**VIA ELECTRONIC MAIL**

To: Kim Gifford
From: Diane Millman
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Re: Final HOPE Act Safeguards and Research Criteria
Date: November 30, 2015

The NIH has made public the "Final Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected With HIV" ("Final Safeguards"). This memo summarizes the NIH's response to the ASTS comments on the Safeguards when they were published in proposed form (the "Proposed Safeguards") earlier this year.

Transplant Center/Transplant Team Experience Requirements

First, ASTS comments on the Proposed Safeguards emphasized the need to liberalize the criteria for transplant centers authorized to conduct HIV+ to HIV+ transplants pursuant to the HOPE Act. Specifically, ASTS requested NIH to establish the following eligibility criteria for this research:

> ii. In order for a transplant hospital to initiate HIV+ to HIV+ transplantation, at a minimum, the transplant hospital must have performed at least 5 HIV – to HIV+ transplants of the designated organ(s) over the last four years, or, in the alternative, 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.

While the preamble to the Final Safeguards indicates that NIH accepted the ASTS recommendation on this issue, there are a number of differences between the final NIH criteria and the ASTS recommendation. The final criteria state:

> 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.

Thus, while the ASTS recommended that the transplant surgeon's experience with HIV- to HIV+ transplants "count" in determining a transplant center's eligibility to perform HIV+ to HIV+ transplants , the NIH final criteria apparently[1] would not take the transplant surgeon's experience into consideration in

[1] The criteria do indicate that 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.

determining whether the minimum criteria are met. While it is possible that this decision was made because the individual transplant surgeon involved in a particular HIV+ to HIV+ may not be completely predictable, the final criteria do not include an explanation for this deviation from the ASTS recommendation.

In addition, the final criteria would not authorize a transplant center to conduct HIV+ to HIV+ transplants pursuant to the HOPE Act if the center had conducted five HIV- to HIV+ transplants over the past five years, but the transplant team does not meet the experience requirements. This might be the case, for example, if transplant team members with experience in HIV- to HIV+ transplants were no longer with the center.

Living Donor HIV+ to HIV+ Transplants

In its comments, ASTS strongly urged NIH to eliminate those provisions of the Proposed Safeguards that would have authorized HIV+ to HIV+ transplants involving living donors and to adopt Final Safeguards that authorize only the conduct of research involving HIV+ deceased donors. NIH rejected this approach and includes living donor HIV+ to HIV+ transplants in the Final Safeguards "so that, if investigators choose to pursue this line of research, that research can be conducted with appropriate informed consent, safeguards, and rigor." In so doing, NIH adds:

> 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.

The consent process for living donors must, among other things, 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

The Final Safeguards include the following minimum eligibility criteria for HIV+ 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.

iii. 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.

Minimum Eligibility Criteria for Deceased Donors with Known History of HIV Infection.

The Proposed Safeguards would have precluded the use of organs from prospective donors with more than 50 copies/ml. of HIV-1 RNA detectable by ultrasensitive or real-time polymerase chain reaction (PCR) assay; with any history of viral load over greater than 1000 copies/ml in the prior 12 months; or with a CD4 count less than 200/microliters. ASTS' comments urged expansion of these criteria in various respects.

The Final Safeguards and Research Criteria take an approach that is even more flexible than that proposed by ASTS, requiring only that, for a donor with a known history of HIV and prior treatment with ART:

> 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.

In addition, the Final Safeguards require:

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.

Pre-Transplant Biopsies

In response to the proposed Safeguards, ASTS had recommended that NIH consider requiring a pre-transplant biopsy of HIV+ donor organs and retention for at least five years. As indicated above, the NIH has adopted this recommendation for deceased donors.

Additional notes and observations

The Final Safeguards focus on liver and kidney transplantation. 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 document notes that 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 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.