid. Wt <60kg dose: 30 mg bid	Wt >60kg dose: 40 mg bid. Wt <60kg dose: 30 mg bid	Wt >60kg dose: 20 mg q12–24h. Wt <60kg dose: 15 mg q12–24	Wt >60kg dose: 20 mg q24h. Wt <60kg dose: 15 mg q24h	Wt >60kg dose: 20 mg q24h. Wt <60kg dose: 15 mg q24h, on days of dialysis dose post dialysis. (Grasela, 2000)	No data: Wt >60kg dose: 20 mg q24h. Wt <60kg dose: 15 mg q24h	Some hepatic metabolism and degradation by pyrimidine pathway. 40% of drug excreted unchanged.
Zalcitabine (Hivid®, ddC)	0.75 mg tid	0.75 mg tid	0.75 mg bid	0.75 mg qd	No data: 0.75 mg qd, on days of dialysis dose post dialysis (likely to be dialysed out)	No data: 0.75 mg qd, on days of dialysis dose post dialysis	Insignificant liver metabolism. 62–75% excreted unchanged in the urine. 10% excreted unchanged in the feces.

Table 14-10: Dosing of Antiretroviral Agents in Renal Insufficiency and/or Hepatic Insufficiency (continued)

<i>Drug Name</i>	<i>Usual adult dose</i>	<i>Dosing for GFR > 50 mL/min</i>	<i>Dosing for GFR 10-50 mL/min</i>	<i>Dosing for GFR < 10 mL/min</i>	<i>Dosing in Hemodialysis (HD)</i>	<i>Dosing in Peritoneal dialysis (PD)</i>	<i>Hepatic clearance/Comments</i>
Lamivudine (Epivir®; 3TC)	150 mg bid or 300 mg qd	150 mg bid	150 mg qd	150 mg x1 then 50 mg qd (some recommend 150 mg qd due to good safety profile and convenience)	150 mg x 1 then 25-50 mg qd; Dose after HD	50 mg qd; Limited data	Intermittent hemodialysis does not warrant a further change in dose from that defined by CrCl (Johnson, 1996).
Emtricitabine (Emtriva®) (FTC)	200 mg qd	200 mg qd	30-49 mL/min: 200 mg q 48hr. 15-29 mL/min: 200 mg q 72 hr. < 15 mL/min: 200 mg q 96 hr	200 mg qd	200 mg q 96 hr. (30% of dose removed with 3 hr. HD; on days of dialysis, dose post-HD)		
Abacavir (Ziagen®) ABC	300 mg bid or 600 mg qd	300 mg bid	300 mg bid	300 mg bid	Usual dose [In 4 patients undergoing HD or PD, the pharmacokinetics of abacavir were not altered (Thompson, 1998)]	Usual dose [In 4 patients undergoing HD or PD, the pharmacokinetics of abacavir were not altered (Thompson, 1998)]	Pharmacokinetics are unchanged in renal failure (Iziedine, 2001b). Animal studies: 12% unchanged Abacavir in the urine. Only 2% metabolized to carbovir. Consider ABC 200 bid with hepatic insufficiency.
Tenofovir (Viread®)	300 mg qd	300 mg qd 30-49 mL/min: 300 mg q48h.	<30 mL/min: 300 mg q72-96h	300 mg q7days	300 mg q 7 days following dialysis (54% removed with 4 hours high flux HD-healthy volunteer PK data) May require more if patient requires more than three 4-hour HD sessions.	No data; Not recommended by manufacturer. Interval adjustment likely.	Note: Dosing recommendations based on single dose PK data in healthy volunteer. HIV infected patients with Cr clearance less than 60 mL/min were excluded from clinical trials.

Efavirenz (Sustiva®)	600 mg qhs	Usual dose**	Usual dose likely**	Usual dose likely**	600 mg qhs, No significant removal with HD (Izzedine, 2000a)	600 mg qhs, Not removed with PD (Gill, 2000)	Data limited in renal failure. Extensive liver metabolism 14–34% excreted in urine as glucuronide metabolite and 16–61% excreted in stool.
Nevirapine (Viramune®)	200 mg qd x 14 days then 200 mg bid	Usual dose	Usual dose	Usual dose	Usual dose post-HD. Small amount removed (Izzedine, 2001a)	Usual dose post dialysis. 16 mg removed in dialysate in a 24 hour period.	Extensive liver metabolism to hydroxylated metabolites which are renally cleared. Less than 5% excreted unchanged in the urine.
Delavirdine (Rescriptor®)	400 mg tid	Usual dose**	Usual dose likely**	Usual dose likely**	No data: Unlikely to be removed in dialysis due to high protein binding**	No data: Unlikely to be removed in dialysis due to high protein binding**	Extensive liver metabolism.
Nelfinavir (Viracept®)	750 mg tid or 1250 mg bid	Usual dose	Usual dose	Usual dose	Usual dose. Removed with HD, MUST be given post-HD on days of dialysis (Izzedine, 2000a)	Usual dose. Not removed with PD (Tillotson, 2000)	Pharmacokinetics are unchanged in renal failure (Izzedine, 1999). Extensive liver metabolism to active oxidative metabolites. Major biliary excretion with less than 2% renal excretion.
Indinavir (Criviant®)	800 mg tid* or IDV 800/RTV 100–200 mg bid (increased incidence of kidney stones with RTV 200 mg—generally recommended only in pt also on EFV or NVP)	Usual dose*	Usual dose	Usual dose	Usual dose. Very small amount removed in dialysis (Izzedine, 2000b)	No data: Usual dose likely** (Low probability of significant amount being removed in dialysis due to low protein binding)	Pharmacokinetics are unchanged in renal failure (Izzedine, 2000b). Extensive liver metabolism to glucuronide and oxidative metabolites. Major biliary excretion with approximately 10% renal excretion.

Table 14-10: Dosing of Antiretroviral Agents in Renal Insufficiency and/or Hepatic Insufficiency (continued)							
Drug Name	Usual adult dose	Dosing for GFR > 50 mL/min	Dosing for GFR 10-50 mL/min	Dosing for GFR < 10 mL/min	Dosing in Hemodialysis (HD)	Dosing in Peritoneal dialysis (PD)	Hepatic clearance/Comments
Ritonavir (Norvir®)	600 mg bid (High dose not well tolerated, dose may be lowered if used with another PI)	Usual dose	Usual dose	Usual dose	Small amount dialyzed out, dose post HD (Izzedine, 2001b)	No data: Usual dose likely**, dose post dialysis on days of dialysis (Unlikely to be removed in dialysis due to high protein binding, however due to low volume of distribution small amount possibly removed)**	Pharmacokinetics are unchanged in renal failure (Izzedine, 2001b). Extensive liver metabolism to isopropylthiazole (active metabolites) and other inactive metabolite. Major biliary excretion with approximately 4–10% renal excretion.
Saquinavir (Invirase® (Capsule); Fortovase® (soft gel capsule))	Invirase 600* mg tid (not recommended as sole PI); Fortovase 1200 mg tid or INV 1000 mg/RTV 100 mg q12h.	Usual dose	Usual dose	Usual dose	Not dialyzed out (Izzedine, 2001b)	No data: Usual dose likely** (Unlikely to be removed in dialysis due to high protein binding and large volume of distribution.)	Pharmacokinetics are unchanged in renal failure (Izzedine, 2001b). Extensive first pass metabolism which accounts for saquinavir's low bioavailability. Major biliary excretion with only 1–3% renal excretion.
Amprenavir (Agenatrase®)	1,200 mg bid* or APV 600 mg/RTV 100 mg q12h.	Usual dose	Usual dose likely	Usual dose likely	No data: Usual dose likely	No data: Usual dose likely	Impaired hepatic function moderate—consider dose reduction 450 mg bid; severe—300 mg bid.
LPV/RTV (Kaletra®)	400/100 mg bid	Usual dose	Usual dose likely	Usual dose likely	Usual dose. Not removed with HD (Izzedine, 2001c)	No data: Usual dose likely	

Atazanavir (Reyataz®)	400 mg qd* or ATV 300/RTV 100 qd.	Usual dose	Usual dose likely	Usual dose. Dose post-HD	Usual dose likely	ATV is not recommended in patients with severe hepatic insufficiency. ATV AUC increased by 45% with mild to moderate hepatic impairment. Consider decreasing ATV to 300 mg/day in subjects with mild to moderate hepatic impairment. Clinical data using the lower dose in hepatic insufficiency has not been assessed.
Fosamprenavir (Lexiva®)	1400 mg* q12h or FAPV 700/100 RTV q12h.	usual dose	usual dose likely	No data. Usual dose likely.	No data. Usual dose likely.	
Enfuvirtide (Fuzeon®)	90 mg SQ q12h	usual dose	usual dose likely	No data. Usual dose likely.	No data. Usual dose likely.	

* Approved adult dose, but usually use lower doses with ritonavir boosting for most PIs.

** Prediction based on pharmacokinetic principles. Drugs likely to be removed have a $V_d < 0.7$ L/kg, protein binding $< 80\%$, and size < 1500 Dalton

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XV: RESOURCES

Judith Ellis, MS, and Helen Schietinger, MA, ACRN

I. HOW TO USE THIS CHAPTER



















A chapter devoted to additional resources is an essential part of this guide. First, HIV clinical care evolves so rapidly that some information in the guide will soon be out of date. Second, a wealth of information is available that supplements these chapters in specialized areas of care. It is our intention to include some of the most important resources for clinical care of women with HIV, but the list is by no means exhaustive. Readers can explore the links provided on websites to find other informative sites.









































































In this electronic information age, the term resources includes internet sites and electronic documents as well as organizations and published documents, so the chapter includes a range of mechanisms for obtaining more information. However, the web-based resources are considered primary because they are available from anywhere in the world and are usually updated on a periodic basis. Phone contact information is provided where available, so that those without access to the internet can still obtain information.

The resources are listed alphabetically in a grid that identifies major topics addressed by each resource as well as the type of information available. There is a brief description of the resource and website and phone contact information. The phone numbers with 800, 888, and 866 prefixes are only toll-free in the U.S.

Regarding special populations, the purpose of the resources chapter is to supplement the guide itself. We refer the reader to Chapter VIII, Addressing Cultural Issues to Improve Quality of Care, to discover tools to enhance the cultural competency of service providers and service agencies. In addition, many of the resources contain some information, such as fact sheets, about or for groups of people with special needs, such as people who are homeless, incarcerated, or transgendered. Special populations are usually only one aspect of a resource; there are not many resources specifically concerning racial/ethnic minorities or other special populations. The search function on many websites is a useful tool for locating information on specific topics or special populations. For example, providers caring for lesbians with HIV can find relevant information on their needs by searching The Body and the American Psychological Association Office on AIDS websites.

