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Realizing HOPE: The Ethics of Organ Transplantation from HIV infected Donors

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Abstract

The HIV Organ Policy Equity (HOPE) Act now allows transplantation of organs from HIV infected (HIV+) living and deceased donors to HIV+ individuals with end-stage organ disease in the United States. Although clinical experience with such transplants is limited to a small number of HIV+ to HIV+ deceased donor kidney transplants in South Africa, unprecedented HIV+ to HIV + liver transplants and living donor kidney transplants are also now on the horizon. Initially all HIV+ to HIV+ transplants will occur under research protocols with safeguards and criteria mandated by the National Institutes of Health (NIH). Nevertheless, this historic change brings ethical opportunities and challenges. For HIV+ individuals in need of organ transplant, issues of access, risk, and consent must be considered. For potential HIV+ donors, there are additional ethical challenges of privacy, fairness and the right to donate. Careful consideration of the ethical issues involved are critical to the safe and appropriate evaluation of this novel approach to transplantation.

The HIV Organ Policy Equity (HOPE) Act now permits transplantation using organs from HIV infected (HIV+) donors to HIV+ recipients in the United States. This historic law brings ethical opportunities and challenges.

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Acquiring organs from those known or suspected to be HIV+ has been banned since 1988. The ban was instituted at a point in the acquired immunodeficiency syndrome (AIDS), epidemic when there was no effective treatment, diagnostics were unreliable, and there was a clear risk of transmission with blood products. Given the broad ethical mandate to avoid harm, this policy made sense at the time.

Since then, the landscape has changed dramatically. Effective antiretroviral therapy (ART) has transformed HIV infection from a death sentence to a chronic disease in many parts of the world. While morbidity and mortality from infections has sharply decreased, the burden of other complications including end-stage renal disease and end-stage liver disease has grown proportionally as people with HIV live longer (1, 2). Large studies demonstrate a clear benefit of organ transplantation with HIV-uninfected donors for HIV+ patients with end-stage organ disease. However access to transplantation remains limited for HIV+ individuals since not all centers have adopted this practice and HIV+ individuals face disproportionately higher mortality while awaiting this life-saving therapy. Thus, there has been an increase both in the need for organ transplantation among HIV+ patients and an ethical obligation to provide such treatments.

Unfortunately, this expanded eligibility for transplantation exacerbates an already existing shortage of available organs in the US. Fairly resolving questions of allocation during scarcity is a familiar ethical problem in organ transplantation for which complex algorithms have been implemented (3). Nonetheless, many patients die due to lack of available organs. Accordingly, a morally prudent course is to seek safe and effective means to attenuate organ scarcity. One such approach involves the use of infected donors for recipients infected with the same pathogen.

Building on the success of using organs infected with hepatitis C virus (HCV+) for kidney and liver transplants (4–6), in 2010, a small case series from South Africa demonstrated that kidney transplantation using HIV+ deceased donors for HIV+ recipients was feasible and that early outcomes were reasonable (7). In the US, a study based on national registries estimated that there could be 500–600 HIV+ deceased donors annually (8). These data suggested that the federal restriction on the use of HIV+ organs was problematic in determining if such organs could be used safely to provide needed transplants for HIV+ patients and to indirectly mitigate organ scarcity in general.

Consequently, the HOPE Act was proposed in 2011. This proposed policy change was officially endorsed by American Medical Association, and supported by dozens of transplant organizations, other medical organizations and HIV advocacy groups. Although there was broad support from the public and scientific community, obtaining Congressional and White House attention took time (9). Ultimately, the HOPE Act was unanimously passed by the House and Senate, and signed into law by President Obama on November 21, 2013, with a phased implementation period of two years (9, 10).

The HOPE Act had a three-part mandate. First, the Department of Health and Human Service (DHHS) was required to revise the long-standing federal ban on HIV+ organ donors which was accomplished on June 8, 2015 (10). Second, the Organ Procurement Transplant

Network (OPTN), which oversees US organ transplant practices, was required to revise standards of quality to include policies for donated HIV+ organs. Specifically, OPTN has created what is known as an “open variance.” Any transplant center that plans to implement HIV+-to-HIV+ transplants must apply to join the open variance, provide documentation of local Institutional Review Board (IRB) approval, and submit regular data monitoring safety reports. This is to ensure that the changes will not reduce the safety of organ transplantation. These changes were implemented on November 21, 2015 (11). Finally, DHHS was charged with developing guidelines for clinical research involving HIV+ organs. DHHS delegated this task to the National Institutes of Health (NIH) who had input from the Centers for Disease Control and Prevention, the Health Resources and Services Administration, the Centers for Medicare & Medicaid Services, the Food and Drug Administration (FDA) and community stakeholders. On November 25, 2015, the Final Human HOPE Act Safeguards and Research Criteria were published (12). Our institution opened the first clinical trial under these criteria and received approval from OPTN on January 8, 2016 (NCT02602262). The objective of this trial is to evaluate the safety of HIV+ to HIV+ kidney and liver transplantation and to assess the survival benefit of accepting an HIV+ organ compared to waiting for an HIV-uninfected donor.

