August 17, 2015

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Room 6B21, MSC 9827
Bethesda, Maryland 20892-9897

RE: HIV Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV

Dr. Odim:

The American Society of Transplantation supports the proposed HOPE Act Safeguards and Research Criteria in general with the exception of:

- **The AST does not feel that living donors should be considered at this early stage.**
- **The AST does not feel that donors with active viremia should be considered at this early stage. However, there can be some flexibility to include donors with low level viral loads from 50-200 copies/mL.**
- **The AST feels that experience should reflect the total experience of the team, not individual members.**
- **The AST strongly encourages careful consideration of how data will be collected and the regulatory impact of conducting the research required by this study.**

On behalf of the American Society of Transplantation (AST), representing the majority of professionals engaged in the field of solid organ transplantation, we applaud the ongoing work and commitment to advancing transplant medicine and the lives of thousands of individuals currently awaiting a lifesaving donor organ. The AST has carefully reviewed the proposed HIV Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV, seeking feedback from its Infectious Disease, Kidney, Liver, and Live Donor Communities of Practice. While generally supportive of the criteria proposed to implement safeguards and standards of quality for research and transplantation of organs infected with human immunodeficiency virus (HIV) as part of HOPE Act implementation, we respectfully request consideration of the following comments:

Phased Approach

The core object of this research is to inform the safety, efficacy and feasibility of using organs from HIV infected donors for transplantation into HIV infected patients. As such, we feel strongly that research should start more conservatively, and if the initial data are supportive, expand the research

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further. For the initial phase, we would recommend including only deceased donors with undetectable HIV viral loads, either due to appropriate antiretroviral therapy or who biologically control their viremia. We would defer the use of HIV+ living donors or viremic deceased donors until the safety of using deceased donors with undetectable viral loads is demonstrated.

HIV+ Living Donors Should Not Be Utilized in the Initial Phase of Research

We do not believe that HIV+ living kidney donors should be used. HIV+ patients have a higher risk of kidney and liver disease, and similar to other donors at higher risk for kidney and liver disease (e.g. those with hypertension, diabetes, etc.) we believe that such donors should be deferred. Recently published data (AG Abraham et al, End-stage renal disease among HIV-infected adults in North America, ***Clin Infect Dis***. 2015; 60:941-949) utilized data from 38,354 HIV-infected adults aged 18-80 from the AIDS Cohort Collaboration for Research and Design and included 159,825 person-years' worth of observation and benchmarked this against rates in HIV uninfected from the USRDS data. The investigators found that the risk of developing ESRD among HIV-infected patients was significantly higher than the expected rate in HIV seronegative patients from the USRDS data. Specifically, they found that "the ESRD risk was approximately 6 times higher in black HIV-infected adults compared to their white counterparts, a disparity in risk that remained after accounting for sex, intravenous drug use, HIV severity, ART use, baseline eGFR, co-morbidity, history, and age differences." Further, "the overall standardized incidence ratio contrasting the expected number of ESRD cases in HIV-infected non-IDU participants by age-, race-, and sex-specific strata to the observed was 3.2 (95% CI, 2.8–3.6). When stratified by race/ethnicity, the standardized incidence ratio was 4.5 (95% CI, 3.9–5.2) for blacks, 1.5 (95% CI, 1.0–2.2) for whites, and 1.7 (95% CI, 1.1–2.5) for Hispanics, compared with race/ethnicity-specific USRDS reference data. By calendar period, the overall standardized incidence ratio was 3.9 (95% CI, 3.3–4.6) in 2000–2004 and 2.8 (95% CI, 2.4–3.3) in 2005–2009." "HIV-infected ESRD cases were more likely to be of black race, have diabetes mellitus or hypertension, inject drugs, and/or have a prior AIDS-defining illness".

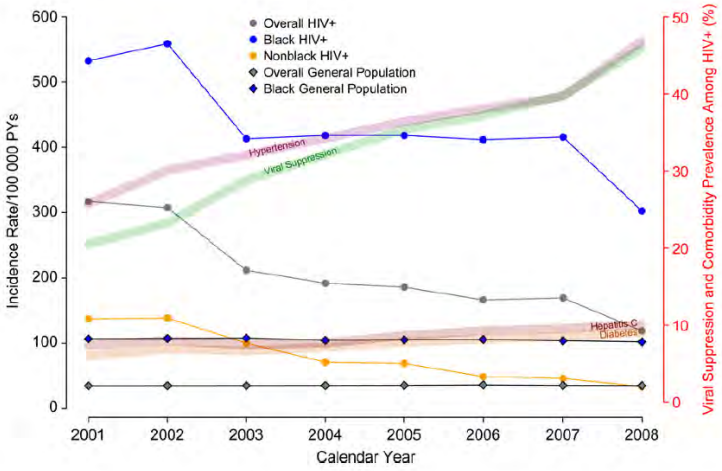


Figure 1. Age- and sex-standardized incidence of end-stage renal disease among human immunodeficiency virus (HIV)-infected adults stratified by race and compared with age- and sex-standardized rates in the general population (US Renal Database System). Incidence rates are 3-year rolling averages. Abbreviation: PY, person-years.