II. RESOURCES WITH TOPIC AREAS

Provider and Consumer Resources	Type User	Type Info	Epidemiology	Treatment and Care	Prevention	Pediatrics and Adolescents	Obstetrics and Gynecology	Adherence	Psychosocial Support and Quality of Life	Substance Abuse	Research and Clinical Trials	Nutrition	Occupational Exposure	Quality Improvement	Palliative Care	Care in Resource Poor Settings
<p>Adult AIDS Clinical Trials Group* (AACTG) Website for the NIH-funded AIDS Clinical Trials Groups. See Pediatric AIDS Clinical Trial Group for clinical trials in pregnant women. Contact: http://aactg.s-3.com</p>	A	1														
<p>AIDS Alliance for Children, Youth & Families National association providing advocacy, education and support for children and families affected by HIV/AIDS. (formerly the AIDS Policy Center for Children, Youth & Families) Contact: http://www.aids-alliance.org 1-202-785-3564, 1-888-917-AIDS (2437)</p>	A B	1, 3, 4, 6														
<p>AIDS Education Global Information System (AEGIS) Website with HIV information and resources from the mainstream press, professional journals, and legal and legislative sources Contact: http://www.aegis.com</p>	A	1, 5														
<p>AIDS Education and Training Centers (AETC) Regional centers that provide HIV training and education, including preceptorships for health care providers; national and international centers that provide technical assistance in evaluation and specific areas of clinical care, such as hepatitis and palliative care; the resource center that provides resource materials on a wide range of HIV-related topics and links to the other centers. Contact: http://www.aidsctc.org</p>	A	1, 3, 4, 5														

<p>AIDSInfo* Website of U.S. Public Health Service treatment guidelines, continually updated (living documents), clinical trials, and drug and vaccine information. (The AIDS Clinical Trials Information Services and AIDS Treatment Information Services have been integrated into AIDSInfo.) Contact: http://www.aidsinfo.nih.gov 1-800-HIV-0440, outside US 1-301-519-0459 TTY 1-888-480-3739 (Spanish speakers; Monday through Friday, 12 to 5 pm Eastern Time)</p>	<p>A B</p> <p>1, 2, 3, 5</p>	<p>       </p>	<p>       </p>	<p>       </p>	<p>       </p>
<p>AIDS Info NYC Website with information from community-based organizations in New York City for people living with HIV and AIDS. Contact: http://www.aidsinfo.nyc.org</p>	<p>B</p> <p>1, 3, 6</p>	<p>  </p>	<p>  </p>	<p>  </p>	<p>  </p>
<p>AIDSmeds.com Website for consumers that provides HIV treatment information and tools for understanding and tracking HIV treatment. Contact: https://www.aidsmeds.com</p>	<p>B</p> <p>1, 3, 4, 6</p>	<p>  </p>	<p>  </p>	<p>  </p>	<p>  </p>
<p>AIDS Treatment Data Network (ATDN) Organization with information about HIV treatment for consumers. Provides adherence and case management services in New York City, tracks Medicaid and the AIDS Drug Assistance Program (ADAP) nationwide (provides information to help individuals access drugs), and provides treatment information on the web. Contact: http://www.atdn.org 1-212-260-8868, 1-800-734-7104</p>	<p>B</p> <p>1, 3, 5, 6</p>	<p>  </p>	<p>  </p>	<p>  </p>	<p>  </p>
<p>American Academy of HIV Medicine (AAHIVM)* Professional association for HIV specialists that promotes excellence in HIV/AIDS care and offers HIV credentialing for physicians, nurse practitioners, and physicians assistants. Contact: http://www.aahivm.org/new/index.html</p>	<p>A</p> <p>1, 3, 5</p>	<p></p>	<p></p>	<p></p>	<p></p>

Type of User **Type of information**

A: Health Care Provider

B: Consumer

1: Website

2: Guidelines

3: Printed Material


























4: Phone/Email/Chat/Consultation

















5: Meetings/Conferences














6: Consumer Education










* Member to access some information





























Note: Websites were accessed 3/04.























































Provider and Consumer Resources	Type User	Type Info	Epidemiology	Treatment and Care	Prevention	Pediatrics and Adolescents	Obstetrics and Gynecology	Adherence	Psychosocial Support and Quality of Life	Substance Abuse	Research and Clinical Trials	Nutrition	Occupational Exposure	Quality Improvement	Palliative Care	Care in Resource Poor Settings	
<p>American College of Obstetricians and Gynecologists (ACOG)* Professional association for specialists in obstetrics and gynecology that provides guidelines and information in reproductive care of women. Contact: http://www.acog.org</p>	A	1, 2, 3, 5, 6															
<p>American Foundation for AIDS Research Organization with focus on basic and clinical research, clinical trials information, public and professional education, public policy, prevention science, and global initiatives. Contact: http://www.amfar.org</p>	A B	1, 3, 4, 6															
<p>American Psychological Association Office on AIDS Organization that provides information, training, and technical assistance on HIV/AIDS-related topics associated with coping, mental health services, prevention, community collaboration, and ethics. Contact: http://www.apa.org/pi/aids</p>	A B	3, 6															
<p>Association of Nurses in AIDS Care (ANAC)* Professional association that provides information and advises members about clinical and policy issues related to nursing and HIV care and offers HIV credentialing for RNs (ACRN). Contact: http://www.anacnet.org 1-800-260-6780</p>	A	1, 3, 5															
<p>The Body Website with comprehensive HIV information and resources for consumers. Contact: http://www.thebody.com</p>	B	1, 4, 5, 6															

<p>The Body Pro* Website with medical treatment information, comprehensive care and prevention information, interactive Q & A, and access to written information. Contact: http://www.thebodypro.com</p>	A	1, 2, 4, 5					<p>Canadian AIDS Treatment Information Exchange (CATIE) Canadian website with comprehensive HIV information and resources for consumers, including drugs, other medical treatments, and complementary therapies, in English and French. Contact: http://www.catie.ca</p>	B	1, 3, 4, 5, 6					<p>CDC Division of HIV/AIDS Prevention Website of the Centers for Disease Control and Prevention with guidelines and information on prevention of HIV for providers. Contact: http://www.cdc.gov/hiv/dhapp.htm</p>	A	1, 2					<p>CDC National Prevention Information Network (CDCNPIN) Comprehensive reference, referral, and distribution service for information on HIV/AIDS, sexually transmitted diseases (STDs), and tuberculosis (TB), with information specialists who can assist in identifying appropriate resource materials. Contact: http://www.cdcnpin.org 1-800-458-5231, TTY/TDD 1-800-243-7012 (Monday through Friday, 9 am to 6 pm Eastern time)</p>	A B	1, 3, 4, 5, 6	 				<p>Critical Path AIDS Project Website with information on treatment, prevention, policy, and advocacy as well as free internet and email services for consumers. Contact: http://www.cripaath.org</p>	A B	1, 4, 5, 6					<p>Community Programs for Clinical Research on AIDS (CPCRA)* Website of a network of research sites composed of community-based health care providers who offer their patients the opportunity to participate in research where they get their health care. Contact: http://www.cpcra.org</p>	A	1					<p>Type of User A: Health Care Provider B: Consumer</p> <p>Type of information 1: Website 2: Guidelines</p> <p>3: Printed Material 3: Phone/Email/Chat/Consultation 4: Meetings/Conferences</p> <p>6: Consumer Education * Must be member to access some information Note: Websites were accessed 3/04.</p>
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Provider and Consumer Resources	Type User	Type Info	Epidemiology	Treatment and Care	Prevention	Pediatrics and Adolescents	Gynecology	Adherence	Psychosocial Support and Quality of Life	Substance Abuse	Research and Clinical Trials	Nutrition	Occupational Exposure	Quality Improvement	Palliative Care	Care in Resource Poor Settings
<p>Gay Men's Health Crisis Women and Family Services Organization in New York City that provides information and services for people with HIV. Includes Women and Family Services Department and Lesbian AIDS Project. Contact: http://www.gmhcr.org</p>	B	1, 3, 6														
<p>Growth House Website with comprehensive database on end-of-life issues, including death with dignity, hospice, palliative care, grief, bereavement, and related topics. Contact: http://www.growthhouse.org</p>	A B	1, 3, 5, 6														
<p>Healthy Initiatives for Youth (HIFY) Organization that provides information to youth about HIV prevention and training and technical assistance to professionals providing services to youth. Contact: http://www.hify.com</p>	A B	3														
<p>HEPP Report (HIV and Hepatitis Education Prison Project) Publication of the HIV and Hepatitis Education Prison Project (HEPP) that contains in its archives numerous articles about HIV in incarcerated women. Contact: http://www.hivcorrections.org 1-401-277-3651</p>	A	1, 3														
<p>HIVandHepatitis Website of clinical information and resources on hepatitis and HIV. Contact: http://www.hivandhepatitis.com</p>	A B	1, 4, 5, 6														

HIVdent Website with information on the dental manifestations of HIV and AIDS, including information for persons living with HIV/AIDS and their dental care providers. Contact: http://www.hivdent.org	A B	1, 2, 5, 6																																																																																																																																																																																																																																																																																																																																															
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Provider and Consumer Resources	Type User	Type Info	Epidemiology	Treatment and Care	Prevention	Pediatrics and Adolescents	Obstetrics and Gynecology	Adherence	Psychosocial Support and Quality of Life	Substance Abuse	Research and Clinical Trials	Nutrition	Occupational Exposure	Quality Improvement	Palliative Care	Care in Resource Poor Settings	
<p>HRSA Information Center Clearinghouse of free publications on HIV, nutrition, maternal and child care, and numerous other health-related topics of concern to HIV providers. Contact: http://www.ask.hrsa.gov 1-800-400-2742, 1-888-275-4772</p> <p>International Association of Physicians in AIDS Care (IAPAC)* Professional association for physicians that provides information and medical education, and advocates to expand access to health care services and life-saving drugs and technologies. Contact: http://www.iapac.org 1-312-795-4930</p> <p>International Center for Research on Women (ICRW) Organization that conducts research, capacity building, and advocacy on issues affecting women's economic, health, and social status in low- and middle-income countries. Contact: http://www.icrw.org</p> <p>International HIV/AIDS Alliance Organization that supports communities in developing countries to play a full and effective role in the global response to AIDS. Contact: http://www.aidsalliance.org</p>	A B	1, 3															
	A	1, 3, 5, 6															
	A	1, 3, 4, 5															
	A	1, 3															

<p>Johns Hopkins University AIDS Service Website with detailed medical treatment information as well as comprehensive care and prevention information; interactive Q & A, and access to written information. Contact: http://www.hopkins-aids.edu</p> <p>To order <i>Medical Management of HIV Infection</i> or write The Johns Hopkins University AIDS Service, PO Box 5252, Baltimore MD 21224.</p>	A	1, 3, 6																	
<p>Kaiser Family Foundation Organization that informs the U.S. HIV/AIDS policy discussion and funds global HIV prevention. Contact: http://www.kff.org</p>	A	1, 3																	
<p>Medscape Website of medical information and education tools for medical specialists, primary care physicians, and other health professionals. Contact: http://www.medscape.com</p>	A	1, 5																	
<p>National AIDS Hotline A website and phone hotline to answer consumer questions and provide referrals about HIV and AIDS. Confidential inquiries about prevention, risk, testing, treatment, and other HIV/AIDS-related concerns. Contact: http://www.ashastd.org/nah 1-800-342-AIDS (1-800-342-2437). TTY 1-800-243-7889; Spanish 1-800-344-7432 (24 hours a day)</p>	B	1, 3, 4, 6																	
<p>National Association of People with AIDS (NAPWA) Organization that advocates for and provides information and support to people living with HIV/AIDS. Contact: http://www.napwa.org 1-202-898-0414</p>	B	1, 3, 5, 6																	












Type of User **Type of information**




















A: Health Care Provider
B: Consumer

1: Website
2: Guidelines

3: Printed Material
4: Phone/Email/Chat/Consultation
5: Meetings/Conferences

6: Consumer Education
* Must be member to access some information
Note: Websites were accessed 3/04.

