DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Final Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected With HIV

AGENCY: National Institutes of Health, HHS.
ACTION: Notice.

SUMMARY: The U.S. Department of Health and Human Services (HHS), through the National Institutes of Health (NIH), announces the publication of Final Safeguards and Research Criteria for transplantation of HIV-positive donor organs in HIV-positive recipients. All such transplants must occur under an institutional review board (IRB)-approved research protocol that is compliant with federal regulations governing human subjects’ research. The goal of this research is to increase knowledge about the safety, efficacy, and effectiveness of solid organ transplantation (SOT) utilizing HIV-positive donors in HIV-positive recipients.

A summary of public comments on the previously published Draft Safeguards and Research Criteria and HHS’ responses follow, as well as the Final Safeguards and Research Criteria.

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SUPPLEMENTARY INFORMATION: HHS initially published the Draft Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV, subsequently referred to as the “Draft Safeguards and Research Criteria,” in the Federal Register on June 18, 2015, for a 60-day public comment period ending August 17, 2015. In the months leading up to the draft publication, HHS presented the research criteria at national meetings of transplantation and HIV medicine professionals and received their input. Several teleconferences were held with transplantation community stakeholders from the private, nonprofit, and government sectors.

HHS received comments from a total of 13 individuals/entities on the Draft Safeguards and Research Criteria. Comments were submitted by transplant centers, Organ Procurement Organizations (OPOs), the Organ Procurement and Transplantation Network (OPTN), United Network of Organ Sharing (UNOS), HIV and transplantation professional societies, and a municipal agency. Overall, these comments were supportive of the HOPE Act and the Draft Safeguards and Research Criteria. Many commenters made useful suggestions that provided clarity and were incorporated into the Final Safeguards and Research Criteria. While the comments will not be addressed individually in this response document, questions, comments, and suggestions about specific aspects of the Draft Safeguards and Research Criteria are addressed by topic below.

HOPE Act: Scope

The HOPE Act permits HIV-positive to HIV-positive organ transplantation under IRB-approved research protocols conforming to the Final Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV, which were developed as directed in the HOPE Act. Patients receiving HIV-positive kidneys from deceased HIV-positive donors in South Africa (Muller, 2015) had survival rates of 84 percent and 74 percent at 1 and 5 years, respectively; however, there is presently no evidence for the safety, efficacy, and effectiveness of HIV-positive to HIV-positive transplantation in North America. The Final Safeguards and Research Criteria are meant to support the acquisition of new clinical knowledge and mechanistic insights about HIV-positive to HIV-positive organ transplantation in the United States. The results of this research will be evaluated by the Secretary of HHS and the OPTN to determine whether and how the OPTN standards for organ transplantation shall be revised to address HIV-positive organ donors.

One commenter raised concerns about the negative impact of adverse outcomes at transplant centers conducting research in HIV-positive to HIV-positive transplants on transplant program-specific reports. This commenter proposed “that transplants performed with HIV-positive donor to HIV-positive recipients are not included in the center specific reports. The risk of transplanting these patients is unknown, and there is no risk adjustment for it on the center specific reports. There will potentially be a strong disincentive for centers to do these patients leading to fewer patients receiving HIV-positive transplants.” Clearly this is an important issue but one that is beyond the authorities delegated to the NIH to enable implementation of the HOPE Act (i.e., to develop safeguards and research criteria).

Living Donors

Several commenters stated that HIV-infected living donors may be at long-term risk for renal and/or liver disease and therefore their centers would not use HIV-infected living donors. Another commenter felt it was premature to embark on living donors without prior experience with deceased HIV-positive donors and recommended a staged approach. The HOPE Act (2013) does not include any language addressing the use of living HIV-infected donors.

The long-term risks of living organ donation to the donor might be greater for those infected with HIV than for those who are not. At the same time, the desire to donate an organ, (e.g., to save or prolong a life) is strong, and evaluation of the risks and benefits of such a decision is personal and unique to a given donor/recipient pair. Evidence for the safety of organ donation by an HIV-infected individual will only be generated by clinical research. HHS has included living donors in these Safeguards and Research Criteria so that, if investigators choose to pursue this line of research, that research can be conducted with appropriate informed consent, safeguards, and rigor.

The decision to participate in HIV-positive to HIV-positive clinical research is made freely, based on informed consent in the absence of coercion. The health care team must provide a rigorous, transparent education and informed consent process that describes alternatives, risks, potential benefits, unknowns, and the need for long-term follow-up. These discussions must address how research-related injuries are managed and paid for, and must specifically include the present uncertainties about the outcomes for both HIV-positive living donors and the recipients of HIV-positive organs. Participation of knowledgeable, independent advocates for both the HIV-positive recipient and the HIV-positive donor is required by these Safeguards and Research Criteria.

Independent Advocates

Some commenters strongly supported the requirement for independent advocates for both HIV-positive recipients and prospective HIV-positive living donors. Others viewed this as unnecessary given the expertise of the principal investigator and study team and current OPTN standards. With
respect to informed consent, the role of the independent advocate complements that of the investigator and does not replace it. The investigator is assumed to have the expertise necessary to discuss risks, benefits, expectations, and alternatives. The advocate is an additional knowledgeable person who is neither a member of the research team nor the patient’s health care provider, whose role is to provide information, answer questions, and provide assurance of equal access to health care regardless of the patient’s decisions regarding research participation. For example, the advocate can assure that the transplant candidate is aware that he or she has the right to be offered and to accept an HIV-negative deceased donor organ should one become available, and can assure the prospective living donor of confidentiality and support should he or she determine that donation is not in his or her own best interest.

Transplant Hospital Experience

Several commenters from academic institutions, professional societies, and the OPTN indicated that the requirements for physicians’ and surgeons’ prior experience in HIV-negative to HIV-positive organ transplant were excessive and would result in few centers being able to participate in the research allowed under the HOPE Act. In response to the wide consensus on this issue, we have accepted the specific suggestion of the American Society of Transplant Surgeons (ASTS). Section 3 of the Final Safeguards and Research Criteria describe collective team experience, rather than individual experience.

