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Jonah Odim, MD
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Human Immunodeficiency Virus (HIV) Organ Policy Equity Act (HOPE Act) Safeguards and Research Criteria for Organs Infected with HIV.

Dear Dr. Odim:

On behalf of the American Society of Transplant Surgeons (ASTS), I am pleased to have the opportunity to comment on the National Institutes of Health (NIH) Proposed Safeguards and Research Criteria for Organs Infected with HIV (the "Proposed Research Criteria"). ASTS is a medical specialty society composed of more than 1800 transplant surgeons, physicians, scientists, advanced transplant providers, and other transplant professionals dedicated to advancing the art and science of transplantation through leadership, advocacy, education, and training.

Preliminarily, we wish to applaud NIH for the balanced approach to implementation of the HOPE Act that is reflected in the Proposed Research Criteria. We recognize that designing clinical research criteria for use by IRBs throughout the country involving a vulnerable patient population and a complex surgical procedure is a difficult one—not least because of a lack of precedent. We congratulate the NIH generally, and you personally, for designing a proposal that recognizes the need for both scientific rigor and flexibility in the design of clinical trials in this emerging and highly promising field. Accordingly, the comments and suggestions provided below should be read in the context of our overall strong support for the NIH's proposal.

First, we strongly urge NIH to reconsider and modify the proposed requirements set forth at Section 3.1.ii of the Proposed Research Criteria related to the transplant team, which requires that:

> ii. In order for a transplant hospital to initiate HIV+ to HIV+ transplantation, there must be a study team consisting of (at a minimum) a transplant surgeon, a transplant physician, and an HIV physician, each of whom have experience with at least 5 HIV- to HIV+ transplants with the designated organ(s) over the last four years. This constitutes the minimal experience necessary and the IRB should evaluate key personnel (transplant surgeon, transplant physician, and HIV physician) in the context of total expertise and experience with respect to HIV and/or organ transplantation.

While we agree that clinical studies involving HIV+ to HIV+ transplants should be conducted by institutions with substantial institutional experience in transplanting HIV+ recipients, we believe it likely that few, if any, transplant hospitals have transplant teams who would meet this criterion. As a result, few, if any, clinical research studies involving HIV+ to HIV+ transplantation would be performed if this standard is finalized as proposed. Thus, finalizing the transplant team criteria as proposed would sharply curtail the availability of HIV+ to HIV+ transplants for HIV infected recipients who have no other treatment options and would undermine Congress' intent in enacting the HOPE Act. In lieu of the requirements set forth in proposed Section 3.1.ii, we suggest the following:

> ii. In order for a transplant hospital to initiate HIV+ to HIV+ transplantation, *the transplant hospital must have performed at least 5 HIV- to HIV+ transplants of the designated organ(s) over the last four years*, or, alternatively, the study team must consist of (at a minimum) a transplant surgeon, a transplant physician, and an HIV physician *who collectively* have experience with at least 5 HIV- to HIV+ transplants with the designated organ(s) ~~over the last four years~~. This constitutes the minimal experience necessary and the IRB should evaluate key personnel (transplant surgeon, transplant physician, and HIV physician) in the context of total expertise and experience with respect to HIV and/or organ transplantation.

(Proposed changes in *italics*.) This alternative standard strikes an appropriate balance between the need for the transplant team to have significant experience in transplanting HIV+ recipients and the need to ensure that research in this field progresses. Moreover, this alternative standard recognizes that transplant teams function as a unit and transplant team members share experience and expertise: Each team member contributes unique skills and knowledge, and not all team members need to have the same level of experience in transplanting HIV+ recipients any more than all team members need to have the same level of surgical skill or knowledge of HIV disease processes. It also removes the potential of confusing *currency* and *experience* by removed the currency requirement regarding the last four years.