Provider and Consumer Resources	Type User	Type Info	Epidemiology	Treatment and Care	Prevention	Pediatrics and Adolescents	Obstetrics and Gynecology	Adherence	Psychosocial Support and Quality of Life	Substance Abuse	Research and Clinical Trials	Nutrition	Occupational Exposure	Quality Improvement	Palliative Care	Care in Resource Poor Settings	
<p>National Association on HIV Over Fifty (NAHOF) Organization that promotes the availability of a full range of educational, prevention, service, and health care programs for persons over age fifty affected by HIV. Contact: http://www.hivoverfifty.org</p>	A B	1, 3, 5															
<p>National Clearinghouse for Alcohol & Drug Information (NCADI) Website of Federal agencies that provides drug and alcohol information as well as descriptions of Federal prevention initiatives. Contact: http://www.health.org</p>	A B	1, 3, 6															
<p>National Clearinghouse on Child Abuse/Neglect Information Website for professionals and others seeking information on child abuse and neglect and child welfare; national child abuse hotline. Contact: http://hccatch.acf.hhs.gov Hotline: 1-800-422-4453 (24 hours a day)</p>	A B	1, 3, 4, 5, 6															
<p>National Clinicians' Post-Exposure Prophylaxis Hotline (PEpline) National toll-free hotline counsels health care workers with job-related exposure to HIV, hepatitis, and other blood-borne pathogens and offers treating clinicians up-to-the-minute advice on managing occupational exposures (i.e., needlesticks, splashes, etc.). Contact: http://www.ucsf.edu/hivcntlr/pepline 1-888-448-4911 (24 hours a day)</p>	A	1, 4															

<p>National Network to End Domestic Violence (Hotline) Organization that provides national domestic violence hotline and local resources for women and advocates legally, legislatively, and educationally against domestic violence. Contact: http://www.nnedy.org 1-800-799-SAFE (7233), TDD 1-800-787-3224 (24 hours a day)</p>	<p>A B</p>	<p>1, 3, 4</p>										
<p>National Library of Medicine (NLM) Website that enables readers to conduct literature searches of the professional medical and HIV/AIDS-related literature including abstracts from relevant conferences. Contact: http://www.nlm.nih.gov</p>	<p>A</p>	<p>1</p>										
<p>National Minority AIDS Council Organization dedicated to developing leadership within communities of color to address the challenges of HIV/AIDS. Contact: http://www.nmac.org 1-202-483-6622</p>	<p>A B</p>	<p>1, 3, 5, 6</p>										
<p>National Minority AIDS Education and Training Center Center of the AIDS Education and Training Centers that builds capacity for HIV care and training among minority health care professionals and health care professionals serving communities of color. Contact: http://www.nmaetc.org</p>	<p>A</p>	<p>1, 4</p>										
<p>New Mexico AIDS Infonet Website with non-technical fact sheets on treatment for consumers. Contact: http://www.aidsinfonet.org</p>	<p>B</p>	<p>1, 3, 6</p>										
<p>New York Online Access to Health Website for consumers with a range of topics relevant to HIV/AIDS and women. Contact http://www.noah-health.org</p>	<p>B</p>	<p>1</p>										

Type of User

A: Health Care Provider

B: Consumer

3: Printed Material









4: Phone/Email/Chat/Consultation





















5: Meetings/Conferences

6: Consumer Education

* Must be member to access some information

Note: Websites were accessed 3/04.

Provider and Consumer Resources	Type User	Type Info	Epidemiology	Treatment and Care	Prevention	Pediatrics and Adolescents	Obstetrics and Gynecology	Adherence	Psychosocial Support and Quality of Life	Substance Abuse	Research and Clinical Trials	Nutrition	Occupational Exposure	Quality Improvement	Palliative Care	Care in Resource Poor Settings
<p>NIAID Database for Anti-HIV Compounds Website with computerized databases of chemical structures and biologic data on antiretroviral drugs. Contact http://www.niaid.nih.gov/daids/dtpdb</p> <p>Partnership for Caring Organization that provides resources, education, advocacy, and a hotline on palliative care and end-of-life issues such as living wills. Contact: http://www.partnershipforcaring.org 1-202-296-8071, hotline 1-800-989-9455 (Monday through Friday, 9 to 5 pm Eastern time)</p> <p>Pediatric AIDS Clinical Trials Group (PACTG) Website for NIH-funded HIV clinical trials in children and pregnant women. Contact: http://www.pactg.s-3.com</p> <p>Population Council Organization that conducts research and develops policy on reproductive health and family planning, including HIV-related issues, internationally. Contact: http://www.popcouncil.org</p>	A	1														
	A B	1, 2, 3, 4, 5, 6														
	A	1														
	A	1, 2, 3														

<p>Project Inform Organization that provides consumers with treatment information and tools for living with HIV, including confidential treatment information by phone and Project Wise, a program focused on HIV/AIDS treatment information and advocacy for women. Contact: http://www.projectinform.org Treatment hotline 1-800-822-7422 (toll-free in the United States) 1-415-558-9051 (in the San Francisco Bay area or internationally), (Monday through Friday, 9 am to 5 pm; Saturday, 10 am to 4 pm Pacific time)</p>	<p>B</p> <p>1, 3, 4, 5, 6</p>					
<p>Reproductive Health Online (Reproline) Website for JHPIEGO, affiliate of Johns Hopkins University, with information and training tools on reproductive health topics in low resource settings. Spanish, French, Portuguese, and Russian. Contact: http://www.reproline.jhu.edu</p>	<p>A</p> <p>1, 2, 3, 4, 5</p>					
<p>San Francisco AIDS Foundation Organization that provides consumers with information about prevention, care, and experimental treatments. Contact: http://www.sfaa.org</p>	<p>B</p> <p>1, 3, 6</p>					
<p>Trevor Project Helpline National 24-hour suicide prevention hotline for gay, lesbian, bisexual, transgender and questioning youth in crisis. The Trevor Project provides a training film for providers to promote tolerance for gay and questioning youth. Contact: http://www.thetrevorproject.org 1-866-4 U Trevor, 1-866-450-8078.</p>	<p>A B</p> <p>1, 4, 6</p>					

Type of User **Type of information**

A: Health Care Provider

B: Consumer

1: Website

2: Guidelines

3: Printed Material

4: Phone/Email/Chat/Consultation

5: Meetings/Conferences

6: Consumer Education

* Must be member to access some information

Note: Websites were accessed 3/04.

Provider and Consumer Resources	Type User	Type Info	Epidemiology	Treatment and Care	Prevention	Pediatrics and Adolescents	Obstetrics and Gynecology	Adherence	Psychosocial Support and Quality of Life	Substance Abuse	Research and Clinical Trials	Nutrition	Occupational Exposure	Quality Improvement	Palliative Care	Care in Resource Poor Settings
<p>UNAIDS: Joint UN Programme on AIDS International program of the United Nations that provides technical assistance and global information to countries and communities to address HIV/AIDS. Contact: http://www.unaids.org</p>	A	1, 3, 5, 6														
<p>Warmline: The National HIV Telephone Consultation Service Telephone consultation service for health care professionals with questions on any topic related to HIV care. Contact: http://www.ucsf.edu/hivctr/warmline/index.html 1-800-933-3413 (Monday through Friday, 6 am to 5 pm Pacific Time)</p>	A	1, 4														
<p>The Well Project Web portal for women living with HIV with treatment information, discussion groups, organizational tools, slide sets, searchable clinical trials listings, and resource information. Contact: http://www.thewellproject.com</p>	A B	1, 3, 4, 5, 6														
<p>WhatUDO Organization targeting youth for HIV prevention (information, activities, chat rooms). Contact: http://whatudo.org</p>	B	1, 6														
<p>Women Alive Organization by and for women living with HIV, with local services in Los Angeles as well as Internet services. Contact: http://www.women-alive.org 1-800-554-4876, 1-323-965-1564</p>	B	3, 4, 6														

XVI. INTERNATIONAL ISSUES

*Suniti Solomon, MD; Dorothy Kasonde, MBChB, MMed;
Valdiléa Gonçalves Veloso dos Santos, MD, MSc; Jean R. Anderson, MD*

I. INTRODUCTION

Of the estimated 40 million individuals living with HIV/AIDS around the world, approximately 95% live in resource-constrained settings and have fragmented health care systems and of these, over 50% are women (UNAIDS, 2003). This represents what Peter Piot, the Executive Director of UNAIDS, has called the “increased feminization of the epidemic.” In a recent address to the World Bank, he said “Every year we see an increase in the number of women infected with HIV...Because of global inequality, women living with HIV/AIDS often experience more stigma and discrimination. And since women are the main care givers and source of household labour, their illness means the collapse of family community care systems and household protection.” (Piot, 2003). One of the legacies of HIV in the developing world and especially in women is the millions of orphans, estimated to comprise 15% of all children in the worst affected countries by 2010. Recognizing the global burden of HIV disease and the inequity in availability of resources, including antiretroviral drugs, and the resulting erosion of decades of progress in health and economic indicators, there has been a growing consensus that international response and collaboration are critical and growing political momentum. In the 2003 State of the Union address President Bush committed US\$15 billion to fight HIV/AIDS over the next five years and in November 2003 the US Congress allocated US\$2.4 billion to international AIDS activities for the 2004 budget year. These funds are managed by the Global AIDS Coordinator's office by the newly appointed Ambassador, Randall Tobias. The Global Fund to Fight AIDS, TB and Malaria represents a partnership between governments around the world, civil society, the private sector, and affected communities to provide resources directly to resource-constrained countries to address their specific HIV care and prevention needs. The United Nations 3 by 5 initiative is led by WHO and UNAIDS with the goal of getting 3 million people on antiretroviral treatment by 2005.

This chapter includes a discussion of the special considerations and challenges for HIV+ women in three representative countries from three representative regions. While this cannot represent all countries and regions struggling with the HIV pandemic, each of the countries discussed presents a unique perspective on the HIV/AIDS pandemic from resource-constrained settings: India is the second most populous country in the world with over one billion people; although HIV prevalence there is currently only approximately 0.7%, this translates into almost 4 million persons living with HIV/AIDS and trends show prevalence to be increasing. It is one of the few countries that initiated

HIV prevention activities in the very early stages of the epidemic. In 2002, India started prevention of HIV transmission from mother to child on a large scale using single dose nevirapine. In April 2004, there is planned a roll out of combination antiretroviral therapy (d4t, 3TC, and nevirapine) to all those who need it in the six states of India with the highest prevalence.

Zambia is a high-prevalence country (approximately 16%) in the highest prevalence region in the world, sub-Saharan Africa. Among Zambians 15-24 years of age, women are two-and-a-half times as likely to be HIV-infected as men (Zambia Demographic and Health Survey, 2001-2002). Each of these three discussions is anchored by women who have a long and distinguished history as care providers and/or advocates for women living with HIV in these three countries.

Brazil is a country with limited resources that has made the political commitment to provide antiretroviral therapy for all of its citizens with HIV infection and has seen decreases in morbidity and mortality equal to that seen in resource-rich countries.

II. INDIA

In India 85% of women with HIV were infected through heterosexual contact and over 90% reported a single lifetime partner, generally their spouse (John, 1993; Gangakhedkar, 1997; Newman, 2000). Blood transfusion was the source of infection in almost 8% of women; single unit transfusions are commonly given during childbirth and abortion to manage hemorrhage. Common clinical manifestations in HIV-infected women include vaginal and oral candidiasis, pulmonary tuberculosis, skin lesions, genital ulcers, weight loss, and diarrhea.

There are a number of cultural beliefs and practices that present special challenges to HIV care and prevention. In India there are different values placed on the birth of a female and a male child. A woman's primary social function is to assure caste community and continuity of property through the birth of sons. Only sons can perform certain rituals, such as funeral rites for their parents. Furthermore, parents must often pay large dowry amounts for their daughters' marriage. This has resulted in overwhelming importance given to bearing sons, resulting in use of prenatal ultrasound commonly for sex determination with elective termination of female fetuses and a low overall female to male ratio of 100:144. Therefore, women begin life as devalued and considered a liability.

In ancient times India offered to the world the renowned treatise on sexuality *The Kamasutra*. Sexual imagery found a pride of place in temple sculptures and elaborate rituals covered marriage, nuptial nights, pregnancy, and childbirth, recognizing sex and reproduction as part of the social process. Such openness about sex and sexuality is now nearly absent. As a woman attains puberty, she is expected to maintain a culture of silence when confronted with issues of her own sexuality, preventing

access to information. There is a great deal of pressure to maintain virginity until marriage. Many women engage in alternative and even risky sexual behaviors, such as anal sex, in an effort to maintain their virginity. When women do engage in sex, their ignorance and the continued culture of silence make them unable to negotiate safer sex practices.

As with virginity, motherhood is considered a virtue and using barrier methods or non-penetrative sexual practices is seen as an affront to the concept of motherhood. The worst offense a woman is held guilty of is the inability to bear children. Her life is reduced to violence, rejection, and misery. The pressure to have children is equally great among HIV serodiscordant couples. In one study from an HIV care center in south India, 44% of couples were serodiscordant for HIV, but many women were willing to risk acquiring HIV in order to conceive a child (Solomon, 2003). "I would rather be HIV positive than a barren woman," said Aruna, one HIV-uninfected woman whose husband has HIV infection. "If my neighbor sees me as she goes out to work, she considers it so inauspicious that she will go back home to cleanse herself under the shower." Parents-in-law of these women may extend threats that their sons will marry a second time and produce a child by his second wife.