Immunologic Criteria (CD4+ T-Cell Counts, HIV Viral Load)

Several commenters expressed concerns about the usefulness and relevance of requiring a minimum CD4+ T-cell count/percentage in the donor. They argued that the CD4+ T lymphocyte count will not predict allograft function, and that, among HIV-positive to HIV-positive transplants in South Africa, excellent outcomes were observed in recipients of kidneys from donors with CD4+ T-cell counts well below 200. These commenters urged flexibility and the elimination of this minimum immunologic criterion. In response to these comments, Section 1 of the Final Safeguards and Research Criteria was revised to indicate that, although collection of CD4+ T cell counts and percentages during the donor evaluation is required, no minimum criterion is imposed for organ acceptance. Some commenters preferred excluding any donors with detectable plasma viral load due to the risk of transmitting drug resistance. Unfortunately, it will not be possible in all cases to mitigate the risk of transmitting viral resistance by setting viral load limits and/or assessing antiretroviral resistance profiles in the time available for donor evaluation. It is expected that in many cases, potential donors will have adequate medical history available to inform the transplantation team’s assessment and maximally reduce the risk of transmitting resistant virus. For these reasons, the Final Safeguards and Research Criteria do not stipulate a limit on the allowable viral load in a donor. The transplant team should only transplant the organ if the team is confident they can define a post-transplant antiretroviral regimen that will be safe, tolerable, and effective. Concerns about transmitted drug resistance must be included in the recipient informed consent process for the research study. In addition, at the time of an organ offer, the recipient informed consent must address the transplant team’s assessment of risk specific to the characteristics of the offered organ.

Biospecimens

Several commenters emphasized the importance of a pre-transplant donor organ biopsy. The final updated research criteria include a requirement for performance of a pre-implantation “back-table” biopsy for post-transplantation patient management and future scientific and mechanistic studies. Although there are no further specimen requirements, we strongly encourage the inclusion of serial biospecimens (e.g., allograft tissue, urine, serum, and cells) in the individual research protocols. These specimens will be a valuable resource to the community in studies relating to superinfection risks, for example. Failure to collect such specimens, particularly in organ donors, would be a regrettable lost opportunity.

Required Outcomes

Several commenters expressed concerns about data collection, quality, and reporting. The HOPE Act requires the Secretary of HHS to review the results of research conducted under the Act. One purpose of the criteria presented in the Final Safeguards and Research Criteria is to ensure that all investigators conducting research in HIV-positive to HIV-positive transplantation collect similar data elements. This standardization will facilitate the subsequent review mandated in the HOPE Act.

Conclusion Regarding Comments Received

HHS appreciates the time and effort taken by commenters to respond to the Request for Comments. The comments represented the deliberative efforts of truly dedicated individuals and organizations in transplantation and HIV medicine. All the responses were helpful in revising the draft Human Immunodeficiency Virus (HIV) Organ Policy Equities (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV.

The Final Safeguards and Research Criteria for transplantation of HIV-positive (HIV+) donor organs in HIV-positive (HIV+) recipients are as follows:

<table>
<thead>
<tr>
<th>ABBREVIATIONS</th>
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<tbody>
<tr>
<td>AIDS .................</td>
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<tr>
<td>APOL1 ..................</td>
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<tr>
<td>ART .......................</td>
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<tr>
<td>CD4 .......................</td>
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<td>CMS ........................</td>
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<td>CNS ........................</td>
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<td>FDA ........................</td>
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<td>FIPSE ........................</td>
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<td>GESIDA ........................</td>
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<td>HAART ........................</td>
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<td>HBV ........................</td>
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<td>HCT/Ps ........................</td>
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<td>HCV ........................</td>
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### ABBREVIATIONS—Continued

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus.</td>
</tr>
<tr>
<td>HOPE Act</td>
<td>HIV Organ Policy Equity Act.</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalized Ratio.</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board.</td>
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<tr>
<td>mL</td>
<td>Milliliter.</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health.</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-Nucleoside (or Non-Nucleotide) Reverse Transcriptase Inhibitor.</td>
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<tr>
<td>NRTI</td>
<td>Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitor.</td>
</tr>
<tr>
<td>OI</td>
<td>Opportunistic Infection.</td>
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<tr>
<td>OPO</td>
<td>Organ Procurement Organization.</td>
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<tr>
<td>OPTN</td>
<td>Organ Procurement and Transplantation Network.</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction.</td>
</tr>
<tr>
<td>PML</td>
<td>Progressive Multifocal Leukoencephalopathy.</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic Acid.</td>
</tr>
<tr>
<td>SOPs</td>
<td>Standard Operating Procedures.</td>
</tr>
<tr>
<td>SOT</td>
<td>Solid Organ Transplantation.</td>
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<tr>
<td>SRTR</td>
<td>Scientific Registry of Transplant Recipients.</td>
</tr>
<tr>
<td>UNOS</td>
<td>United Network for Organ Sharing.</td>
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<tr>
<td>μL</td>
<td>Microliter.</td>
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### DEFINITIONS

- **ABO compatible** — People who have one blood type (A, B, AB, or O) form proteins (antibodies) that cause their immune system to react against other blood types. This is important when a patient needs to receive blood (transfusion) or an organ transplant. The blood types must be matched to avoid an ABO incompatibility reaction. ABO compatible is when the blood types are matched.

- **Antiretroviral therapy (ART) resistance.** — When an HIV strain develops drug resistance and/or genetic mutations associated with drug resistance.

- **Types/classes of HIV/AIDS antiretroviral drugs (current at publication).** —
  - (1) Entry inhibitors.
  - (2) Fusion inhibitors.
  - (3) Nucleoside reverse transcriptase inhibitors (NRTIs).
  - (4) Non-nucleoside reverse transcriptase inhibitors (NNRTIs).
  - (5) Integrase inhibitors.
  - (6) Protease inhibitors.
  - (7) Multi-class combination products.

- **HIV strain** — Distinct genetic variants of the HIV retrovirus, conferring characteristics such as susceptibility or resistance to ART medications.

- **HIV-negative** — Not testing positive for HIV by serology and/or nucleic acid testing using FDA-licensed, approved or cleared test devices.

- **HIV-positive** — HIV-infected by serology and/or nucleic acid testing using FDA-licensed, approved, or cleared test devices.

- **HIV undetectable viral load** — (The conventional definition at the time of the publication of this research criteria document, based on current clinical technology/practice): HIV ribonucleic acid (RNA) below 50 copies with current technology.

- **Opportunistic infection** — Infections that are more frequent or more severe because of immunosuppression in HIV-infected persons.

- **Suppressed viral load** — HIV RNA below 50 copies with current technology.

- **Viral detection threshold** — HIV RNA below 50 copies with current technology at time of publication of this research criteria document.