In another series from the Veterans' Affairs medical system of 22,156 HIV-infected veterans (primarily male) without pre-existing ESRD receiving health care in the between 1996 and 2004, 366 cases of ESRD occurred, corresponding in 3 cases/1,000 person-years. (V Jotwani et al, Risk factors for ESRD in HIV-infected individuals: traditional and HIV-related factors. ***Am J Kidney Dis***. 2012; 59:628-635), a rate well in excess of what would be expected for HIV negative patients.

This lifetime risk of ESRD in HIV infected individuals is so significant that it exceeds the risk threshold for donation and is similar to that seen in non-infected individuals with other high risk states such as established diabetes, or hypertension treated with multiple agents. The AST recommends excluding HIV infected living kidney donation initially. Additional research should be conducted to identify subsets of HIV infected patients at lower risk of developing ESRD that could be considered at a later time.

While the document states, “Donors co-infected with hepatitis are not excluded from HIV+ to HIV+ transplant; however, careful consideration must be given when evaluating a donor co-infected with HBV and/or HCV,” we would defer the use of any co-infected living donor for liver transplant.

We believe that many HIV positive patients will not be considered desirable donors for this study due to the frequency of liver disease related to hepatitis co-infection or substance abuse. While there is limited data available on accelerated rates of cirrhosis in HIV patients, a study of 2168 HIV+ individuals confirmed cirrhosis in 181, with HCV responsible for 82.3% of these confirmed cases (Castellares et al. Liver Cirrhosis in HIV-Infected Patients: Prevalence, Aetiology and Clinical Outcome. ***J Viral Hep***. 2008; 15:165-72.)

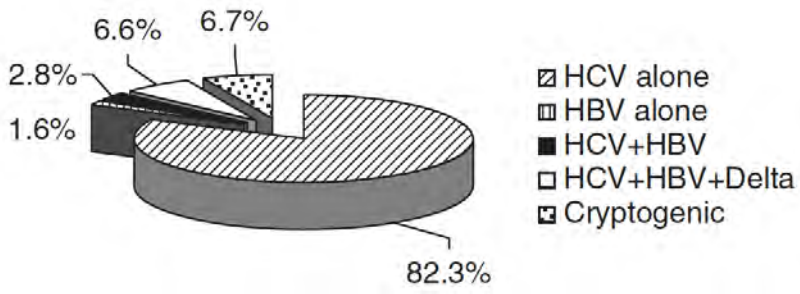


Fig. 1 Aetiology of liver cirrhosis in the HIV study population.

The U.S. Department of Veterans Affairs website also indicates similar concerns in the HIV+ veteran population (http://www.hiv.va.gov/provider/manual-primary-care/liver-disease.asp). The VA notes abnormalities in liver enzyme levels as common among HIV-infected persons, even in the absence of HCV or HBV infection, highlighting cross-sectional studies that show a high prevalence of elevated AST (20%), ALT (15%), and alkaline phosphatase (43%). The VA recognizes alcohol consumption as common among people with HIV infection, indicating that rates of heavy drinking among people with HIV are almost twice those found in the general population, and highlighting alcohol use disorders diagnosed in 33% of HIV-infected veterans in its care in 2007.

Donors with Detectable HIV Viral Loads Should Not Be Utilized in the Initial Phase of Research

For the first phase of research, we would defer from using deceased donors with detectable HIV viral loads, and we would recommend only using deceased donors with well-controlled (non-viremic) HIV. Although the experience in South Africa with viremic donors was largely successful (E Muller et al, HIV-Positive–to–HIV-Positive Kidney Transplantation — Results at 3 to 5 Years, ***N Eng J Med***. 2015; 372:613-620), there are higher rates of resistance to anti-retroviral therapy in the United States, which could result in loss of control of HIV and/or need for a poorly tolerated salvage regimen. Therefore, the risk of an adverse outcome from using viremic deceased donors is too great for the initial phases of research into HIV-to-HIV transplantation. Ideally, the recipient should be able to simply continue their pre-transplant HIV regimen in the post-transplant setting. At this time, HIV genotyping (testing for resistance to anti-retroviral therapy) is not available in a rapid enough timeframe to ensure against transmission of retroviral resistance at the time of deceased donor organ transplant. Furthermore, we should be realistic about what we can discover in real time. Research coordinators would generally be very challenged to be able to obtain prior resistance testing results in the rapid fashion required with deceased donation, especially where such results are held as highly confidential, may not be available after hours (i.e. if in a clinic chart), and sometimes are not recorded in standard electronic medical records.