Violence against women is a fact of life in India. A woman has the duty of pleasing her husband; if she refuses sex, she risks violence, abuse, and abandonment. These women tolerate their husband's infidelity and abuse and submit to their demands to avoid further abuse, remaining in these relationships for fear of abandonment. The culture of silence is maintained and many view this violent relationship as "normal." A woman is raped every 34 minutes in India and a woman is burnt to death over dowry every 93 minutes (UNIFEM, 2000).

AN INNOVATIVE PROGRAM FOR WOMEN

YR Gaitonde Center for AIDS Research and Education (YRG CARE) is an innovative program for women that offers a number of services to women with or at risk for HIV. Couples counselling and testing promotes open communication between genders and can reduce practices of blaming the woman and can encourage both partners' involvement in decision-making, help them plan their future together, reduce risks and improve their quality of life. Family counselling is also offered to help other family members realise that the couple needs all their support to achieve a better quality of life.

In India marriages are not "made in heaven". Parents arrange them, usually within the same caste and religion. The first step is to match horoscopes; if the majority of the houses in the astrological charts of the prospective groom and bride match, their parents meet and finally the couple are introduced to each other. This usually occurs when the man is 24–25 years of age and the woman is 18–21 years. At YRG Care there is a marriage counseling center where HIV seropositive men or women who are under pressure to marry are counseled, their needs assessed, and efforts made to introduce them to suitable partners.

There is a cohort of 1908 women followed at YRG CARE, of which 693 are HIV-negative married to husbands with HIV. These women are under great pressure from the parents-in-law to bear children, but neither the husband or wife is able to discuss HIV-related issues, including the need for safe sex, because of the stigma attached to HIV disease. Through counseling services at the center, these couples are given various options including adoption; artificial insemination using donor semen; antiretroviral therapy for the husband to reduce plasma viral load, in turn decreasing HIV transmission from husband to wife while trying to conceive; or artificial insemination with washed semen from the husband. This service allows these couples hope, while helping protect the woman both from rejection and from HIV.

Other services offered through YRG CARE include provision of at least one balanced meal daily to a woman and her husband when he is in the hospital through a novel scheme called "365 Good Friends," in which people donate money on their birthday, sufficient for 50 meals. This saves the woman from having to cook and bring food from home to the hospital, as would usually occur. This initiative is presently assisted by the Andrew Ziegler Foundation, which is helping YRG CARE to find 'Good Friends' who will donate \$100 towards daily meals to improve the nutrition of our patients.

YRG CARE also provides HIV and sexuality education to industrial employees. This has resulted in many requests to also conduct such programs for the employees' family members and for women in the neighboring community. It was felt that such knowledge would empower these individuals in their efforts to prevent the spread of HIV.

There remain many challenges for HIV prevention and management for women in India. Girls must be provided with the same educational opportunities as boys, both in terms of general academics and in the area of sexuality. Because gender inequities and power dynamics inherently involve both sexes, it is important that men be included when addressing issues affecting women. It may be helpful to better educate and sensitize both young women and young men about sexuality and about gender with the goal of reducing risky behaviors and violence, while enhancing information-seeking behavior and female equality. . Another important source of power is access to economic resources and assets. Educational programs along with skills training programs and microcredit loan schemes can help women to achieve economic independence.

Women in sex work have historically been disempowered and are at risk for exploitation, violence, and infection. Programs that organize and mobilize sex workers have been successful in increasing the power of these women and their communities. Organizations from all over India have combined into The National Network of Sex Workers to improve social, economic, and health conditions. These programs must be strengthened and expanded. The development of female-controlled methods of HIV/STI prevention, particularly those that can be used in secrecy, should be a major research priority and has significant implications both for sex

workers and for women in primary relationships. In one study 89% of men would allow their non-primary sexual partners to use microbicides to prevent HIV and STI transmission and only 42% would allow their primary sexual partners to use them (Srikrishnan, 2001).

Although over 48% of Indians are women, they represent less than 10% of individuals in the parliament, the State High Courts and Supreme Courts, and in Civil Service administration. Political representation of women will be important to further advance many issues relating to women's health and empowerment (Rao Gupta, 2002).

Lack of access to health care prevents women from having control over their lives. Since it is often difficult to access services without the permission or monetary support of their husbands and in-laws, steps must be taken to provide services to women in convenient, low cost, and discreet environments. In YRG CARE 61% of men and 76% of women who needed antiretroviral therapy were not able to secure the drugs. In a family wherein both husband and wife require antiretroviral therapy and the finances are sufficient for one person only, the man is usually the one who accesses the medications. HIV-infected women are also less likely to have laboratory investigations such as CD4 counts or viral loads. The Government of India currently has a project funded by the Global Fund for AIDS, TB and Malaria for prevention of mother-to-child transmission (PMTCT) which will supply ARV therapy not only to prevent MTCT but also for treatment of parents with CD4 counts less than 200/mm³ in 11 centers in the country.

III. ZAMBIA

It is estimated that some 1.2 million Zambians are living with HIV/AIDS and prevalence in women is 12.9%, with significantly higher rates in women as compared to men throughout most of the reproductive years. The prevalence rates for both men and women are two-fold higher in urban than in rural areas. Although awareness about HIV/AIDS is high, this does not translate into positive action for prevention and both uptake of voluntary counseling and testing (VCT) and condom use are low (Zambia Demographic and Health Survey, 2001-2002). Women are most often offered VCT during antenatal care, after a spontaneous abortion or stillbirth, with death or failure to thrive in a child, with presentation of a sick child or partner to the clinic, after death of a partner, or when seeking treatment for frequent illnesses.

In sub-Saharan Africa tuberculosis (TB) is the most common HIV-related opportunistic infection (OI) and a leading cause of death. TB has special implications for the health of women: a study of 775 maternal deaths at the University Teaching Hospital of Zambia (Ahmed, 1999) found that 255 were due to TB and in 92% of these cases the woman was HIV+. TB endometritis is a major cause of infertility. The most recent national statistics indicate that 70% of TB patients have HIV infection (Zambia Demographic and Health Survey, 2001-2002).

Sexually transmitted infections (STIs) are a major problem in sub-Saharan Africa in general, including Zambia. STI prevalence is 56% among sex workers in Zambia (Family Health International, unpublished data, 2003). The East, Central, and Southern African Commonwealth region has adopted syndromic management of STIs, in which immediate treatment is given for all major causes of certain presenting symptoms (e.g., genital ulcers), based on local information about etiologies of the symptom and drug susceptibility patterns. Etiologic diagnosis with cultures and other laboratory tests is not generally available. Syndromic management is cost-effective and encourages people to access treatment at all levels of care. However, it does not identify those individuals with asymptomatic infection, which is more common in women. Contact tracing may help identify sexual partners, especially wives, who may be asymptomatic. Presumptive treatment should be offered to all sexual partners of persons being treated syndromically.

Invasive cervical cancer is the most common gynecologic malignancy in Zambia and is considered an AIDS-defining condition in the presence of HIV infection. Rates of preinvasive cervical lesions are significantly increased in the presence of HIV and both prevalence and severity increase with progressive immunosuppression. Routine Pap smear screening is not generally available throughout Africa, in either urban or rural areas, and women usually present in advanced stages of disease. As antiretroviral treatment becomes more available, invasive cervical cancer may become a still greater problem as women with HIV live longer with their infection but still suffer the consequences of HPV infection and progressive cervical dysplasia.

Although malaria does not appear to be more severe or more prevalent in HIV-infected individuals in general, in HIV+ pregnant women HIV hinders the ability to control *Plasmodium falciparum* infection and peak parasite prevalence occurs earlier in pregnancy. While in the HIV-uninfected pregnant woman a single dose of sulfadoxine pyrimethamine (SP) is sufficient to clear parasitemia, two to three doses are required in the HIV+ woman (Schulman, 1999). Malaria is a principal cause of severe anemia and intrauterine growth restriction in pregnancy (Steketee, 1996); in the HIV+ woman anemia related to malaria is exacerbated by nutritional deficiencies or wasting, other infections, and HIV-related illnesses. Malaria is estimated to be responsible for more than 20% of all maternal deaths in sub-Saharan Africa. Placental parasitemia is increased in the presence of HIV and may increase risk of MTCT.

CHALLENGES TO PREVENTION AND TREATMENT:

- The environment of poverty (these issues apply to sub-Saharan Africa in general): Literacy and education levels are low, particularly for women, and these factors are associated with lower use of condoms (Zellmir, 2003; Zambia Demographic and Health Survey, 2001-2002). Because of high unemployment levels, women may turn to sex work in exchange for favors or money

needed to feed and educate their children, further increasing their risk of acquiring HIV. Lack of clean accessible water increases the incidence of diarrheal diseases and risk of malnutrition in those with HIV. Overcrowding in households occurs with several generations in an extended family often living together in small houses because of unemployment and because of incorporation of AIDS orphans into these families. Women and girls in these settings may be at increased risk for domestic and sexual violence and for neglect of their own health care needs. In several countries in Africa there is civil unrest and war. This has led to increased HIV risk for women, who are vulnerable to rape and intentional impregnation. Where there have been peacekeeping soldiers from high-HIV prevalence areas sent to low-prevalence countries, women in those countries have been at increased risk for contracting HIV. Women who are refugees from war and drought or famine are also at increased risk for HIV because of their vulnerability to violence and to sexual coercion and because of extreme economic dependence. Finally, health care infrastructures and resources are inadequate for the diagnosis and management of HIV disease and other general health conditions.

- Violence against women and sexual violence occurs in 4.4% of ever-married women (50% in the last 12 months). (Zambia Demographic and Health Survey, 2001-2001)
- Cultural issues (many of these issues apply to other countries in Africa, not just Zambia): Women are care providers but their work is not considered in monetary terms. When the husband dies his relatives come to claim the property because the woman did not contribute money for the purchase of land, house, or household goods. Because of their lack of monetary resources, women are economically dependent on their partners. They have no bargaining power to negotiate for safe sex, as the man will go outside the home for sex. Married women who demand the use of condoms are accused of not trusting their husbands and female condoms cannot be used without the permission of the husband. Even with condom use, some men believe they can be made sick if the semen does not flow out, so they make a small hole at the tip of the condom. It is believed that wives who are faithful cannot get HIV or other STIs. Often, even if a man receives STI treatment or HIV testing, his wife will refuse, as she will be blamed for bringing disease to the marriage. Certain sexual practices increase the risk of HIV infection for women. Dry sex is considered more pleasing and women use herbs or other substances to dry the vaginal mucosa, increasing risk of trauma during intercourse and risk of HIV transmission. Female genital mutilation is commonly practiced in many areas throughout Africa in order to reduce the woman's libido, as it is believed that a respectable woman does not enjoy sex. Infertile couples seek the wife's sister as a surrogate mother without regard to HIV status. In many African cultures polygamy is practiced and legally supported; it is commonly believed that a man will become impotent if they are in a

monogamous sexual relationship. “Sexual cleansing” after the death of the husband is practiced in some Zambian communities. With this practice the widow is expected to have sex with her husband’s chosen relative in order to remove the husband’s shadow from the woman’s body; otherwise, any man who has sex with the widow will die. In South Africa sexual assault of children has increased dramatically because many men believe that they can be cured of HIV by having sex with a child. Older men (who may already be HIV-infected themselves) often seek out very young women or girls because they believe that older women are likely to be HIV + . In one study, 66% of women had unprotected sex in their last sex act with a non-regular partner.