### Executive Summary

The HOPE Act requires the HHS Secretary (the Secretary) to develop and publish criteria for research involving transplantation of human immunodeficiency virus-infected donor organs to HIV-positive recipients. A summary of the criteria for conducting clinical research in HIV-positive to HIV-positive organ transplantation is included in the chart below, and the criteria are set forth in six broad categories (Donor Eligibility, Recipient Eligibility, Transplant Hospital Criteria, Organ Procurement Organization (OPO) Responsibilities, Prevention of Inadvertent Transmission of HIV, and Study Design/Required Outcome Measures). These criteria are in addition to current policies and regulations governing organ transplantation and human subjects’ research. The goals of these criteria are, first, to ensure that research using organs from HIV-positive donors is conducted under conditions protecting the safety of research participants and the general public; and second, to ensure that the results of this research provide a basis for evaluating the safety of solid organ transplantation (SOT) from HIV-positive donors to HIV-positive recipients.

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Donor Eligibility:</td>
<td>No evidence of invasive opportunistic complications of HIV infection.</td>
</tr>
<tr>
<td>All HIV-positive deceased donors.</td>
<td>Pre-implant donor organ biopsy.</td>
</tr>
<tr>
<td></td>
<td>Viral load: no requirement.</td>
</tr>
<tr>
<td>Category</td>
<td>Criteria</td>
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<tr>
<td><strong>Deceased donor with known history of HIV infection and prior antiretroviral therapy (ART).</strong></td>
<td>The study team must describe the anticipated post-transplant antiretroviral regimen(s) to be prescribed for the recipient and justify its conclusion that the regimen will be safe, tolerable, and effective.</td>
</tr>
</tbody>
</table>
| **HIV-positive living donor** | Well-controlled HIV infection defined as:  
  - CD4+ T-cell count ≥500/μL for the 6-month period before donation.  
  - HIV-1 RNA <50 copies/mL.  
  - No evidence of invasive opportunistic complications of HIV infection.  
  Pre-implant donor organ biopsy. |
| **Recipient Eligibility** | CD4+ T-cell count ≥200/μL (kidney).  
  CD4+ T-cell count ≥100 μL (liver) within 16 weeks prior to transplant and no history of opportunistic infection (OI); or ≥200 μL if history of OI is present.  
  HIV-1 RNA <50 copies/mL and on a stable antiretroviral regimen.  
  No evidence of active opportunistic complications of HIV infection.  
  No history of primary central nervous system (CNS) lymphoma or progressive multifocal leukoencephalopathy (PML). |
| **Transplant Hospital Criteria** | Transplant hospital with established program for care of HIV-positive subjects.  
  HIV program expertise on the transplant team.  
  Experience with HIV-negative to HIV-positive organ transplantation.  
  Standard operating procedures (SOPs) and training for the organ procurement, implanting/operative, and postoperative care teams for handling HIV-infected subjects, organs, and tissues.  
  Institutional review board (IRB)-approved research protocol in HIV-positive to HIV-positive transplantation.  
  Institutional biohazard plan outlining measures to prevent and manage inadvertent exposure to and/or transmission of HIV.  
  Provide each living HIV-positive donor and HIV-positive recipient with an "independent advocate".  
  Policies and SOPs governing the necessary knowledge, experience, skills, and training for independent advocates. |
| **OPO Responsibilities** | SOPs and staff training procedures for working with deceased HIV-positive donors and their families in pertinent history taking; medical chart abstraction; the consent process; and handling blood, tissues, organs, and biospecimens.  
  Biohazard plan to prevent and manage HIV exposure and/or transmission. |
| **Prevention of Inadvertent Transmission of HIV.** | Each participating Transplant Program and OPO shall develop an institutional biohazard plan for handling organs from HIV-positive donors that is designed to prevent and/or manage inadvertent transmission or exposure to HIV.  
  Procedures must be in place to ensure that human cells, tissues, and cellular and tissue-based products (HCT/Ps) are not recovered from HIV-positive donors for implantation, transplantation, infusion, or transfer into a human recipient; however, HCT/Ps from a donor determined to be ineligible may be made available for nonclinical purposes. |
| **Required Outcome Measures:**  
  **Wait List Candidates** | HIV status.  
  CD4+ T-cell counts.  
  Co-infection (hepatitis C virus [HCV], hepatitis B virus [HBV]).  
  HIV viral load.  
  ART resistance.  
  Removal from wait list (death or other reason).  
  Time on wait list. |
| **Donors (all)** | Type (Living or deceased).  
  CD4+ T-cell count.  
  Co-infection (HCV, HBV).  
  HIV viral load.  
  ART resistance. |
| **Living Donors** | Progression to renal insufficiency in kidney donors.  
  Progression to hepatic insufficiency in liver donors.  
  Change in ART regimen as a result of organ dysfunction.  
  Progression to acquired immunodeficiency syndrome (AIDS).  
  Failure to suppress viral replication (persistent HIV viremia).  
  Death. |
| **Transplant Recipients** | Rejection rate (annual up to 5 years).  
  Progression to AIDS.  
  New OI.  
  Failure to suppress viral replication (persistent HIV viremia).  
  HIV-associated organ failure.  
  Malignancy.  
  Graft failure.  
  Mismatched ART resistance versus donor.  
  Death. |

The HOPE Act research criteria focus on liver and kidney transplantation, where there is substantial experience with HIV-negative to HIV-positive transplantation. The intent is not to exclude the possibility of HIV-positive to HIV-positive transplantation of other organs; however, transplant organ-specific teams must gain experience.
with HIV-negative to HIV-positive transplantation before embarking on the more complex and less well-defined issues with HIV-positive to HIV-positive transplantation. The minimum combined experience required of the transplant physician and HIV physician on the team is five organ-specific cases over 4 years.

The HOPE Act requires the Secretary and the Organ Procurement and Transplantation Network (OPTN) to review the results of the scientific research conducted under these criteria to determine whether the results warrant further revisions to the OPTN’s standards of quality. Under the HOPE Act, the Secretary may in the future determine that participation in research under such criteria is no longer required for HIV-positive to HIV-positive transplants.

Background

Public Law 113–51, The HOPE Act, requires the HHS Secretary (the Secretary) to, among other things, “develop and publish criteria for conduct of research relating to transplantation of organs from donors infected with human immunodeficiency virus (HIV) into individuals who are infected with HIV before receiving such organs.” (See Public Health Service Act section 377E(a) [codified at 42 U.S.C. 274f–5]). In addition, pursuant to section 377E(c) of the HOPE Act, the Secretary is required, in conjunction with the OPTN, to review the results of that research to determine whether revisions should be made to the standards of quality adopted under section 372(b)(2)(E) of the Public Health Service Act (OPTN standards for the acquisition and transportation of donated organs) and the regulations governing the operation of the OPTN (42 CFR 121.6).