Second, we strongly urge NIH to eliminate Section 1.1.2 of the Proposed Research Criteria ("Living Donors Infected With HIV") and to explicitly authorize only the conduct of research involving HIV+ deceased donors. Until the clinical community better understands the safety and efficacy of HIV+ to HIV+ transplantation, it is premature to perform transplants from HIV+ living donors. As a professional society, we believe such transplants have the potential to place HIV+ living donors at substantial risk, and we cannot sanction such research until more is known about the risks and benefits of procedures involving HIV+ deceased donors.

Third, we urge NIH to authorize additional flexibility with respect to the draft *Minimum eligibility criteria for deceased donors with a known history of HIV infection* (Proposed Research Criteria, Section 1.1.1. ii). The proposed minimum eligibility criteria require prospective donors to have:

> b. Fewer than 50 copies/ml. of HIV-1 RNA detectable by ultrasensitive or real-time polymerase chain reaction (PCR) assay.

We believe that, while inclusion of HIV+ donors with more than 50 copies/ml of HIV-1 RNA detectable by ultrasensitive or real-time PCR assay is not recommended, use of HIV+ organs with 50-200 copies/ml of HIV-1 RNA should not be categorically precluded when there is no evidence of treatment failure. We believe that the inclusion of HIV+ donor organs with 50-200 copies/ml of HIV-1RNA should be left to the clinical judgment of the transplant team.

In addition, the draft *Minimum eligibility criteria for deceased donors with a known history of HIV infection* (Proposed Research Criteria, Section 1.1.1) also precludes the use of HIV+ organs if there has been any history of a viral load greater than 1000 copies/ml in the prior 12 months (Proposed Section 1.1.1.ii (c)). We suggest that this criterion be modified to provide an exception where a viral load of greater than 1000 copies/ml is associated with, or documented for a period prior to, the initiation of treatment.

Also, the draft *Minimum eligibility criteria for deceased donors with a known history of HIV infection* (Proposed Research Criteria, Section 1.1.1) precludes the use of HIV+ organs if the CD4 count is less than 200/microliter. Based on data from the group in South Africa (personal communication, Dr. Elmi Muller, transplant surgeon, University of Cape Town, South Africa), many of their donors had CD4 counts < 200. Since utilization of these donors resulted in good outcomes, we would recommend elimination of the CD4 count requirement as long as the donors met the other requirements outlined in the NIH document.

Fourth, we urge additional flexibility with regard to the Minimum eligibility criteria for deceased donors with newly diagnosed HIV infection. A previously undiagnosed HIV+ donor who has no track record of viral load or CD4 counts is likely to be relatively healthy and a good donor candidate.

Finally, with respect to Section 6 of the Proposed Research Criteria, related to Study Design and Required Outcomes Measures, we note that transplant centers performing HIV+ to HIV+ transplants would not be required to conduct pre-transplant biopsies of HIV+ organs or to obtain or preserve serum samples from the donor and recipient. While we hesitate to urge the establishment of research criteria that interfere with the clinical judgment of the transplant team for fear of establishing a dangerous precedent, we believe it is highly likely that examination of tissue obtained through a pre-transplant biopsy of the donor organ and examination of serum specimens of both the donor organ and the recipient would be necessary in the event of a superinfection. For this reason, we urge that, at the very least, the Proposed Research Criteria be modified to highly recommend a pre-transplant biopsy of HIV+ donor organs (both kidney and liver). Tissue samples should be stored in accordance with the College of American Pathologists (CAP) guidelines/recommendations for good clinical practice for at least five years. In a ddition, we urge

that the final Research Criteria include a strong recommendation that a minimum 10-20 cc of cells/serum be collected from the donor and that serum be collected from the recipient at one month, 6 months, and a year. We also recommend that the data collection requirements be modified to clarify that ART resistance data may be ascertained through clinical chart review.

We appreciate the opportunity to comment on the Proposed Research Criteria. If you have any questions regarding ASTS' comments or if we can provide any additional information, please do not hesitate to contact ASTS Executive Director, Kimberly Gifford, at *kim.gifford@asts.org* or 703-414-7870.

Sincerely,

Charles M. Miller, MD
President