- **Stigma:** Stigma concerning HIV is widespread throughout Africa and leads to a vicious cycle of fear and denial. The consequences of this cycle include discrimination, rejection, increased risk of HIV transmission, and decreased likelihood that infected individuals will appropriately access care and treatment for HIV and related opportunistic infections, such as TB. Health care providers who worry about stigma or fear becoming infected through work activities may have problems with disclosure of VCT results to patients (Zambia Nursing Council, 2001) and may be unwilling to care for those known or suspected to have HIV. Stigma is cited as the primary reason for the low VCT uptake in PMTCT programs. In most hospitals doctors and nurses will not write HIV as the cause of death on a death certificate because of stigma.

INNOVATIVE INITIATIVES

- In village initiation ceremonies traditional women counselors (“Alangizi”) are being trained to incorporate couple counseling to promote HIV knowledge and use of condoms.
- The Forum for African Women Educationists (FAWE) has trained teachers to counsel girls, many in boarding schools during their adolescent years, about HIV/AIDS, and advocates for pregnant girls to remain in school and to return to school after giving birth.
- Home-based care (HBC) is supported by faith-based and community organizations to provide care within the home for chronically ill persons using community volunteers. These programs offer VCT, spiritual care, help in writing wills, assistance with chores, administration of medicine, and assistance with personal hygiene. Although volunteers were at first stigmatized, they now have the respect of the community and are often called upon for advice because of their knowledge about HIV and care.
- Programs that provide access to water and sanitation have incorporated HIV awareness and basic hygiene information.
- PLWHA networks have started income-generation activities at various centers, with money raised used to improve nutrition and help pay school tuition for children.

- An initiative in Southern Africa supported by Family Health International, including partnerships with international and local non-governmental and community-based organizations, provides commercial sex workers in border areas with HIV information, condoms, VCT, and STI treatment.

IV. BRAZIL

It is estimated that approximately 623,000 individuals are living with HIV/AIDS in Brazil (Szwarcwald, 2001); women account for 30% of cases reported and are now the fastest-growing segment of the population in terms of AIDS cases. The male:female ratio for AIDS has fallen from 24:1 in 1985 to 2:1 in 1997 and among adolescents is now 1:1. (Brasil, 2003). The HIV/AIDS epidemic began to explode in Brazil in the 1980s when the country was emerging from a military dictatorship and in the midst of a redemocratization process. In 1988 the country's new constitution recognized health as a constitutional right for all citizens; this facilitated the adoption of the prevention and care policy that characterizes the Brazilian approach to fighting HIV/AIDS and paved the way to the successful implementation of universal and free access to highly active antiretroviral therapy (HAART) for all HIV-infected citizens in Brazil. Currently more than 115,000 people have had access to free ARV treatment provided through government financing and generic versions of a number of ARV agents are produced by several publicly-owned companies. Since the introduction of HAART, a sharp decline in the incidence of AIDS and an 80% decrease in AIDS-related mortality has occurred in Brazil, similar to that seen in the most developed countries (Levi, 2002; Gotlieb, 2003). The median survival after a diagnosis of AIDS has increased from 5.8 months for patients diagnosed between 1982 and 1989 (Chequer, 1992) to 58 months for those diagnosed in 1996 (Marins, 2003). The decrease in hospitalizations has saved more than US\$2.2 billion from 1997 to 2001, more than offsetting the US\$1.8 billion invested in fighting HIV/AIDS during the same period. Today Brazil provides technical assistance on HIV/AIDS to Portuguese-speaking African countries.

However, the reduction in AIDS deaths among women has lagged behind the reduction in deaths among men with AIDS, and this is true in all regions of the country (Fonseca, 2002; Gotlieb, 2003). The epidemic began later in women and women with HIV continue to experience delays in diagnosis and treatment. Health care providers may be less likely to think about HIV infection in women and women themselves often do not perceive themselves to be at risk. In a study conducted in Sao Paulo, 53% of HIV-infected women interviewed did not perceive themselves to be at risk before learning of their HIV status and, of those who did perceive themselves at risk before testing, 29% believed they were at risk only after their partners became ill (Ventura-Filipe, 2000). Women may also prioritize the health care of their children and infected partners over that of their own care, potentially postponing care and compromising adherence to antiretroviral therapy.

Once women are diagnosed with HIV, health care providers are frequently not prepared to provide the needed support with HIV-infected women reporting limited receptiveness for discussing sexuality and childbearing wishes with their providers (Paiva, 2002). Furthermore, the fact that gynecologic care and family planning services are often located in places separate from those providing HIV/AIDS care is a barrier to integrated care for women.

The most frequent clinical manifestations in a cohort of 297 women with HIV/AIDS followed in Rio de Janeiro included oral candidiasis, weight loss >10%, vaginal candidiasis, recurrent bacterial sinusitis, tuberculosis, and multidermatomal herpes zoster. Tuberculosis, *Pneumocystis carinii* pneumonia, and esophageal candidiasis were the most common AIDS-defining illnesses (Grinsztejn, 2001). In the same cohort, prevalence of sexually transmitted infections (STIs) were high, including HPV (51.2%), syphilis (10.8%), hepatitis B (14.7%), and trichomoniasis (9.8%). Among HPV-infected women, 92% were infected with oncogenic subtypes. Vaginal candidiasis was identified in 20.9% and bacterial vaginosis in 18.2%. (Grinsztejn, 2001). The high rate of HPV infection has special relevance in Brazil, since cervical cancer is still a major cause of morbidity and mortality and is the most frequent cancer in Brazilian women, with approximately 20,000 new cases of cervical cancer and 6000 deaths due to cervical cancer each year. Overall, survival and disease progression rates appear to be similar in HIV-infected women and men, with initially observed differences largely explained by differences in stage of disease, access to care and treatment, and initiation of timely therapy.

Because of gender and social inequities and prejudices, Brazilian women continue to face enormous barriers in prevention of HIV; it is difficult to discuss safer sex with partners and women have very little bargaining power when trying to introduce and sustain condom use. Frequently, women who do use condoms use them primarily for contraception, not as a means to prevent sexually transmitted infections or HIV, and HIV-infected women who use more effective contraceptive methods are less prone to use condoms (Fernandes, 2000; Magalhaes, 2002). In a cross-sectional study designed to assess safe sexual behavior among heterosexual couples, women who had known about their partner's HIV infection for a longer period of time were less likely to report safe behavior than those who had recently found that their partner was HIV-infected (Guimaraes, 2001). The partner's desire not to use a condom is a frequently reported reason for inconsistent use, even among HIV-infected women with HIV-uninfected partners. In a study conducted in Sao Paulo 25% of HIV-negative men did not use condoms even after knowing about their female partner's HIV infection (Magalhaes, 2002). In 1999 the favorable results of an acceptability study conducted in six urban areas led the Ministry of Health to purchase and distribute female condoms free of charge, prioritizing HIV-infected women, commercial sex workers, and women attending selected reproductive health services. In 2002 a total of 4 million female condoms were purchased for distribution.

Poverty, lack of family or social support, sexual abuse, and domestic violence are problems frequently faced by women in Brazil and represent a major public health problem. These problems increase risk of acquiring HIV and other STIs and increase the likelihood that HIV-infected women will not receive the care they need. In interviews conducted among HIV-infected women being followed in Rio de Janeiro, domestic violence was reported by 24.2% and sexual abuse by 24.6%. The monthly family income was US\$330 or less in over 60% of women, and 56% of women were unemployed at the time of the interview. Twenty-five percent of women had no support from family or friends and 20% had lost at least one child to AIDS (Friedman, 2002). In 2001 the Ministry of Health began to provide antiretroviral prophylaxis for victims of rape and a special training program to sensitize health care providers about violence against women was developed.

In the last several decades women's access to and use of contraception has increased dramatically in Brazil, resulting in a sharp drop in the fertility rate from 6.3 in the 1950s to 2.3 in 2001 (IBGE, 2003). However, approximately 10 million women have unwanted pregnancies, either due to inadequate use of contraceptive methods or to a lack of knowledge and/or access to them. The high pregnancy rate among teenagers in Brazil, especially among those from poorer social strata, is of special concern. In 1998 32% of 15-year-old girls had had sexual intercourse and in 2002 adolescent pregnancies accounted for approximately 25% of all deliveries in the country. Some studies in Brazil suggest that the knowledge of HIV infection increases the prevalence of contraceptive use, including use of condoms, among women of reproductive age (Magalhaes, 2002; Santos, 2002). There was also a significant increase in dual method use after knowledge of HIV infection, with more than 70% of HIV-infected women choosing hormonal methods also using condoms; however, only 46% of women with tubal ligation also used condoms (Magalhaes, 2002). Nevertheless, HIV infection has not changed women's desire to have children and with interventions available to prevent perinatal transmission of HIV and the increase in survival of HIV-infected people, many women with HIV are choosing to have children. If the health care provider adopts a judgmental attitude about childbearing in the context of HIV infection, this will represent a barrier for care for most HIV-infected women (Santos, 2002; Paiva, 2002).

The Ministry of Health has established the prevention of mother-to-child transmission of HIV as a top priority. Antiretroviral drugs for prophylaxis and treatment, infant formula, and referral for cesarean delivery are widely available (Velo, 1999). However, in 2002 it is estimated that of the 17,000 HIV-infected women who delivered, only about 35% were identified and received ARV prophylaxis. Many doctors still do not offer HIV testing during prenatal care and test results often take too long to receive, resulting in many deliveries in women of unknown HIV serostatus and missed opportunities to prevent mother-to-child transmission. In a cross-sectional study conducted between November 1999 and April 2000

in 12 Brazilian cities highly affected by the HIV/AIDS epidemic, 77.5% of 2,234 postpartum women who were interviewed reported being HIV tested and the HIV test acceptance rate was 92.5%. However, 49.1% reported that they did not receive counseling about HIV prevention during prenatal care and over 50% did not receive explanations about the meaning of their test results (Veloso, 2002). Considering these barriers to diagnosis of HIV and counseling about HIV prevention during pregnancy, and because 95% of all deliveries in Brazil take place in hospitals, the use of rapid HIV testing in labor has become a major strategic intervention for prevention of mother-to-child HIV transmission (Santos, 2001; Nogueira, 2001). However, the overall low quality of prenatal care, as reflected by an unacceptably high maternal mortality rate (161–260/100,000) and incidence of congenital syphilis (24/1000 live births) (Brasil, 1993), remains a primary barrier to both prevention of HIV and appropriate care and treatment for women with HIV living in Brazil.

It is of utmost importance for Brazil that health care providers be better trained and sensitized about gender issues in order to provide a high quality of care and to address unmet needs. The integration of HIV/AIDS care with gynecologic, obstetrical, and family planning services and the availability of social support must be improved so that women in Brazil can be freed from many of the competing needs and other barriers they now face which prevent them from taking full control of their lives, including prevention of HIV and other sexually transmitted infections and access to HIV care and treatment.

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XVII. NUTRITION COUNSELING, CARE AND SUPPORT

World Health Organization

EDITOR'S NOTE:

The following chapter is part of a series of modules being developed by the World Health Organization (WHO) and its partners on the care, treatment, and support of HIV-infected women and their children in resource-constrained settings. We are grateful to WHO for allowing us to reproduce this chapter on nutrition in its entirety for this guide. Although it is focused on the needs of women living in areas with limited resources, it is a valuable review of the current evidence base for the inter-relationship of HIV and nutrition and resulting recommendations, with relevance for HIV-infected women in all settings. Following this chapter are a series of tables, adapted from or developed by other sources, providing additional information which may be useful in areas with greater resources.

We want to acknowledge the following contributors to this chapter: Ellen Piwoz, Support for Analysis and Research in Africa Project, Academy for Educational Development, USA; the WHO Technical Advisory Group on Nutrition and HIV/AIDS; and, the Writing Committee Working Group who contributed to the module on HIV-related care, treatment, and support interventions for HIV-infected women (for a complete list of individuals, see the full report at http://www.who.int/hiv/pub/prev_care/nutrition/en/).