The authority vested in the Secretary under section 377E(a) to develop and publish research criteria was delegated to the Director, National Institutes of Health (NIH), and these research criteria are the subject of this document. They are meant to ensure first, that research using organs from HIV-positive donors is conducted under conditions protecting the safety of research participants and the general public; and second, that the results of this research provide a basis for evaluating the safety of transplantation of organs from HIV-positive donors to HIV-positive recipients.

Process

This document was authored by representatives of the NIH and Centers for Disease Control and Prevention. Additional input from representatives of other federal agencies, including the Health Resources and Services Administration, Centers for Medicare & Medicaid Services (CMS), and the Food and Drug Administration (FDA), was solicited. In addition, perspectives and input were solicited from community stakeholders.

Introduction

The advent of effective antiretroviral therapy (ART) in the mid-1990s for treatment of individuals infected with HIV transformed a rapidly fatal disease into a well-controlled chronic illness. Currently, the life expectancy of individuals infected with HIV and receiving ART early in the course of their disease approaches that of individuals without HIV infection (Wada, 2013, 2014). In this era of greater longevity, liver failure, end-stage renal disease, and cardiovascular disease have emerged as important causes of morbidity and mortality in patients with HIV infection (Neuhaus, 2010).

Organ transplantation prolongs survival and improves quality of life for individuals with end-stage organ disease (Matas, 2014; Kim, 2014). Until recently, however, organ transplantation was unavailable to those infected with HIV due to concerns that pharmacologic immunosuppression to prevent organ rejection would hasten the progression from HIV infection to AIDS, concerns about disease transmission, and reluctance to allocate organs to a population whose outcome was unpredictable (Blumberg, 2009, 2013a, 2013b; Mgbako, 2013; Taege, 2013). Nevertheless, a few transplant programs accepted HIV-positive patients on their transplant waiting lists and accumulated data showing kidney or liver transplantation could be done safely in these patients (Roland, 2002, 2003a, 2003b, 2003c; Blumberg, 2009; Stock, 2010; Yoon, 2011; Terrault, 2012). Subsequently, a prospective, multicenter clinical trial of kidney and liver transplantation in 275 patients demonstrated that, among HIV-positive kidney and liver transplant recipients, patient and graft survival rates were acceptable and within the range of outcomes currently achieved among non-infected transplant recipients. However, the rate of kidney rejection was unexpectedly high, demonstrating that the immune dysregulation resulting from HIV infection, HCV co-infection, and antirejection drugs is complex and incompletely understood. Some of the challenges encountered in that study remain relevant for clinical sites offering organ transplantation to HIV-positive individuals today (e.g., management of drug interactions and toxicities when combining complex medical regimens, management of combined morbidities of two or more active diseases, and the need for ongoing collaboration among medical professionals from different specialties) (Frassetto, 2007, 2014; Locke, 2014). Despite the complexities, this study and others (Ragni, 1999; Frassetto, 2009; Huprikar, 2009; Stock, 2010; Touzot, 2010; Cooper, 2011; Duclos-Vallee, 2011; Reeves-Daniel, 2011; Fox, 2012; Terrault, 2012; Grossi, 2012; Gomez, 2013; Harbell, 2013) demonstrate that kidney and liver transplantation are appropriate in HIV-positive individuals with liver or kidney failure, although gaps in knowledge and many research questions remain. There is much less experience with heart (Calabrese, 2003; Bisleri, 2003; Pelletier, 2004; Uriel, 2009, 2014; Castel, 2011a, 2011b; Durante-Mangoni, 2011 and 2014) and lung (Mehta, 2000; Humbert, 2006; Petrosillo, 2006; Bertani, 2009; Kern, 2014a, 2014b) transplantation in HIV-positive recipients, or mechanical circulatory assistance (Brucato, 2004; Fieno, 2009; Mehmood, 2009; Sims, 2011) as a bridge to transplantation, although case reports and small case series suggest acceptable short-term outcomes are possible.

Prior to the passage of the HOPE Act, U.S. law required that all U.S. transplants for HIV-positive recipients utilize organs from HIV-uninfected donors. (See 42 U.S.C. 273(b)(3)(C), 274(f) and 18 U.S.C. 1122, all prior to amendment by the HOPE Act). The potential for increasing the pool of available organ donors for all recipients by allowing the use of organs from donors infected with HIV for transplantation into recipients infected with HIV (hereinafter referred to as “HIV-positive to HIV-positive transplantation”) is recognized (Boyarsky, 2011, 2015; Mgbako, 2013; Mascollini, 2014; Kucirka, 2015; Richterman, 2015). It is estimated that an additional 500 organ donors per year might be available if HIV-positive individuals were accepted as organ donors for HIV-positive recipients (Boyarsky, 2011). The published experience with HIV-positive to HIV-positive SOT at this time comes from Muller et al from the University of Cape Town in South Africa. Initially, Muller et al (2010) reported 100 percent patient and graft survival in a four-patient pilot study. Subsequently, the same group reported an additional 10 HIV-positive to HIV-positive renal transplants (Muller, 2012). All patients were restarted on ART early postoperatively in the immunosuppressive setting of T-
standards of quality should be further
determine whether the OPTN's
conducted under these criteria to
HOPE Act, the Secretary, together with
transplantation. As mandated by the
HIV-positive to HIV-positive
data requirements of clinical research in
conducting the research. Rather, the
investigator's specific research
questions and the expertise of those
hours. Of note, the South African
HIV-positive deceased donors were
ART-naïve, without history of
opportunistic infection or proteinuria,
and had normal pre-transplant renal
biopsies. While renal function has
remained normal in the recipients, three
have had routine post-transplant renal
biopsies demonstrating new changes
typical of early HIV-associated
nephropathy that were not present in
baseline biopsy specimens. The long-
term significance of these findings
remains unknown and awaits longer
follow-up. All patients had undetectable
plasma HIV viral loads after
transplantation. Graft rejection rates
were 8 percent at 1 year and 22 percent
at 3 years.

This document presents criteria for
conducting research in HIV-positive to
HIV-positive organ transplantation in
the United States. The criteria are
grouped into six broad categories: Donor
Eligibility, Recipient Eligibility,
Transplant Hospital Criteria, OPO
Responsibilities, Prevention of
Inadvertent Transmission of HIV, and
Study Design/Required Outcome
Measures. These research criteria do not
describe all of the necessary
components of a research protocol for
HIV-positive to HIV-positive
transplantation, such as the specific
medication regimens, pre-transplant
induction (if any), maintenance
immunosuppression after
transplantation, or control of HIV
infection. These protocol elements and
others will be determined by an
investigator's specific research
questions and the expertise of those
conducting the research. Rather, the
criteria address the minimum safety and
data requirements of clinical research in
HIV-positive to HIV-positive
transplantation. As mandated by the
HOPE Act, the Secretary, together with
the OPTN, is charged with reviewing
the results of scientific research
conducted under these criteria to
determine whether the OPTN’s
standards of quality should be further
modified and whether some HIV-
positive to HIV-positive transplants
should proceed outside the auspices of
research conducted under such criteria.