In this article we review some inherent ethical issues and concerns that accompany such transplants. Some of these concerns were raised following the initial report of successful HIV+ kidney transplants in South Africa (13–15); here we focus on a broad set of issues relevant to transplant recipients, donors (deceased and living), and others under this new policy.

HIV+ Transplant Recipients

The key ethical considerations for HIV+ transplant recipients relate to access, risk, and consent.

Access

There is a known and substantial burden of end-stage organ disease among HIV+ individuals. Kidney disease is common, affecting up to 1/3 of those infected with HIV (16). In the US, it is estimated that 1.5% of individuals on dialysis are HIV+ and this is higher among minority groups such as African Americans (17). Similarly, liver disease is a leading cause of death in those with HIV infection, attributable in part to the high prevalence of co-infection with hepatitis B and C in this population (18).

There is evidence that kidney and liver transplantation with HIV-uninfected donors offer a survival benefit for HIV+ recipients (19–22). However, access to this life-saving treatment is severely limited in general and is exacerbated for those who are HIV+ as described earlier. Currently there are > 120,000 individuals overall awaiting an organ transplant; in 2014 there were fewer than 10,000 deceased organ donors (23). As a result, many patients die each year on transplant wait-lists. This predicament is compounded for persons living with HIV for several reasons. HIV nephropathy primarily affects African Americans (24) who still encounter disparities in access to kidney transplantation (25). Further, even in the era of modern antiretroviral therapy (ART), HIV+ individuals have lower survival rates on dialysis

(26) and therefore their risk of morbidity and mortality while waiting for an organ is higher. The same has been shown for liver disease, with studies demonstrating that HIV infection imparts an additional mortality risk for individuals on the transplant waitlist (27) and that HIV+ individuals face reduced access to liver transplantation (28).

The HOPE Act overcomes the legal barrier to use of HIV+ organs and provides a novel organ supply from HIV+ donors for HIV+ individuals to address these disparities. It will allow for experience to be gained in monitored research settings to assess safety and efficacy of these innovative transplants. Should they prove to be safe, these transplants could help alleviate the general problem of organ scarcity, potentially benefitting not only persons living with HIV and African Americans in particular, but also HIV-uninfected individuals on the same waitlist since there would be an overall expansion of the donor pool.

Risks

The reported clinical experience with HIV+ organ transplantations is limited to a total of 27 kidney transplants using HIV+ deceased donors at a single center in South Africa (29). We are unaware of any reports of intentional HIV+ donor transplantation using organs besides kidneys. Similarly, we are unaware of reported experience with HIV+ living donors. Although HIV+ organ recipients originally reported have had good patient and graft survival rates, it is unclear whether this experience will be generalizable. Thus, although HIV+ to HIV+ transplants are promising, it remains unclear whether patients will be inadvertently harmed. Accordingly, as experience is garnered, ethical practice demands taking measures to ensure that risks are identified and minimized.

There are physical, psychological and social risks of HIV+ to HIV+ transplants to consider. The risks of necessary immunosuppression after transplantation may be compounded in an HIV+ individual with a compromised immune system. Data suggest that infection rates, including those of opportunistic infections, are not significantly higher in HIV+ organ transplant recipients of HIV-uninfected organs (19). However, the incidence of immunologic rejection is 2–4 times higher in HIV+ recipients (19, 30). The mechanism behind the elevated rejection risk is not entirely clear. It may be due to interactions between the pharmacoenhancer ritonavir used in some antiretroviral regimens with the calcineurin inhibitor class used for immunosuppression; this can be avoided by modifying ART regimens (31). Alternatively, it may be due to underlying immune dysfunction related to HIV-infection, which is more complicated to address. Whether rejection will be further exacerbated with use of an HIV+ organ is unknown.

HIV superinfection (i.e., infection with a second strain of HIV) poses an important potential risk (32). If virus from an HIV+ donor carries drug resistance mutations, it may not be controlled by the recipient's ART regimen. In some cases, this might be addressed by changing the recipient's ART, however, safe ART modifications are complicated given the drug interactions discussed above. Furthermore, HIV can evolve to use a different cellular receptor to infect cells, a process known as a tropism switch from R5 virus to dual-mixed or X4 tropic virus (33). Dual-mixed/X4 tropic viruses have been associated with rapid disease progression (34) and are also resistant to maraviroc, an antiretroviral that blocks the R5

receptor. Therefore, not only is superinfection with drug-resistant virus an issue, but superinfection with an X4 tropic strain could also be problematic.