INTRODUCTION TO CHAPTER

The relationship between nutrition and HIV/AIDS is complex and not fully documented to date. The HIV/AIDS epidemic poses a challenge to the health and overall socioeconomic development in countries that have been greatly affected by the disease, which in turn may affect nutrition and food security. Healthy nutrition plays a role in alleviating the symptoms—e.g., diarrhea, anorexia, sore mouth, muscle wasting—common with HIV disease. There are, however, many gaps in current scientific knowledge on the impact that HIV/AIDS and malnutrition have on each other, the role of nutrition in the management of HIV/AIDS, and interactions between nutrition and ARV treatment. This document reviews the relationship between nutrition and HIV/AIDS and scientific evidence on the role of nutrition in HIV transmission, disease progression, morbidity, and disease management; and makes recommendations on nutrition counseling, care, and support for HIV-infected women, based on current evidence.



I BACKGROUND

A INTRODUCTION

HIV infection affects nutritional status by causing increased energy requirements, reductions in dietary intake, nutrient malabsorption and loss, and complex metabolic alterations that culminate in the weight loss and wasting that are common in AIDS (Babameto, 1997; Macallan, 1999; WHO, 2003). The effect of HIV on nutritional status begins early in the course of infection, possibly even before the individual in question is aware of being infected (Beach, 1992; Bogden, 2000; Friis, 2001a; Friis, 2001b; Semba, 1999).

B MALNUTRITION AND HIV

Nutrition is an important component of comprehensive care for the HIV-infected woman, and is particularly so in resource-limited settings where malnutrition and food insecurity are endemic. Pre-existing malnutrition, i.e. malnutrition occurring before HIV infection, compromises the immune system. The cellular effects of malnutrition on the immune system are similar to those of HIV. They include decreases in CD4 T-cells, suppression of delayed hypersensitivity, and abnormal B-cell responses (Beisel, 1996; Gorbach, 1993; Scrimshaw, 1997).

The impact of nutrition on HIV and disease progression is difficult to study. A systematic review of the literature is being conducted by the WHO Technical Advisory Group on Nutrition and HIV/AIDS. Early studies demonstrated that reduced body cell mass and decreased serum albumin levels were associated with shorter survival in AIDS patients, which was independent of the CD4 cell count (Kotler, 1989; Suttman, 1995). Community-based research studies in the USA revealed that moderate weight loss (< 5%) and severe weight loss (5–10%) over a four-month period were associated with a subsequent increased risk of opportunistic infections, including *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia, cytomegalovirus, and the *Mycobacterium avium* complex, and with mortality (Wheeler, 1998). Other studies showed that clinical outcome was comparatively poor and that the risk of death was comparatively high in HIV-infected patients with compromised micronutrient intake or status (Baum, 1997; Baum, 1998; Semba, 1994a; Tang, 1993; Tang, 1996; Tang, 1997a; Tang, 1997b).

C VITAMIN AND MINERAL DEFICIENCIES AND HIV

Deficiencies of vitamins and minerals, such as vitamins A, B-complex, C, and E, and selenium and zinc, which are needed by the immune system to fight infection, are commonly observed in people living with HIV in all settings (Baum, 1995; Friis, 2001a; Friis, 2001b; Kupka, 2002; Semba, 1999). Deficiencies of antioxidant vitamins and minerals contribute to oxidative stress, a condition that may accelerate immune cell death (Banki, 1998; Romero-Alvira, 1998) and increase the rate of HIV replication (Allard, 1998; Rosenberg, 1990; Schwarz, 1996).

Short-term antioxidant supplementation has been shown to improve body weight and body cell mass (Shabert, 1999), reduce HIV RNA levels and improve CD4 cell counts (Muller, 2000), and reduce the incidence of opportunistic infections (Mocchegiani, 2000) in small studies of adults with AIDS, including those on ARV treatment. In Thailand a larger placebo-controlled randomized trial on 481 ARV-naive HIV-positive men and women revealed that daily micronutrient supplementation for one year reduced mortality in persons with baseline CD4 cell counts below $200 \times 10^6/L$, although supplementation had no effect on the CD4 cell count or on the plasma viral load. Further research is necessary in order to elucidate possible mechanisms for increased survival associated with micronutrient supplementation (Jaimton, 2003).

D. NUTRITION, PREGNANCY AND LACTATION, AND HIV

An HIV-infected woman's nutritional status before and during pregnancy influences both her health and survival and those of her newborn children. The physiological changes that occur during pregnancy require extra nutrients for adequate gestational weight gain in order to support the growth and development of the fetus (National Academy of Sciences, 1989). For women who are malnourished, daily energy-protein supplementation during pregnancy may improve maternal weight gain, increase infant birth weight, and reduce the risks of stillbirth and perinatal mortality (Ceesay, 1997).

HIV infection increases energy requirements because of elevated resting energy expenditure (Grunfeld, 1992; Melchior, 1991; Mulligan, 1997). These additional needs, as well as the nutritional consequences of common HIV-related infections and illnesses, place HIV-infected pregnant and lactating women at greater nutritional risk than HIV-uninfected pregnant and lactating women. A meta-analysis of 31 studies conducted in developed and developing countries reported that intrauterine growth retardation, preterm delivery (< 37 weeks), and low birth weight (< 2500 g) were more common in infants born to HIV-positive mothers than in infants with HIV-negative mothers (Brocklehurst, 1998). The effects of HIV infection on pregnancy outcomes are likely to be more pronounced in women with symptomatic HIV infection, as has been observed in Tanzania (Coley, 2001).

Wasting during pregnancy is also more common in HIV-infected women than in the general population (Villamar, 2002a). A high plasma viral load, which is a marker of advanced disease, has been associated with lower lean and fat body mass in pregnancy (Friis, 2002). Several studies conducted in Africa indicate that an HIV-infected mother's nutritional status, measured by body mass index (BMI), mid-upper arm circumference, and/or weight loss, is an important predictor of mortality during the postnatal period (Lindan, 1992; Nduati, 2001; Zvandasara, 2002). Studies are planned in Malawi and Zambia to determine whether providing adequate nutrition to HIV-infected breastfeeding women can prevent the weight loss and nutritional depletion associated with both HIV infection and lactation.

E. MICRONUTRIENTS AND MOTHER-TO-CHILD TRANSMISSION OF HIV

Malnutrition during pregnancy results in low fetal stores of some nutrients. This impairs immune function and fetal growth and may increase the vulnerability of infants to HIV. Furthermore, poor nutrition during pregnancy may impair the integrity of the placenta, the genital mucosal barrier, and the gastrointestinal tract. In each of these cases the transmission of HIV from mother to infant may be facilitated, although data confirming such relationships independently of maternal HIV disease progression are limited (Dreyfuss, 2002).

Low serum retinol, used as an indicator of vitamin A status, is associated with the shedding of HIV in genital tract secretions and in breast milk (John, 1997; Mostad, 1999; Nduati, 1995). Low serum retinol has also been associated with an increased risk of cervical disease in HIV-infected women (French, 2000). Serum retinol levels decline during infections, however, and consequently it is difficult to interpret correlations between them and HIV.

In randomized clinical trials, daily vitamin A supplementation with 10 000 IU of retinyl palmitate had no effect on vaginal HIV shedding among non-pregnant women in Mombasa (Baeten, 2002) or on maternal antenatal and postnatal morbidity in Durban (Kennedy, 2000). However, a randomized trial among HIV-positive pregnant women in Dar es Salaam indicated that daily vitamin A supplementation increased viral shedding in the lower genital tract (Fawzi, 2004).

Early observational studies found that low serum retinol levels were associated with an increased risk of Mother-to-child transmission (MTCT) (Semba, 1994b; Semba, 1997). Randomized controlled clinical trials with vitamin A and beta-carotene, however, revealed no significant impact on HIV transmission during pregnancy and delivery (Coutsoudis, 1999; Fawzi, 2000; Kumwenda, 2002). The following positive benefits of vitamin A supplementation on birth outcomes were observed.

- In Durban, daily supplementation with vitamin A (5000 IU) and beta-carotene (30 mg) during the third trimester of pregnancy, combined with 200 000 IU vitamin A after delivery, reduced the risk of preterm delivery and was associated with improved maternal postpartum weight retention (Coutsoudis, 1999; Kennedy-Oji, 2001).
- In Blantyre, Malawi, daily supplementation with vitamin A (10 000 IU), beginning at 18–28 weeks of gestation, was associated with increased birth weight, increased weight and length at six weeks, and reduced rates of infant anemia at six weeks (Kumwenda, 2002).

Not all vitamin A supplementation trials have produced positive results. In a randomized trial in Dar es Salaam, mothers received daily vitamin A (5000 IU) and beta-carotene (30 mg) from 12–27 weeks of gestation until the end of lactation, and 200 000 IU of vitamin A were given at delivery. MTCT at 24 months increased by 38% (34.2% versus 25.4%; $P = 0.009$) in infants of mothers randomized to vitamin A. The comparison group received daily multivitamins with no vitamin A (Fawzi, 2002).

This was the only supplementation trial in which daily vitamin A and beta-carotene supplements were provided during breastfeeding. Current WHO recommendations for maternal vitamin A supplementation in high-risk areas do not extend to the breastfeeding period (WHO, 1997).

It is important to emphasize that, in the above studies, vitamin A supplements were given to women and that there were no findings on vitamin A supplementation in children. Studies on such supplementation for HIV-exposed and HIV-infected children aged 6 to 60 months have consistently shown positive effects on morbidity, nutritional status and mortality (Coutsoudis, 1995; Fawzi, 1999; Villamor, 2002b).

In Tanzania, women were randomized to receive a multivitamin product daily containing high levels of vitamins B₁ (20 mg), B₂ (20 mg), B₆ (25 mg), niacin (100 mg), B₁₂ (50 µg), C (500 mg), E (30 mg), and folic acid (0.8 mg). This supplementation was associated with reductions of 39% in fetal deaths, 44% in low birth weight, 39% in preterm delivery before 34 weeks, and 43% in small size for gestational age at birth. Although multivitamin supplementation did not affect the risk of MTCT overall (RR = 1.04) it was associated with reduced transmission in subgroups of women who were nutritionally or immunologically compromised (Fawzi, 2002).

In Zimbabwe, pregnant women were randomized to daily doses of vitamin A (10 000 IU) and 11 other vitamins and minerals (at single RDA levels) or placebo from 22–35 weeks of gestation until delivery. Micronutrient supplementation was associated with increases in birth weight of about 100 g in infants born to HIV-positive mothers. The effects of the supplement on outcomes such as HIV disease progression and transmission were not assessed (H. Friis, personal communication).

F. ANEMIA, IRON SUPPLEMENTATION, AND HIV

Anemia, defined as hemoglobin < 110 g/L, affects more than half of all pregnant women in resource-limited settings, but is more common and often more severe in HIV-infected women than in other women (Meda, 1999; Ramon, 1999; Van den Broek, 1998). Severe anemia, defined as hemoglobin < 70g/L, is associated with many dangerous outcomes for mothers and infants, including the risks of premature delivery and low birth weight in infants, and maternal mortality (Bothwell, 1981; Schorr, 1994). Premature delivery and low birth weight are associated with increased risks of MTCT (Ioannidis, 2001; João, 2003; Moore, 1998; Fawzi, 2001).

For HIV-infected women, anemia is evidently an independent predictor of more rapid HIV progression and mortality (Moore, 1998; Moore, 1999; Zvandasara, 2002) and of increased risk of MTCT (Bobat, 1996; St. Louis, 1993) after controlling for other indicators of maternal disease progression. Iron stores in tissues, on the other hand, typically measured by blood ferritin concentrations, have been associated with increased HIV load in pregnant women in some studies (Friis, 2003) but not in all (Semba, 2001a).

The causes of anemia in HIV infection are complex (Semba, 2001b). In resource-limited settings, anemia during HIV infection may result from:

- cytokine-induced suppression of red blood cell production;
- the use of cotrimoxazole for OI prophylaxis;
- the use of some ARVs (e.g. zidovudine) or drugs for AIDS-associated OI treatment (e.g. gancyclovir) which suppress bone marrow function and red blood cell synthesis;
- coincidental issues such as coinfections with malaria and hookworm;
- poor dietary intake and absorption of iron, folate, vitamin A, riboflavin, and vitamin B₁₂.