This document focuses on liver and
kidney transplantation, as it is only in
liver and kidney transplantation that
there is substantial experience with
transplantation from HIV-negative
donors to HIV-positive recipients
(Sawinski, 2015; Locke, 2015a, 2015b;
Miro, 2015). The intent is not to exclude
the possibility of HIV-positive to
HIV-positive transplantation of other organs
such as the heart or lung in the future;
however, transplant teams must gain
experience with HIV-negative to HIV-
positive transplantation of a specific
organ before taking on the more
complex and less well-defined issues of
HIV-positive to HIV-positive
transplantation of that organ. Centers
developing research protocols for
HIV-positive to HIV-positive transplantation of
organs other than kidney or liver
must have a study team with
demonstrated experience in HIV-
negative to HIV-positive transplants, as
noted in Section 3.1(ii), for the organ
transplant(s) proposed in the research
protocol. Specific criteria for the
transplantation of organs other than the
liver and kidney have not been provided
in this document because no evidence
base exists to support such
recommendations. The study team
developing a research protocol for
HIV-positive to HIV-positive non-renal, non-
liver transplantation must develop and
justify specific criteria for review and
approval by their IRB, based on the
relevant experiences of the study team
and others.

These criteria are in addition to, not
in place of, current policies and
regulations governing organ
transplantation and human subjects’
research. Accordingly, to emphasize the
specific requirements unique to the
investigational transplantation of organs
from HIV-positive donors into HIV-
positive recipients, the research criteria
set forth here do not address related
requirements that exist in federal
regulations or OPTN bylaws or policies
including, but not limited to, obligations
imposed on OPTN transplant hospitals
and transplant programs concerning
informed consent of transplant
recipients and living donors, the
equitable allocation of organs, and organ
offers. The regulations governing the
operation of OPTN are codified at 42
CFR part 121 and OPTN policies and
bylaws can be found at http://
optn.transplant.hrsa.gov/
ContentDocuments/OPTN_Policies.pdf.

Under these research criteria, all HIV-
positive to HIV-positive transplantation
must occur under an IRB-approved
research protocol and shall comply with
any other existing laws, policies, and
regulations governing the conduct of
human subjects’ research (see Public
Law 113–51 and, e.g., 45 CFR part 46,
as applicable). In addition, a transplant
program conducting research in HIV-
positive to HIV-positive transplantation
under these research criteria must
provide each living donor and recipient
with an independent advocate.

Although the criteria set forth in this
document outline the minimum safety
requirements for research involving
HIV-positive to HIV-positive
transplantation, it is expected that
investigators will develop more specific
eligibility criteria based on their
individual research questions and
protocols. In addition, it is likely, that
researchers will wish to collect research
specimens (blood, urine, tissue) in
addition to those specified in the
Research Criteria.

1 Donor Eligibility

HIV-positive living donors and HIV-
positive deceased donors of organs for
transplantation into an HIV-positive
recipient must fulfill applicable clinical
criteria in place for HIV-uninfected
organ donors.

There is substantial concern about the
consequences of transplanting an organ
from an HIV-positive donor to a
recipient infected with a strain of HIV
that differs from the donor’s in terms of
its responsiveness to antiretroviral
therapy (ART). The likelihood and
impact of HIV superinfection in this
context are unknown. Adverse
consequences could range from
transient loss of viral suppression,
necessitating a change in antiretroviral
regimen to a worst-case scenario in
which the new infecting strain of HIV is
unresponsive to available antiretroviral
treatment and the recipient progresses
to AIDS (Redd, 2013). Information
relevant to understanding the known or
potential extent of antiretroviral
resistance in the strain of HIV infecting
the organ donor may be incomplete for
many reasons:

• There may be inadequate virus in
donor specimens for antiretroviral
resistance testing;
• If the specimen is adequate, there
may not be enough time within the
decision-making evaluation window to
fully assess antiretroviral resistance
before the clinical deterioration of the
donor, organ procurement, and
implantation;
• The donor’s history of antiretroviral
treatment may be unknown or
incomplete;
• Results from prior antiretroviral resistance testing may be unavailable. These issues might be especially challenging when considering organ donation from deceased donors whose HIV infection is first identified during donor evaluation. As of 2011, an estimated 1 in 6 U.S. adults living with HIV infection were undiagnosed (Prevention, 2013) and an estimated 16 percent of newly diagnosed, untreated individuals were infected with virus resistant to at least one class of antiretroviral drug (Kim, 2013; Megens, 2013).

It is anticipated that the risk of transmission of resistant HIV strains may be lower from deceased donors with a well-documented history of antiretroviral treatment, undetectable virus at demise, and robust and persistent undetectable viral load for at least 1 year prior to death. However, to impose this as an eligibility criterion would limit the pool of suitable donors and severely limit the ability to study transmission of HIV-positive organs under the HOPE Act. In addition, it will not be possible in all cases to obtain viral loads and/or antiretroviral resistance profiles in the time available for donor evaluation. Transplant teams evaluating a donor must review all available donor and recipient information and be able to propose an antiretroviral regimen that will be equally or more safe, tolerable, and effective for the recipient after transplantation as the regimen in place in the recipient before transplantation. For instance, a donor who only achieves viral suppression with a regimen known to be intolerable to the recipient must not be accepted. If there is doubt about the ability to suppress viral replication after transplantation, the transplant must not move forward.

Donors co-infected with hepatitis are not excluded from HIV-positive to HIV-positive transplant; however, careful consideration must be given when evaluating a donor co-infected with HBV and/or HCV (Terrault, 2012; Miro, 2012; Moreno, 2012; Sherman, 2014; Chen, 2014). Although HCV therapeutic strategies are rapidly evolving (Liang, 2013), it is possible that mixed genotype HCV infections may influence post-transplant treatment of HCV in the recipient. Prior antiretroviral treatment of the donor and/or recipient with agents active against HBV (i.e., lamivudine, emtricitabine, adefovir, and tenofovir) has the potential for inducing or uncovering archived HBV drug resistance in the recipient (Dieterich, 2007; Soriano, 2009; Pais, 2010). In the case of a living HIV-positive organ donor, the risk of future end-stage liver or kidney failure in the donor must be carefully assessed as it is in other at-risk populations currently eligible to donate an organ. For example, kidney disease in HIV-positive patients has been associated with the apolipoprotein 1 (APOL1) coding variants that confer a very high risk of susceptibility and are almost exclusively found in patients of African descent (Freedman, 2013; Genovese, 2010). Living donation of a kidney from a donor having such a variant may be associated with an unacceptable risk of subsequent kidney disease to both the donor and the recipient (Freedman, 2015; Reeves-Daniel, 2011; Parsa, 2013; Riella, 2015).