While we generally oppose the use of viremic donors initially for the initial proof of concept study, later studies might investigate the safety and outcomes of using viremic donors. In such later studies, the recipient candidates must be specifically consented ahead of time about the potential risk posed by using a viremic donor, with frank discussions about the risk of progression of or uncontrolled HIV, salvage regimens, and potential for significant side effects/unpalatable regimens. Also, genotyping should be done on the donor specimen, with results made available (most likely) after the transplant, so that the clinicians caring for the recipient can interpret the results and potentially utilize this information.

Such later studies or initial studies with adaptive design may also wish to start by including patients with documented suppressed virus but a low but measurable single blip, including one at the time of donor evaluation. For example, a donor with HIV VL of 72 c/mL at the time of evaluation who has otherwise had undetectable viral loads prior to this measurement will fall into this category. A single HIV RNA measurement between 50-200 copies/mL is generally considered a clinically insignificant viral "blip" and such blips are not uncommon at the time of acute illness as might be expected at the time of brain death. (Nettles et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. ***JAMA***. 2005;293:817-29). We suggest that transplant programs use good judgment when considering donors with low viral loads.

Given the significant concern for detecting resistance in the donor, all donors, even those without active viremia, should have blood stored for later study and have testing to maximize the detection of resistant variants in patients with low or undetectable viremia. Even in those deceased donors who are not viremic, we recommend using appropriate testing to maximize the ability to detect resistant variants in patients with low or undetectable viremia to identify resistance in donors with suppressed viral loads.

Experience Requirements

There is a center-level requirement for a surgeon, nephrologist, and HIV doctor each to have experience with 5 HIV+ transplants in the last 4 years. These recommendations are not based on any data. In fact, a recent study of 499 HIV+ kidney recipients indicated that post-transplant outcomes were not impacted by center-level experience (Locke et al. Center-Level Experience and Kidney Transplant Outcomes in HIV-Infected Recipients. ***Am J Transplant***. 2015:15:2096-104). This requirement will restrict centers and has no basis based on current data. We recommend language that states a total experience of >5 HIV+ transplants among all members of the team is required.

Outcomes Measures and Data Collection

Post-Transplant Data Collection

The work group acknowledged that this most recent HOPE Act proposal includes research criteria for OPOs and transplant hospitals. UNOS is already programming the UNet^{sm} system to collect relevant donor details and facilitate the safe and equitable allocation of HIV positive organs, but it is our understanding that the post-transplant data collection piece remains in question. We believe that post-transplant data collection should be completed as research and not as required data to the OPTN. It is critical to understand

these data in order to determine whether this is a safe and productive effort. We believe that this will best be pursued as a research endeavor which will allow flexibility and the addition or deletion of elements in real time that will not be possible if managed through a regulatory body like the OPTN.

Recipient Clinical Outcomes Measures
The "required outcome measures" list "ART Resistance." There are many ways to measure this (some extremely expensive, some not even truly clinically available). We recommend that this be clarified to say "ART resistance to the best that can be determined by clinical record review" so as not to imply required additional testing that the clinical might not necessarily feel is clinically appropriate for the recipient.

Regulatory Impact of Outcomes Measures
There is an important regulatory issue to consider with regard to moving forward with transplantation of HIV+ donor organs into HIV+ recipients. Centers that transplant these patients with HIV+ donor organs could have worse outcomes and potentially put themselves at risk for adverse outcomes on their center specific reports. As the transplant community moves forward with increasing the transplant opportunities for HIV+ patients in this way, we offer that the OPTN and SRTR should take into account the potential for inferior outcomes in these patients.

Therefore, we propose that transplants performed with HIV+ donor to HIV+ 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 life-saving organ transplants. The creation of legislation that protects centers is one way to avoid this pitfall and potentially remove such a disincentive.

Other Specific Comments, by Section

1. Re "1.1.1 Deceased Donors"

In "1.1.1 Deceased Donors, Minimum eligibility criteria for deceased donors with a known history of HIV infection: ii. Well-controlled HIV infection", clarification regarding the timing of "Fewer than 50 copies/mL of HIV-1 RNA detectable by ultrasensitive or real-time polymerase chain reaction (PCR) assay" may be warranted, given that some deceased donors may have breaks in therapy (i.e. medication suspended due to trauma resuscitation, critical illness, etc) such that they may have some viral escape.

The proposal states that that HIV+ donor requirements are <50 copies of RNA and no history of viral load>1000. This stringent approach may eliminate potential HIV+ donors for no clinically valid reason. Most donors will have had high viral loads prior to the onset of treatment. Such patients who have appropriately responded to therapy should be considered as potential donors. The key measure is suppressible viremia on therapy.