Iron-folate supplementation is a standard component of antenatal care for the prevention of anemia and the improvement of fetal iron stores during pregnancy. Some studies suggest, however, that supplemental iron given to individuals with HIV may cause increased iron stores in bone marrow and other tissues, oxidative stress, faster HIV disease progression, and subsequent increased mortality (Bolaert, 1996; Friis, 2003). These adverse effects may be more common in individuals with haptoglobin 2-2, a specific type of this heme-binding protein (Delanghe, 1998; Friis, 2003). A recent study in Kenya found no effect on viral load of iron supplements (60 mg) taken twice weekly for four months by HIV-positive adults (Olsen, 2004).

G. NUTRITION AND ARV TREATMENT

Highly active ARV treatment will in almost all adherent patients with fully drug sensitive infection result in suppression of viral replication and dramatic improvement in clinical, immunological, and nutritional status. However, weight loss and wasting may still be observed in some patients on ARV treatment (Wanke, 2000) and are associated with reduced survival (Tang, 2003). This may be complex and relate to poor adherence to therapy, virus resistance, or poor nutrition.

Lipodystrophy in HIV-infected patients (sometimes referred to as fat redistribution, including peripheral lipoatrophy, central fat accumulation, or lipomatosis) is common in adults and also has been recently described in children taking protease inhibitors (PI), analog reverse-transcriptase inhibitors (NRTI), or both, for HIV infection (HIV Lipodystrophy Case Definition Study, 2003; Temple, 2003). This syndrome was first described in 1998 and is characterized by loss of subcutaneous fat from the face, arms, and legs, but some patients may have concomitant deposition of excess fat in the neck and upper back, causing a double chin and a buffalo hump, respectively, and in the trunk (HIV Lipodystrophy Case Definition Study, 2003).

Most HIV-infected patients with lipodystrophy are otherwise relatively healthy, but insulin resistance, hypertriglyceridemia, low serum levels of high-density lipoprotein cholesterol, and occasionally hyperglycemia may develop. Hepatic steatosis with hyperglycemia has been reported, but acanthosis nigricans with lactic acidosis seems extremely rare.

Although several hypotheses have been put forward to account for lipodystrophy, the etiology and pathogenesis of this syndrome remain ill-defined. There is no internationally agreed case definition for HIV-associated lipodystrophy syndrome, which has led to substantial variations in reports of prevalence (20–80%) (Garg, 2004). Epidemiological and prospective studies suggest that lipodystrophy may be attributable to multiple factors, including the ARV drug that has been used, the stage of the HIV disease, and host risk predispositions. Stavudine-based regimens have a higher cumulative prevalence of lipoatrophy than other NRTI- or tenofovir-based regimens. Combinations based on nelfinavir are associated with more rapid fat loss than efavirenz (Temple, 2003).

Some studies indicate that protease inhibitors impair the differentiation of peripheral adipocytes by targeting specific mediators that regulate the expression of adipocyte-specific markers. In general, thymidine-based nucleoside analogues have been most associated with lipoatrophy and protease inhibitors most associated with metabolic syndrome. HIV-associated lipodystrophy probably involves multiple drug-associated events in metabolic pathways and in different tissues, as well as host predispositions (such as age, genetics, HIV stage, and inflammatory stage) (Temple, 2003).

The morphological changes associated with lipodystrophy are disfiguring and potentially stigmatizing, and thus can hinder adherence, cause discomfort and psychological morbidity, and reduce effectiveness of antiretroviral treatment. Furthermore, the frequent associated lipid and glucose metabolic abnormalities might increase the risk of cardiovascular disease. It is not clear to what extent lipodystrophy will emerge in nutritionally challenged groups, or the impact this will have on adherence to therapy. To date most studies have been done in industrialized settings in nutritionally replete populations.

Without a full understating of the molecular mechanisms involved, management approach should be based on some assumptions about probable etiologies and the palliative treatment of specific symptoms. Switching some components of antiretroviral treatment (from protease inhibitors to non-nucleoside reverse-transcriptase inhibitors or abacavir), and use of metformin and recombinant human growth hormone, have led to some success with managing the metabolic manifestations and local fat accumulation (Temple, 2003). However, lipoatrophy remains the most difficult manifestation to manage. Improvement of cosmetic appearance with surgical correction and implants for more obvious morphological manifestations can be considered. With regards to metabolic manifestations, dietary intervention and regular exercises have beneficial effects in dyslipidemia in some patients with lipodystrophy and should be tried before starting fibrates or statins. It is important to note that some statins can interact with antiretrovirals and should be avoided. The presence of hyperglycemia may necessitate the use of oral hypoglycemic drugs or insulin.

Research on the metabolic consequences of ARV treatment and appropriate strategies for their management is a growing field in industrialized countries where HIV-infected adults and children have

had access to long-term treatment. However, studies are necessary in resource-limited settings where management options and follow-up monitoring may be more limited.

II GENERAL PRINCIPLES

A. NUTRITION ADVICE, COUNSELING, CARE, AND SUPPORT FOR HIV-INFECTED WOMEN ARE ESPECIALLY IMPORTANT BECAUSE OF THE DUAL BURDENS OF HIV AND REPRODUCTION (PREGNANCY AND BREASTFEEDING) ON NUTRITIONAL VULNERABILITY

Women living in resource-limited settings are at increased risk of poor nutrition during pregnancy and lactation. HIV-infected women may be at even greater risk because of the effects of HIV on dietary intake, the absorption and use of nutrients, and related metabolic processes. Moreover, they may be socially and psychologically vulnerable as a result of living with HIV. For these reasons they may require enhanced follow-up and support so that they can achieve adequate nutrition during antenatal and postnatal care.

B. ALL ANTENATAL AND POSTNATAL WOMEN CAN BENEFIT FROM NUTRITION ADVICE, COUNSELING, CARE, AND SUPPORT AIMED AT PREVENTING MALNUTRITION DURING PREGNANCY AND IMPROVING REPRODUCTIVE HEALTH AND CHILD HEALTH OUTCOMES

Nutrition counseling, care and support begin with an assessment of a woman's specific circumstances, including her nutritional status, her diet, and the social and other conditions that could prevent her from achieving adequate dietary intake. Nutrition counseling should cover:

- ways of achieving adequate weight gain during pregnancy;
- the prevention of anemia;
- the importance of an adequate diet to support lactation and prevent nutritional depletion associated with childbearing (Adair, 1992; Merchant, 1988).

C. THE FOCUS OF NUTRITION, ADVICE, COUNSELING, CARE, AND SUPPORT VARIES WITH THE HEALTH STATUS OF THE CLIENT

For HIV-infected women who are asymptomatic, emphasis should be placed on the need to stay healthy by improving eating habits and the nutritional quality of the diet, maintaining weight (or gaining adequate weight during pregnancy), preserving lean body mass, continuing physical activity, and ensuring an understanding of food safety. Some women, particularly women who are unable to gain adequate weight during pregnancy, are losing weight, or are experiencing acute food insecurity at home, may require direct food assistance. Food assistance protocols depend on the services and food programs that are available locally. For women who are experiencing HIV-related infections and illnesses and/or

weight loss, the main objective is to minimize the nutritional consequences of the infections by obtaining immediate treatment, maintaining the greatest possible food intake during acute infection, increasing food intake during the recovery period, and continuing physical activity as much as possible so as to preserve lean body mass. For women who have advanced disease or persistent HIV-related infections and illnesses the main objective is to provide comfort and palliative care, with modification of the diet according to the symptoms and with encouragement for eating. For women on ARV treatment the focus of nutrition counseling, care, and support should be the management of drug and food interactions and other side effects of treatment.

D. WOMEN RECEIVING ARV AND OI TREATMENT SHOULD BE GIVEN ADVICE AND COUNSELING ON RELATED NUTRITIONAL ISSUES AND SHOULD BE FOLLOWED UP IN ORDER TO MONITOR AND TREAT ANY ADVERSE NUTRITIONAL COMPLICATIONS

Treatment advice and counseling on nutrition issues related to ARV and OI treatment cover the timing of pill ingestion in relation to meals, the minimizing and management of nutrition-related side effects of prescribed medications (e.g. nausea and vomiting), and the consequences of long-term ARV treatment for body fat distribution and metabolism. Nutrition advice and counseling should also cover the food and water requirements of some ARV drug regimens, e.g. PI-based regimens. The role of diet and exercise in managing body fat distribution and the metabolic changes associated with the long-term use of ARV drugs is not known. However, women should be made aware that, depending on the regimens used, physical changes may occur. Advice should be given on how to cope with such changes. Underlying or new conditions that require dietary modifications, e.g. diabetes mellitus, should be monitored during follow-up care.

III RECOMMENDATIONS

The following recommendations are based on the evidence previously reviewed and, where definitive evidence is lacking, on expert opinion. Where the basis for a specific recommendation is expert opinion this is indicated in the text. See table 17-1 for Summary of Recommendations.

The recommendations cover:

- nutrition assessment;
- nutrition counseling and support;
- use of micronutrient supplements;
- management of wasting;
- nutritional considerations for persons on ARV treatment.

It will be necessary to review these recommendations regularly and to update them as new information becomes available.

A. NUTRITION ASSESSMENT

These recommendations are based on expert opinion.

A baseline nutrition and dietary assessment should be carried out when a woman is first seen during pregnancy or postnatal follow-up, regardless of her HIV status. The purpose of this assessment is to gather information about her current nutritional status and dietary practices and to identify risk factors for developing future nutritional complications.

The baseline nutritional status assessment should include at least the measurement of weight and hemoglobin. If possible, additional body measurements can be taken, such as height (to allow calculation of BMI = kg/m²) and mid-upper arm circumference (to allow a crude estimation of muscle wasting). WHO reference tables can be used to classify maternal nutritional status on the basis of these measurements (WHO, 1995). Data from resource-limited settings indicate that non-pregnant women with BMI values below 18.5 are nutritionally vulnerable and that women who also have mid-upper arm circumference values below 23.0 cm are at even greater nutritional risk (Gartner, 2001; James, 1994).

The dietary assessment should include information on usual eating patterns and intake, appetite and eating problems, and household food security. Each woman should receive a baseline physical examination in order to identify any conditions requiring treatment which affect appetite and the ability to eat or involve altered nutrient absorption. All medications taken on a daily basis should be noted so that nutrient interactions and/or contraindications can be identified. After the baseline assessment, HIV-infected women should return for routine antenatal and postnatal care in accordance with the same protocols that are used for the general population.

B. NUTRITION COUNSELING AND SUPPORT

These recommendations are based on existing WHO guidance, the evidence review, and the report of a WHO technical consultation (WHO, 2003).

DIETARY RECOMMENDATIONS

Dietary recommendations for women with HIV are similar to those for the general population. The following issues have to be taken into consideration (WHO, 2003).

- Energy requirements are increased by 10% for the maintenance of body weight and physical activity in asymptomatic HIV-infected adults because of increased resting energy expenditure.
- During symptomatic HIV and subsequently during AIDS there is an increase in energy requirements of about 20% to 30% for the maintenance of body weight.
- Currently available data do not provide sufficient support for an increase in protein requirements during HIV infection among adults

in general and among pregnant and lactating women in particular. High-protein supplements alone do not prevent wasting or an increase in muscle mass.

- The available evidence suggests that HIV-infected individuals may require more than 1 RDA¹ per day in order to reverse deficiencies in several nutrients. The current recommendation for HIV-infected women is therefore to consume a diet that is nutritionally adequate rather than to rely on high-dose supplements of vitamins and minerals. In areas where there are multiple micronutrient deficiencies, however, a daily supplement given to HIV-infected pregnant and lactating women may improve both birth outcomes and maternal health.