The consent process for an HIV-positive living organ donor must include and document provision to the donor of information regarding: (1) The possibility that the loss of organ function resulting from donation could preclude the use of certain antiretroviral drugs in the future; (2) the risk of kidney or liver failure in the future; (3) the possibility of transmission of occult opportunistic infections to the recipient; and (4) the absence of U.S. experience in HIV-positive to HIV-positive organ transplantation, and thus the unpredictable nature of donor and recipient outcomes (Mgbako, 2013).

HIV-positive transplant candidates who are listed for a transplant in the context of a research study of HIV-positive to HIV-positive transplantation must have the same opportunity as other transplant candidates to receive an organ from an HIV-negative donor, should one become available for them.

1.1 HIV-Positive Donor Eligibility Criteria

The HIV-specific donor eligibility criteria for deceased donors and for living donors are listed (also refer to Table 1). Co-infection with HBV and/or HCV is not an exclusion criterion, although research that includes co-infected donors must address any additional eligibility criteria within their research protocol.

1.1.1 HIV-Positive Deceased Donors

When evaluating HIV-positive deceased donors, it is understood that limited medical history may be available and/or known at the time of the donor evaluation. The OPO must make reasonable efforts to obtain prior medical history so that a transplant center team may best determine the suitability of the potential donor based on the information available. A complete history of antiretroviral regimens and a history of viral load tests and resistance testing are especially valuable for evaluating the likelihood of donor HIV resistance to antiretroviral regimens. A history of OIs or cancers is also of high importance, due to the increased risk for both attributable to HIV, and the additional difficulty of treating some infections and neoplasms in a post-transplant setting. It is possible that deceased donors with lower CD4+ T-cell counts may pose an increased risk of harboring transmissible diseases (e.g., opportunistic infections or neoplasms) that may be difficult to detect during organ harvest and transplantation; teams conducting transplants under the HOPE Act are urged to assess donors with low CD4+ T-cell counts (e.g., ≤200/µL) with special caution and to promptly inform IRBs and protocol sponsors of known or suspected disease transmission events.

Minimum eligibility criteria for all HIV-positive deceased donors:

i. Documented HIV infection using an FDA-licensed, approved, or cleared test device(s).

ii. No evidence of invasive opportunistic complications of HIV infection.

iii. Pre-implant donor organ biopsy to be stored, at a minimum, for the duration of the study (or at least 5 years); additional specimens may be obtained to support specific research goals.

Additional eligibility criteria for HIV-positive deceased donors with a known history of HIV and prior treatment with ART:

i. The study team must describe the anticipated post-transplant antiretroviral regimen(s) to be prescribed for the recipient and justify their conclusion that the proposed regimen will be safe, tolerable, and effective.

1.1.2 HIV-Positive Living Donors

Minimum eligibility criteria for HIV-positive living donors:

i. Documented HIV infection using an FDA-licensed, approved, or cleared test device.

ii. Well-controlled HIV infection, as evidenced by:
   a. CD4+ T-cell count ≥500/µL for the 6-month period preceding donation.
   b. Fewer than 50 copies/mL of HIV-1 RNA detectable by ultrasensitive or real-time polymerase chain reaction (PCR) assay.
   c. A complete history of ART regimens and ART resistance.

iv. The study team must be able to predict a safe, tolerable, and effective regimen to be prescribed for the recipient based on the donor’s current ART regimen as well as the donor’s history of ART resistance.
v. No evidence of invasive opportunistic complications of HIV infection.

vi. A liver biopsy (in liver donors) or a kidney biopsy (in kidney donors) showing no evidence of a disease process that would put the donor at increased risk of progressing to end-stage organ failure after donation, or that would present a risk of poor graft function to the recipient.

2 Recipient Eligibility

A key consideration when evaluating potential HIV-positive transplant candidates is the ability to suppress HIV viral load post-transplant. This includes a thorough assessment by the transplant team of the candidate recipient’s prescribed antiretroviral medications, HIV RNA levels while on medications, adherence to HIV treatment, and any available HIV resistance testing; a similar evaluation of the donor must also be carried out. A transplant should only take place if, after evaluating both recipient and donor, the team is confident they can define a post-transplant antiretroviral regimen that will be safe, tolerable, and effective. If there is any doubt on the part of the transplant team about the ability to suppress viral replication post-transplant, the transplant should not move forward. Concerns about transmitted drug resistance must be included in the recipient informed consent process for the research study. At the time of an organ offer, the recipient informed consent must address the transplant team’s assessment of risk specific to the organ they are being offered.

2.1 HIV-Positive Recipient Eligibility Criteria

The following HIV-specific criteria must be met when screening for an HIV-positive to HIV-positive organ transplant (also refer to Table 1):

- CD4+ T-cell count ≥200/μL (kidney) and ≥100/μL (liver) within 16 weeks prior to transplant; any patient with history of OI must have a CD4 positive T-cell count ≥200/μL.
- HIV RNA less than 50 copies/mL and on a stable antiretroviral regimen.*
- No evidence of active opportunistic complications of HIV infection.
- No history of primary CNS lymphoma or progressive PML.
- Concurrence by the study team that, based on medical history and ART, viral suppression can be achieved in the recipient post-transplant.
- Patients who are unable to tolerate ART due to organ failure or who have only recently started ART may have detectable viral load and still be considered eligible if the study team is confident there will be a safe, tolerable, and effective antiretroviral regimen for the patient once organ function is restored after transplantation.

**In deceased donors with a known history of HIV infection and prior treatment with ART, the study team must describe the anticipated post-transplant antiretroviral regimen(s) to be used by the organ recipient and justify their conclusion that the proposed regimen will be safe, tolerable, and effective.

3 Transplant Hospital Criteria

Expertise in the management of individuals with HIV infection is essential for this research. A transplant hospital participating in HIV-positive to HIV-positive transplantation must include experts in the field of transplantation as well as experts in the management of HIV infection working collaboratively as a part of a study team.