"ii. No known history of a CD4+ T-cell count <200/μL": Although desirable, it may be very challenging to obtain such data in a timely fashion. We recommend focusing on the viral load. CD4 counts would be less likely to be available in a rapid fashion, and current guidelines recommend less frequent testing of CD4 than in the past. Furthermore, the rationale for excluding potential donors with a remote history of CD4 <200/μL but currently with excellent HIV control is not clear; these patients would potentially be quite appropriate donors. Additionally CD4 counts obtained during the period of donor assessment may not be accurate assessments of historical HIV control as the acute event leading to death may impact on CD4 counts.

We would request that more specific comments be made regarding opportunistic infections in deceased donors; for example, "no active opportunistic infections" may not preclude those recovered from primary CNS lymphoma or other HIV-related cancers in remission (leiomyosarcomas, Kaposi's Sarcoma), as we would be reluctant to allow these donors. (There is some confusion, as Table 1 does include mention of "Historically, no, • Chronic cryptosporidiosis. • CNS lymphoma. • PML" for living donors although this is not mentioned elsewhere in the document.). We recommend the phrase, "no known cases of OIs for which there is no medical treatment".

In addition, we would like to highlight the importance of being cognizant of the legality of information sharing with family/friends of the donor who are not aware of the HIV diagnosis, which will complicate the situation further.

2. Re "2.1 Recipient Eligibility Criteria"

"iii. No active OI or neoplasm". Regarding "No active … neoplasm" we would encourage the same criteria already used in the transplant community, which is often no active tumor within the past 2-5 years (depending on tumor type).

"No history of chronic cryptosporidiosis, primary CNS lymphoma, or progressive PML" is recommended for recipients. We would add visceral Kaposi's Sarcoma, and possibly cutaneous KS. Visceral Kaposi's Sarcoma can be quite problematic for both SOT and HIV, and we would recommend reserving recipients with such a history for a second phase of research.

3. Re "Transplant Hospital Criteria":

"Provide each living HIV+ donor and HIV+ recipient with an "Independent Advocate"." We believe that this is already part of OPTN policy and thus would favor making sure that centers are compliant with OPTN policies. Moreover, as part of a research study, individuals will be provided consent documents providing both risk and benefits of such study participation., an added feature of patient subject protection.

4. Re: "OPO Responsibilities".

"SOPs and staff training procedures for working with deceased HIV+ donors and their family 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." We recommend that confidentiality regarding HIV status is maintained, according to hospital, state and other laws and guidance. Although the donor may now be (near) deceased, confidentiality should still be maintained, as dictated by local ordinances.

5. Re: "Donors (all).

Type (Living or deceased). HIV status (HIV+ new diagnosis, HIV+ known diagnosis). CD4+ T-cell count. Co-infection (HCV, HBV). HIV viral load. ART resistance." We recommend that information for all co-infections is provided at the time of procurement as well for the deceased donors, if there were more than "HCV, HBV".

"Required Outcome Measures…Living Donors…Progression to renal insufficiency in kidney donors (serum creatinine >2 mg/deciliter (dL), serum creatinine level twice the pre-donation creatinine level, or proteinuria). Progression to hepatic insufficiency in living donors (international normalized ratio (INR) >1.5 and/or total bilirubin >2.0). 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." Again we recommend against the use of living donors in the initial studies. However, if they are allowed, we recommend that hepatologists confirm that these criteria for hepatic insufficiency are appropriate. We also recommend including cause of death.

"Required Outcome Measures: Transplant Recipients: Rejection rate (Years 1 and 2)… Mismatched ART resistance versus donor." We recommend tracking rejection and other outcomes to 5 years, given some delays in rejection. Also, clarify that changes in ART in recipient post-transplant are well recorded as Required Outcome Measures – which is perhaps implied here but not entirely clear.

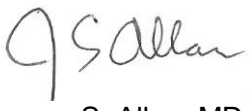
Dr. Elmi Muller's S. African experience indicates that post-transplant outcomes for HIV+ recipients receiving HIV+ kidneys are comparable to HIV+ recipients receiving HIV- kidney transplants (Muller et al. HIV-Positive–to–HIV-Positive Kidney Transplantation — Results at 3 to 5 Years, ***N Eng J Med***. 2015; 372:613-620). We recognize that the U.S. experience may differ due to higher rates of anti-retroviral therapy resistance than what is found in S. Africa.

The AST is pleased to offer our broad comments and observations with respect to the proposed HOPE Act research criteria. We look forward to the implementation of this study and hope that it may ultimately increase the number of organ donors and the number of available organs for transplantation. We would be happy to provide advice on future proposed changes to the criteria. Most importantly, the Society is eager to move forward

and begin the research required to assess the safety, efficacy and feasibility of using HIV positive donors for HIV infected organ recipients.

If you have any questions or require additional information, please do not hesitate to contact AST's Executive Director, Shandie Covington, at (856) 316-0924.

Sincerely,



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