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Increasing the Donor Pool: Organ Transplantation from Donors with HIV to Recipients with HIV

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Abstract

Implementation of the HIV Organ Policy Equity (HOPE) Act marks a new era in transplantation, allowing organ transplantation from HIV+ donors to HIV+ recipients (HIV D+/R+ transplantation). In this review, we discuss major milestones in HIV and transplantation which paved the way for this landmark policy change, including excellent outcomes in HIV D–/R+ recipient transplantation and success in the South African experience of HIV D+/R+ deceased donor kidney transplantation. Under the HOPE Act, from March 2016 to December 2018, there were 56 deceased donors, and 102 organs were transplanted (71 kidneys and 31 livers). In 2019, the first HIV D+/R+ living donor kidney transplants occurred. Reaching the full estimated potential of HIV+ donors will require overcoming challenges at the community, organ procurement organization, and transplant center levels. Multiple clinical trials are ongoing, which will provide clinical and scientific data to further extend the frontiers of knowledge in this field.

INTRODUCTION

In the United States, the need for organ transplantation continues to grow. The latest data from the Organ Procurement and Transplantation Network (OPTN) report that 112,575 people need a lifesaving organ transplant, of which approximately 62% are on an active waiting list. While the number of patients awaiting transplant has increased by roughly fivefold over the past three decades (1991–2019), the number of donors (deceased and living) has increased by only 2.8-fold, compounding the organ shortage crisis (1). One way to address the organ shortage is through expanding the donor pool by recovering organs from novel donor sources.

The life expectancy in HIV+ individuals has increased considerably with significant changes in the landscape of HIV treatment modalities (2–5). Accordingly, so has prevalence of end-stage renal disease (ESRD) and end-stage liver disease (ESLD) (6). Studies have shown favorable outcomes following kidney and liver transplantation even with immunosuppression in the setting of HIV (7–10). However, HIV+ candidates have higher pretransplant mortality than their uninfected counterparts (11, 12). Utilizing organs from HIV+ donors is one strategy to alleviate morbidity and mortality by increasing access to transplantation for HIV+ candidates. In this article, we briefly review the history of HIV transplantation, the implementation of the HIV Organ Policy Equity (HOPE) Act of 2013, risks of transplantation from HIV+ donors to HIV+ recipients (HIV D+/R+ transplantation), and progress to date.

HISTORY OF TRANSPLANTATION IN PEOPLE LIVING WITH HIV

During the AIDS epidemic in the 1980s (13), HIV testing and treatment options were lacking worldwide. The risk of transmission was high, and in order to avoid harm, the use of organs from HIV+ donors for transplantation was banned under the National Organ Transplant Act of 1984. Much has evolved in both the management of HIV and transplantation in years since. In the HIV field, effective antiretroviral therapy (ART) has substantially reduced AIDS-related mortality, with life expectancy reaching that of the general population (14, 15). As a result, non-AIDS-related chronic complications including ESRD and ESLD have increased. Data from 13 cohorts examining cause of mortality among HIV patients in 1996–2006 showed that 7% of the deaths resulted from liver disease and 1.5% from kidney disease (5). Similar trends were also seen in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) collaboration of 11 cohort studies conducted in 1999–2011 (16).

For many years, there were concerns about the safety and efficacy of transplantation for HIV+ individuals with end-stage organ disease due to the perceived risk of giving immunosuppressive medications to this population. However, data from the landmark Multisite HIV Transplant Recipient (HIVTR) Study—a prospective nonrandomized clinical trial of HIV D–/R+ kidney transplantation—showed excellent 1- and 3-year patient and graft survival outcomes for HIV+ recipients (8, 9).

SOUTH AFRICAN EXPERIENCE

Building on the experience in the United States, transplant surgeon Dr. Elmi Muller performed the first HIV D+/R+ kidney transplant in Cape Town, South Africa, in 2008. This pioneering work was born out of necessity; South Africa has the largest HIV epidemic in the world, with a 20% prevalence of HIV among adults, totaling 7 million people living with HIV (PLWH) (17). Historically, owing to the lack of public sector resources, HIV+ patients with ESRD in South Africa were denied state-funded hemodialysis. Only 20% of South Africans have private health insurance which permits access to dialysis as an interim bridge to transplantation.

In 2010, pilot data from the first four HIV D+/R+ deceased donor kidney transplants from South Africa were published, demonstrating good outcomes and no serious opportunistic infections or progression of HIV in recipients (18, 19). The study was expanded into a prospective observational study including 27 HIV D+/R+ kidney recipients. This cohort had an overall survival of 84% and 76% and graft survival of 93% and 84% at 1 and 5 years, respectively. HIV remained well controlled post-transplantation (20).

Given these encouraging results, there was interest in this practice in the United States. However, there were important differences to be considered between the countries. In South Africa, with extreme organ shortages, diminished access to dialysis, proportionately more HIV+ potential deceased donors, and limited resources, the need for HIV D+/R+ kidney transplantation could be categorized as more urgent. In contrast, the United States has a relatively low prevalence of HIV, roughly 0.6% (21), with widespread availability of ART and hemodialysis. However, studies in the United States have shown that kidney transplantation confers a clear survival benefit for those with HIV and ESRD (22), and access to transplant remains inadequate (23). Expansion of the donor pool to include HIV+ donors in the United States is one way to mitigate inequity of access to transplant.

THE HOPE ACT: INCEPTION TO IMPLEMENTATION

Before an Act of Congress could be proposed, work needed to be done to estimate the impact of a policy change. The first study to project the number of HIV+ donors looked at national inpatient hospital data and HIV Research Network consortium data to estimate 500–600 HIV+ deceased donors annually (24). This would provide a substantial expansion of the donor pool. With a growing demand for organs and disproportionate mortality among HIV+ individuals waiting on the transplant list, physician investigators, transplantation professionals, and community organizations advocated for legislative change.