3.1 Specific Transplant Hospital Criteria

1. An established program for the care of individuals infected with HIV.

2. A liver biopsy (in liver donors) or a kidney biopsy (in kidney donors) showing no evidence of a disease process that would put the donor at increased risk of progressing to end-stage organ failure after donation, or that would present a risk of poor graft function to the recipient.

3. Specific Transplant Hospital Criteria

i. Organ recipients who are unable to tolerate ART due to organ failure or who have only recently started ART may have detectable viral load and still be considered eligible if the study team is confident there will be a safe, tolerable, and effective antiretroviral regimen to be used by the recipient once organ function is restored after transplantation.

**In deceased donors with a known history of HIV infection and prior treatment with ART, the study team must describe the anticipated post-transplant antiretroviral regimen(s) to be used by the organ recipient and justify their conclusion that the proposed regimen will be safe, tolerable, and effective.

3. Transplant Hospital Criteria

Expertise in the management of individuals with HIV infection is essential for this research. A transplant hospital participating in HIV-positive to HIV-positive transplantation must include experts in the field of transplantation as well as experts in the management of HIV infection working collaboratively as a part of a study team.

3.1 Specific Transplant Hospital Criteria

i. An established program for the care of individuals infected with HIV.

ii. In order for a transplant hospital to initiate HIV-positive to HIV-positive transplantation, there must be a study team consisting of (at a minimum) a transplant surgeon, a transplant physician, and an HIV physician. The transplant physician and HIV physician collectively must have experience with at least 5 HIV-negative to HIV-positive transplants with the designated organ(s) over the last 4 years. This constitutes the minimal experience necessary, and the IRB must evaluate key personnel (i.e., transplant surgeon, transplant physician, and HIV physician) in the context of total expertise and experience with respect to HIV and/or organ transplantation (confirm and document HIV-negative to HIV-positive transplant experience of the team).

iii. Defined SOPs and training for the hospital personnel involved in procurement and/or implantation regarding the following issues:

   a. Donor evaluation
   b. Organ recovery
   c. Handling, processing, packaging, shipping, and transporting of blood, lymph nodes, tissues, and organs to and/or within the transplant hospital
   d. Transplant procedure

iv. Transplant hospitals with an IRB-approved research protocol in HIV-positive to HIV-positive transplantation

3. Table 1—Summary of Donor and Recipient Eligibility Criteria for HIV-Positive Sero-Concordant Organ Transplant Pairs Under the HOPE Act

<table>
<thead>
<tr>
<th>HIV-Related variables</th>
<th>Deceased donor</th>
<th>Living donor</th>
<th>HIV-Positive recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current CD4+ T-cell count (T lymphocytes/μL)</td>
<td>No requirement</td>
<td>≥500 for 6 months prior to organ donation.</td>
<td>If no history of OI • ≥200</td>
</tr>
<tr>
<td>Plasma HIV RNA viral load (copies/mL)</td>
<td>No requirement**</td>
<td>&lt;50</td>
<td>If history of OI • ≥200 (kidney) • ≥100 (liver)</td>
</tr>
<tr>
<td>Opportunistic infection</td>
<td>No invasive OI</td>
<td>No invasive OI</td>
<td>CD4+ T-cell count measured within 16 weeks of transplantation &lt;50*</td>
</tr>
<tr>
<td>HIV-Related variables</td>
<td>Deceased donor</td>
<td>Living donor</td>
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</tr>
</tbody>
</table>

*Organ recipients who are unable to tolerate ART due to organ failure or who have only recently started ART may have detectable viral load and still be considered eligible if the study team is confident there will be a safe, tolerable, and effective antiretroviral regimen to be used by the recipient once organ function is restored after transplantation.

**In deceased donors with a known history of HIV infection and prior treatment with ART, the study team must describe the anticipated post-transplant antiretroviral regimen(s) to be used by the organ recipient and justify their conclusion that the proposed regimen will be safe, tolerable, and effective.
must inform the OPTN of additional organ-specific acceptance criteria for organs from HIV-positive donors.

v. Transplant hospitals with an IRB-approved research protocol in HIV-positive to HIV-positive transplantation with HIV-positive candidates on the wait list willing to accept an HIV-positive organ must specify any additional acceptance criteria to the OPO.

vi. The transplant hospital must verify the HIV status of both the donor and the recipient.

vii. Defined SOPs and training regarding an institutional biohazard plan, which outlines the measures taken to prevent and manage inadvertent exposure and/or transmission of HIV.

3.2 Independent Advocates

A transplant program conducting research in HIV-positive to HIV-positive transplantation under these research criteria must provide each HIV-positive living donor and recipient with an independent advocate.

In the setting of a living donor transplant, there must be two independent advocates, one for the donor and another for the recipient. Each advocate must be independent of the research team and must have knowledge and experience with both HIV infection and organ transplantation.

At a minimum, transplant hospitals conducting research in HIV-positive to HIV-positive transplantation shall develop policies and procedures addressing the role, knowledge, and experience of independent advocates in the setting of HIV infection, transplantation, medical ethics, informed consent, and the potential impact of external pressure on the HIV-positive recipient’s decision, and HIV-positive living donor’s decision (if applicable) about whether to enter the HIV-positive to HIV-positive transplant research study.

3.2.1 Independent HIV-Positive Recipient Advocate

Transplant programs performing HIV-positive to HIV-positive transplants must designate and provide each HIV-positive recipient and prospective HIV-positive recipient with an independent advocate who is responsible for protecting and promoting the rights and interests of the HIV-positive recipient (or prospective HIV-positive recipient). The independent advocate for the HIV-positive recipient must:

i. Promote and protect the interests of the HIV-positive recipient (including with respect to having access to a suitable HIV-negative organ if it becomes available) and take steps to ensure that the HIV-positive recipient’s decision is informed and free from coercion.

ii. Review whether the potential HIV-positive recipient has received information regarding the results of SOT in general and transplantation in HIV-positive recipients in particular and the unknown risks associated with HIV-positive to HIV-positive transplant.

iii. Demonstrate knowledge of HIV infection and transplantation.