Healthy women require an additional energy intake of 200 kcal/day during pregnancy and of 500 kcal/day during lactation. Protein and most vitamin and mineral requirements are also increased (National Academy of Sciences, 1989). Nutrient requirements are greater in women with low pre-pregnancy weight, inadequate weight gain during pregnancy, and poor diet quality and diversity, and in women who engage in physically demanding activities with high levels of energy expenditure.

FOOD SAFETY RECOMMENDATIONS

WHO recommendations on food safety for the general population also apply to HIV-infected women and should be part of their counseling and support. These recommendations cover the following key areas:

- keeping hands and food preparation areas clean;
- separating raw foods from cooked foods and the utensils used with them;
- cooking fresh and reheated foods thoroughly; keeping food at safe temperatures; using safe water and raw materials.

More detailed guidance on these areas is available (WHO, 2001).

RECOMMENDATIONS FOR THE TREATMENT AND MANAGEMENT OF INFECTIONS

Immediate treatment for all conditions and symptoms affecting health and nutrition is an important first response in HIV-related care. Moreover, symptom-based nutritional management may help to minimize the nutritional consequences of HIV-related illnesses and treatments.

C. IRON SUPPLEMENTATION

These recommendations are based on existing WHO guidance.

WHO currently recommends daily iron-folate supplementation (400 µg folate and 60 mg iron) during six months of pregnancy in order to prevent anemia, and twice daily supplements in order to treat severe anemia (hemoglobin < 70 g/L). The available data do not support a change in this recommendation for women living with HIV.

1 Recommended daily allowance for nutrients that are essential for health. Daily intakes below RDA levels may be associated with negative health outcomes.

D. VITAMIN A SUPPLEMENTATION

Well-designed randomized controlled trials have shown that, in HIV-infected women, daily antenatal and postnatal vitamin A supplementation does not reduce MTCT and that, in some settings, it may increase the risk of HIV transmission. Because of the lack of a beneficial effect of vitamin A supplementation and, indeed, a harmful effect in one study, the daily vitamin A intake during pregnancy and lactation should not exceed the RDA.

In areas where vitamin A deficiency is endemic, WHO currently recommends a single high dose of vitamin A (200 000 IU) for women as soon as possible after delivery and not later than 6 – 8 weeks after delivery. Research is in progress to assess further the effect of single-dose postpartum vitamin A supplementation in HIV-infected women. At present the WHO recommendation for postpartum vitamin A supplementation should be followed for HIV-positive women.

E. MANAGEMENT OF WASTING

These recommendations are based on expert opinion relating to all women.

- Screen for causes of weight loss, including household food insecurity and underlying diseases, especially tuberculosis and chronic diarrhoea, and treat as needed.
- Counsel on increased nutritional needs and appropriate local foods.

For women who are HIV-infected

- Refer for consideration of commencement of ARV treatment.
- Refer for additional care, including programs that can provide family food assistance in cases where food insecurity is identified.
- Advise that physical exercise be taken in order to increase strength and muscle mass.

F. NUTRITIONAL CONSIDERATIONS FOR PERSONS ON ARV TREATMENT

These recommendations are based on WHO ARV treatment guidelines (WHO, 2003) and expert opinion.

- Provide treatment advice on dietary needs or restrictions of specific ARV drug regimens (e.g. food and water requirements of some PI-based regimens).
- Provide health education, information, and advice on managing common side-effects, such as diarrhea, nausea, and vomiting.
- Counsel on dietary modifications as needed in response to the metabolic syndrome associated with ARV treatment.

Table 17-1: Summary of Recommendations

Recommendation	HIV + asymptomatic	HIV + symptomatic	On ARV treatment
<i>Nutrition assessment</i>	Yes	Yes	Yes
<i>Dietary recommendations</i> - Energy intake - Protein intake - Micronutrient intake	Increase by 10% No Change At least 1 RDA or daily supplement	Increase by 20–30% No Change At least 1 RDA or daily supplement	
<i>Food safety counseling</i>	Yes	Yes	Yes
<i>Symptom-based nutritional advice</i>	No	Yes	Yes
<i>Iron supplementation</i>	As per existing WHO guidelines	As per existing WHO guidelines	As per existing WHO guidelines
<i>Vitamin A supplementation</i>	As per existing WHO guidelines; daily intake not to exceed 1 RDA.	As per existing WHO guidelines; daily intake not to exceed 1 RDA.	As per existing WHO guidelines; daily intake not to exceed 1 RDA.
<i>Management of wasting</i>	No	Screen for causes and treat as needed; counsel on increased food consumption; refer for ARV treatment and family food assistance as needed	Screen for causes and treat as needed; counsel on increased food consumption; refer for review of ARV treatment as it may indicate treatment failure/ need to switch to second line therapy; refer for family food assistance as needed
<i>Nutritional considerations for persons on ARV treatment</i>	No	No	Provide advice on dietary needs and restrictions; counsel on management of nausea and related side effects; manage toxicity and treatment failure as per WHO guidelines.



The following tables, compiled by the editor, are provided as a supplement to the information in this chapter.

Table 17-A: Baseline Nutrition Assessment	
History:	<p>Usual weight</p> <p>Weight history since HIV infection</p> <p>Appetite</p> <p>Food intolerances or allergies</p> <p>Medications and side effects</p> <p>Use of alternative/complementary therapies (e.g., acupuncture, herbal medicines)</p> <p>Use of nutritional supplements</p> <p>Use of alcohol, narcotics, stimulants, illicit drugs</p> <p>Presence/history of opportunistic illnesses or symptoms which may affect nutritional status</p> <p>Other significant medical conditions</p> <p>Mental health status/cognitive function, depression, dementia</p> <p>Social, cultural, financial issues affecting food availability or preparation</p> <p>Amount of regular exercise</p> <p>History of eating disorder</p> <p>Dietary history and intake (e.g., 24 hr recall, 3 day food record; food frequency)</p>
Examination:	<p>Height</p> <p>Weight</p> <p>Body mass index (BMI kg/m²)</p> <p>General examination: assess overall nutritional state, look for physical findings (e.g., oral thrush, mouth ulcers) which may affect intake</p> <p>Triceps skinfold and mid-upper arm circumference (used to estimate body muscle and fat stores)</p> <p>Waist, hip, neck circumference (used to document changes/trends in body fat distribution)</p>
Laboratory:	<p>Hemoglobin</p> <p>CD4 count/HIV-RNA level</p> <p>Serum iron, total iron binding capacity (TIBC)</p> <p>Serum albumin, prealbumin</p> <p>Renal function</p> <p>Hepatic enzymes</p> <p>Fasting lipid profile</p> <p>Fasting glucose</p> <p>Magnesium, folate</p> <p>Micronutrient levels, if indicated (e.g., vitamin B 12, vitamin A, zinc, selenium)</p>
<p>Source: Adapted from Knox TA, Zafonte-Sanders M, Fields-Gardner C, Moen K, Johansen D, Paton N. Assessment of nutritional status, body composition, and human immunodeficiency virus-associated morphologic changes. <i>Clin Infect Dis</i> 2003; 36:S63-S68.</p>	

Table 17-B: Screening Tools for Nutritional Risk Assessment – The following tools have been adopted and adapted for use in the screening of HIV/AIDS patients:

Scored Patient-Generated Subjective Global Assessment

Revised Subjective Global Assessment for HIV-Infected Individuals

Quick Nutrition Screen

Nutrition Referral Criteria for Adults with HIV/AIDS

Public Awareness Checklist of the Nutrition Screening Initiative

HIV/AIDS Medical Nutrition Therapy Protocols

Source: Nerad J, Romeyn M, Silverman E et al. General nutrition management in patients infected with human immunodeficiency virus. Clin Infect Dis 2003;36:S52-62.

(These tools are described in more detail in this review)

Table 17-C: Common Reasons for Problems Eating

Loss of appetite

Feeling full too fast

Oral thrush or mouth sores

Tooth or gum disease

Difficult or painful swallowing

Nausea/vomiting

Bloating/gas/heartburn

Diarrhea/constipation

Dry mouth

Changes in taste or smell

Fatigue

Depression

Dehydration

Source: Adapted from Health Care and HIV: Nutritional Guide for Providers and Clients. Rockville MD: HIV/AIDS Bureau, Health Resources and Services Administration; 2002. (Available in English and Spanish at <http://www.aidsctc.org> under Educational and Training Resources).

Table 17-D: Common Causes of Weight Loss and Wasting

Inadequate intake:	Lack of appetite <i>Depression</i> <i>Nausea</i> <i>Medication side effects</i> <i>Pain</i> <i>Changes in taste or smell</i> <i>Advanced HIV/AIDS</i> Difficult or painful chewing or swallowing (oral/esophageal thrush, mouth sores)
Loss of nutrients	Malabsorption Vomiting/diarrhea
Increased caloric needs	HIV-related infections Advanced HIV/AIDS
<i>Source: Adapted from Health Care and HIV: Nutritional Guide for Providers and Clients. Rockville MD: HIV/AIDS Bureau, Health Resources and Services Administration; 2002. (Available in English and Spanish at http://www.aidsetc.org under Educational and Training Resources.)</i>	

Table 17-E: Nutritional Needs by Stage of HIV Infection

Asymptomatic HIV	-Education about nutritional needs -Balanced intake of macro-nutrients (calories, protein, carbohydrates, fat) and micronutrients (vitamins and minerals) -Education and monitoring for changes in body fat distribution/other metabolic changes and management, if indicated -Education about safe food handling and preparation -Education about potential food-drug interactions -Identification/correction of misinformation
Symptomatic HIV/AIDS	-Address symptoms/side effects of treatment affecting nutrition -Prevention of weight loss/wasting -Monitoring for and management of metabolic changes; addressing changes in body fat distribution -Evaluate for possible food-drug interactions
End-stage HIV/AIDS	-Address symptoms/side effects of treatment affecting nutrition -Maintain hydration
<i>Source: Adapted from Health Care and HIV: Nutritional Guide for Providers and Clients. Rockville MD: HIV/AIDS Bureau, Health Resources and Services Administration; 2002. (Available in English and Spanish at http://www.aidsetc.org under Educational and Training Resources.)</i>	

Table 17-F: Indications for Nutrition Counseling and/or Referral

Physical evidence of nutritional problem:

- Significant and/or rapid weight loss (>5% unintentional weight loss over 4 weeks or >10% over 4-6 months)
- Obesity

Nutritional concerns with HIV-related therapies

- Evidence of body fat redistribution
- Possible food/nutrient-drug interactions
- Metabolic abnormalities* (glucose intolerance, elevated lipids)

Symptoms likely to affect nutritional status

- Painful or difficult chewing or swallowing
- Changes in taste or smell
- Chronic nausea/vomiting
- Chronic diarrhea
- Chronic pain

HIV-related illnesses**

- Chronic oral/esophageal candidiasis
- Oral/esophageal ulcers
- Dental or gingival disease
- Central nervous system disease (especially if associated with decrease in functional or cognitive capacity)
- Other active opportunistic illness

Drug and/or alcohol abuse

Depression

Pregnancy

Other medical or psychiatric co-morbidities**

- Diabetes mellitus
- End-stage renal disease
- Hepatic disease
- Cancer
- Other medical conditions which may affect nutritional status or needs: (hypertension, osteoporosis/osteopenia*, significant psychiatric illness, other intercurrent illness)

Harmful nutritional practices

- Evidence for hypervitaminosis/excessive supplement intake
- Inappropriate use of diet pills, laxatives, other over-the-counter medications
- Eating disorder

Food allergies/intolerance

Enteral or parenteral feedings

Significant food insecurity

Sedentary lifestyle or excessive exercise

* Glucose intolerance and abnormalities in serum lipids may not necessarily be associated with HIV therapies; similarly osteoporosis/osteopenia has recently been linked to use of antiretroviral therapy

**Some HIV-related diseases may be seen independently from HIV and some medical co-morbidities may be directly or indirectly related to HIV

The urgency of counseling or referral need is based on the specific problem(s), their severity, and overall nutritional and medical status of the woman.

Source: Jean R. Anderson, MD

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