Assessment of such physical or biological risks will be complicated. Organ Procurement Organizations (OPOs) are the non-profit organizations responsible for evaluating donors and for recovering organs for transplant centers. For HIV+ deceased donors, knowledge regarding the presence of drug resistance or X4 tropic virus may be limited. Although these assays are available clinically, getting results may take several days and there is a relatively short window during which a team can decide to accept an organ offer. While it is possible this information may be available in the medical record, historically OPOs do not have experience reviewing HIV-specific risks and related medical data.

Whether using an HIV+ donor kidney carries a higher risk of recurrent kidney disease in the HIV+ recipient is also unknown. In the South Africa cohort, histologic changes similar to those seen in HIV-associated nephropathy have been observed in the transplanted kidney but have not been associated with significant impairment in kidney function (29). The risk of HIV-associated nephropathy and focal segmental glomerulosclerosis in African Americans has also been linked to genetic variants of the protein Apolipoprotein L1 (35). Therefore donor race may also impact outcomes.

The choice of accepting an HIV+ organ also carries psychological risk as patients must weigh the unknown wait time for an HIV-uninfected organ versus the fear and unknown biologic risks associated with accepting one that is HIV+. Such issues may be more vexing in clinical situations where temporizing measures such as dialysis are burdensome or unavailable, as in hepatic failure. Further, there are additional ethical factors to consider. For instance, given the biological uncertainty of control of HIV infection of recipients, there could be risks for their sexual partners.

Steps have been taken to minimize such risks. The HOPE Act mandates that HIV + to HIV+ transplants first occur in the context of research, which necessarily adds a level of oversight and additional protections compared to standard clinical practice. The NIH guidelines define minimum outcome data, donor and recipient inclusion criteria, and transplant center requirements for experience with HIV+ to HIV+ transplants. Within two years, DHHS and OPTN will review research outcomes and determine whether HIV+ to HIV+ transplantation should be expanded to clinical practice outside of research settings (10, 12).

Consent

Consistent with the ethical requirement to respect autonomy, the consent process is critical to ensure that patients' decisions are informed and voluntary. Factors to consider include the decision-making capacity of the individual, comprehension of the risks, benefits and alternatives, and the voluntary nature of the decision. To ensure these criteria are met, an independent recipient advocate is required under the NIH guidelines (12). This advocate must protect the rights and interests of the potential HIV+ recipient since investigators and transplant teams may have financial and non-financial conflicts of interest in having the patient enroll in the research. It is morally incumbent upon those seeking consent to make

these conflicts transparent during the consent process and manage them using standard institutional mechanisms.

Potential HIV+ Donors

For HIV+ potential donors, there are also ethical challenges and opportunities. For example, respecting the privacy interests of the deceased may be complex when addressing disclosure of HIV+ status in cases where next of kin may be unaware. With the passage of the HOPE Act, persons living with HIV now have the opportunity, indeed the right, to authorize deceased donation or become living donors under an IRB-approved protocol. Thus, the legal prohibition related to restricting donation is removed. This approach is consistent with the recent FDA revision of its lifetime ban on blood donation for men who have had sex with men, changing this to a one-year blood donor deferral policy (36). Together, these policy shifts are consistent with the principle of justice that compels fairness among equals and may even help mitigate stigma associated with HIV-infection.

For any living kidney donor there is a biological risk of progression to end-stage renal disease after donation – albeit small (37). Whether there would be an additive attributable risk in someone with well-controlled HIV infection is unknown. In addition, certain antiretroviral medications should be avoided in those with compromised renal function, so future HIV treatment options could be limited for some HIV+ living donors. Given the ethical mandate to avoid harm, these concerns must be identified, discussed with potential donors, and monitored closely.

Beyond physical risks, there are psychological and social risks such as feeling pressure to donate versus concerns about personal well-being. Similarly, living HIV+ donors may be especially prone to (or immune from) guilt over transplant failure. Accordingly, a consent process that takes into account these HIV specific concerns is essential. In addition to mandated clinical outcomes reporting, social and psychological outcomes should be assessed.

Others

Finally, there are potential risks for other patients and for healthcare workers in permitting such donation. Although concerns have been raised that HIV+ organs may inadvertently be transplanted into HIV-uninfected recipients (12), this has not happened in analogous settings, such as transplant of HCV+ organs. Similarly, despite universal precautions, there is a worry that there may be excess risk to healthcare workers associated with recovering and transplanting HIV+ organs. However, there are requirements for OPOs and hospitals to implement policies that are specifically designed to prevent HIV exposures in healthcare workers and inadvertent transmission of HIV to HIV-uninfected recipients (12).

Realizing HOPE

The HOPE Act mandates that, for the time being, transplants using HIV+ organs occur exclusively within research protocols that are approved by Institutional Review Boards and follow published NIH guidelines. This approach promises an ethically sound way of

determining if this practice is safe and effective, while ensuring that the rights and interests of patients and donors are protected. If data from initial studies are favorable, there should be a commitment to more widespread implementation to ensure fair access to therapies.

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