3.2.2 Independent HIV-Positive Living Donor Advocate

Transplant programs performing HIV-positive donor transplantations must designate and provide each living HIV-positive donor and living prospective HIV-positive donor with an independent advocate who is responsible for promoting and protecting the rights and interests of the HIV-positive donor (or prospective donor). More specifically, the independent advocate for the HIV-positive living donor must:

i. Promote and protect the interests of the HIV-positive donor (including with respect to having ample opportunity to withdraw consent from donation) and take steps to ensure that the HIV-positive donor’s decision is informed and free from external pressure.

ii. Review whether the potential HIV-positive donor has received information regarding (a) risks of organ donation in general, as well as the additional potential risks that are specific to the HIV-positive donor, including accelerated organ failure, and limitations of future use of specific antiretroviral agents; and (b) the unknown outcome of HIV-positive to HIV-positive organ transplantation.

iii. Demonstrate knowledge of HIV infection and transplantation.

4 OPO Responsibilities

Clinical research in HIV-positive to HIV-positive organ transplantation requires a partnership between OPOs and transplant programs. OPOs participating in the evaluation and allocation of HIV-positive organs to centers conducting research in HIV-positive to HIV-positive transplantation must adhere to the following criteria:

i. Develop SOPs and staff training procedures to effectively work with the family and other sources of medical history of HIV-positive donors in assessing medical and behavioral risks; HIV clinic and pharmacy medical record abstraction; obtaining research consent from next of kin of HIV-positive donors; performing physical examination of HIV-positive donors; collecting blood, tissue, and other biospecimens (e.g., urine, bronchoalveolar lavage, spleen, lymph nodes, and biopsy material); and handling, processing, storing, labeling, and shipping of the biospecimens.

ii. Conduct training in obtaining relevant and pertinent HIV-positive history, duration of HIV infection, opportunistic illnesses and their therapy, risk factors for HIV, CD4+ T-cell counts (lows and highs), HIV resistance, ART medication history use and response, history of ART resistance, present ART, HIV viral loads, and HIV genotype and tropism, when known.

iii. Develop a biohazard plan to prevent and manage exposure to or transmission of HIV.

These criteria are in addition to, not in place of, current Organ Procurement and Transplantation Network (OPTN) policies and bylaws, state or local laws, and federal regulations governing organ transplantation and research that pertains to OPOs.

5 Prevention of Inadvertent Transmission of HIV

Although the use of HIV-positive organs may help alleviate transplant shortages and reduce patient waiting list times, there also are patient safety concerns to consider. Prevention or management of inadvertent transmission of HIV or exposure of an HIV-negative recipient to organs or tissues from an HIV-positive donor due to identification error is paramount (Ison, 2009, 2011a, 2011b). The transplant community, with regulatory oversight at multiple levels, has been able to achieve a high level of safety through routine procedures and clinical practice. The precautions taken with ABO compatible donor-recipient pairs and HCV-infected donor organs in HCV-infected recipients (Morales, 2010; Kucirka, 2010; Mandal, 2000; Tector, 2006) are existing models. However, vulnerabilities still exist, and mishaps still occur. For instance, the risks of error during manual transcription of information are well documented.

Each transplant hospital shall have an institutional biohazard plan for handling of HIV-positive organs—to include, for example, organ quarantine measures, electronic information capture on infectious disease testing results, communication protocols between OPOs and transplant hospitals—that is designed to prevent and/or manage inadvertent transmission of or exposure to HIV.
Tissues (e.g., cornea, blood vessels, or cartilage) not associated with the organ to be transplanted and organs are often recovered from organ donors. The FDA regulates human cells, tissues, and cellular and tissue-based products (HCT/Ps) that are intended for implantation, transplantation, infusion, or transfer into a human recipient under the authority of section 361 of the Public Health Service Act and the implementing regulations in 21 CFR part 1271. Under 21 CFR part 1271, persons with risk factors for, or clinical evidence of, relevant communicable diseases, or whose test results are positive or reactive for relevant communicable diseases (including HIV) are ineligible to donate HCT/Ps. Procedures must be in place to ensure that HCT/Ps are not recovered from HIV-positive donors for implantation, transplantation, infusion, or transfer into a human recipient; however, HCT/Ps from a donor who has been determined to be ineligible may be made available for nonclinical purposes.

6 Study Design/Required Outcome Measures

There is a wide range of clinical and immunologic questions that might be addressed in the context of research in HIV-positive to HIV-positive transplantation. These include, for example, questions related to HIV superinfection; incidence and severity of OIs (including transmission of occult OIs from donor to recipient); immunologic mechanisms contributing to the increased rate of kidney rejection observed in HIV-positive recipients; quality of life for recipients of HIV-positive to HIV-positive transplantation; outcomes of living HIV-positive donors; and a host of others. The questions will be determined by the investigators who design research protocols for studying HIV-positive to HIV-positive transplantation. However, to ensure that all studies of HIV-positive to HIV-positive transplantation can contribute to evaluation of the safety of the procedure, the following key donor and recipient characteristics and outcome measures must be incorporated into the design of all clinical trials of HIV-positive to HIV-positive transplantation.

6.1 Wait List Candidates

- HIV status
- CD4+ T-cell count
- Co-infection (HCV, HBV)
- HIV viral load
- ART resistance
- Removal from wait list (death or other reason)
- Time on wait list

6.2 Donors (all)

- Type (living or deceased)
- HIV status (HIV-positive new diagnosis, HIV-positive known diagnosis)
- CD4+ T-cell count
- Co-infection (HCV, HBV)
- HIV viral load
- ART resistance
- Pre-transplant donor allograft biopsy

6.3 Living Donors (6, 12, and 24 Months Following Organ Donation)

- Progression to renal insufficiency in kidney donors:
  - Proteinuria defined as urinary protein excretion >150 mg/day or urine protein/creatinine ratio >0.2
  - eGFR <60 mL/minute/1.73m²
- Progression to hepatic insufficiency in liver donors (INR >1.5 and/or total bilirubin >2.0)
- Change in ART regimen as a result of decreased organ function
- Progression to AIDS
- Failure to suppress viral replication (persistent viremia)
- Death

6.4 Transplant Recipients

- Rejection rate (annual up to 5 years)
- Progression to AIDS
- New OIs
- Failure to suppress viral replication (persistent viremia)
- HIV-associated organ failure
- Malignancy
- Graft failure
- Mismatched ART resistance versus donor
- Death

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Dated: November 20, 2015.

Francis S. Collins,
Director, National Institutes of Health.

[FR Doc. 2015–30172 Filed 11–24–15; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Center for Scientific Review; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), notice is hereby given of the following meetings. The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: Center for Scientific Review Special Emphasis Panel; Member Conflict: Reproductive Biology.

Date: December 8, 2015.

Time: 1:00 p.m. to 4:00 p.m.

Location: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892, (Virtual Meeting).

Contact Person: Michael Knecht, Ph.D., Scientific Review Officer, Center for Scientific Review, National Institutes of Health.