Deft political maneuvering to ensure bipartisan support made passage of the HOPE Act possible, nearly 3 years after work on the legislation began (25). Many medical and patient advocacy groups worked together to publicly support the change. Favorable coverage in mainstream press generated momentum and the support of politicians and civil servants to introduce the bill. The HOPE Act was signed into law by President Barack Obama in November 2013 (26) (**Figure 1**).

The HOPE Act mandated that the Secretary of Health and Human Services formulate criteria for conducting HIV D+/R+ transplantation research. Accordingly, in 2015, the Department of Health and Human Services (HHS) put forth the HOPE Safeguards and Research Criteria (27) (**Figure 1**). The Safeguards were meant to ensure the safety of research participants, healthcare workers and the public, and to collect data to evaluate the safety and efficacy of HIV D+/R+ transplantation. The Research Criteria focused mainly on kidney and liver transplantation, where there was more published experience; however, they allowed consideration of transplantation of other organs (heart, lung, kidney/pancreas), if transplant centers had adequate experience. In addition, the HOPE Act states that, with time and follow-up data, HHS will determine if HIV D+/R+ transplants can be completed outside of research protocols (28).

Following the establishment of research criteria, the first study of HIV D+/R+ transplantation (NCT02602262) was opened by Johns Hopkins University in 2015 (29). This was an observational pilot study of HIV D+/R+ kidney and liver deceased donor transplants to assess safety, outcomes, and potential complications. The first HIV D+/R+ kidney and liver transplants were performed under this protocol in March 2016 (29) (**Figure 1**).

In 2018, HOPE in Action, a larger, multicenter prospective clinical trial (NCT03500315), was initiated by the same group in partnership with the National Institutes of Health to evaluate

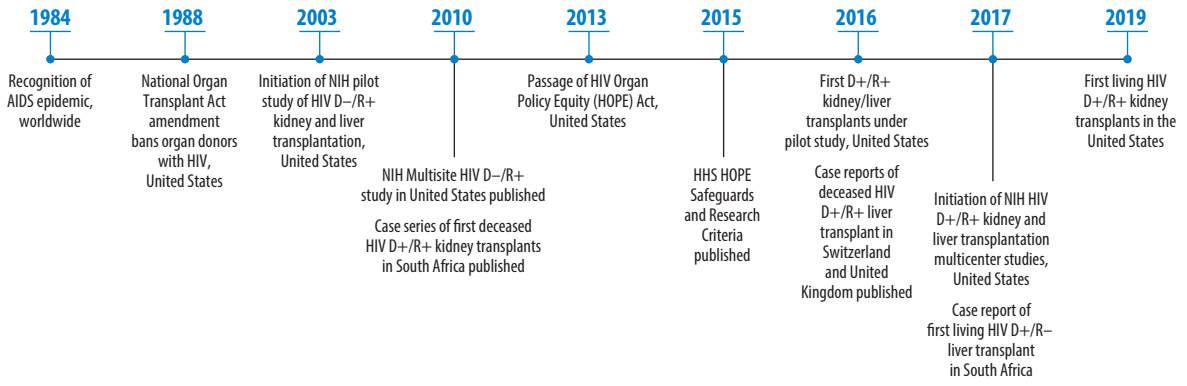

Figure 1

Milestones in organ transplantation from HIV+ donors to HIV+ recipients (HIV D+/R+ transplantation). The timeline includes recent changes in US law to allow the use of organs from donors with HIV for transplant candidates with HIV. Abbreviations: HHS, Department of Health and Human Services; NIH, National Institutes of Health.

outcomes from receiving a kidney transplant from an HIV+ deceased donor compared to those from an HIV– donor. At completion, this trial is expected to report outcomes on 160 HIV+ kidney transplant recipients from more than 20 centers in the United States. In 2019, a clinical trial to assess feasibility, safety, and effectiveness of HIV D+/R+ liver transplantation was initiated at 19 US centers (NCT03734393); it aims to include 80 HIV+ liver transplant recipients in total (**Figure 1**).

RISKS OF HIV D+/R+ TRANSPLANTATION FOR RECIPIENTS

The initial idea of organ transplantation in HIV was met with two major concerns: HIV disease progression in the setting of immunosuppression, and increased susceptibility to opportunistic infections. In the Multisite HIVTR study of HIV D–/R+ transplantation, 13% (20/150) of kidney recipients and 16% (18/110) of liver recipients experienced transient loss of HIV RNA control. This was not due to immunosuppression but rather occurred with interruption of ART; with reinitiation, viral suppression was achieved. In the same study, for recipients who received antithymocyte globulin (ATG) for induction immunosuppression, there was an initial decline in CD4 cell counts. However, this was followed by gradual CD4 cell recovery over 1–3 years. Even with this early CD4 decline, there were only 6 opportunistic infection cases reported: 2 cutaneous Kaposi sarcomas, 2 esophageal candidiases, 1 pneumocystis pneumonia, and 1 cryptosporidiosis (9). A study from the Scientific Registry of Transplant Recipients of HIV D–/R+ kidney recipients showed that ATG induction was associated with lower rates of infection and graft loss compared to no induction or use of an interleukin-2 receptor antagonist (30). These data have been reassuring; however, theoretically, there could be increased donor-derived infections with the practice of HIV D+/R+ transplantation.

Potential risks of D+/R+ transplantation include the following:

1. HIV superinfection: Transmission of a distinct strain of HIV from the donor leading to failure of ART from resistance or change in tropism with loss of HIV control.
2. HIV latent reservoir: Possible transmission of donor dormant drug resistant HIV from latent cellular reservoir to recipient leading to occult resistance.

3. Infections following transplant: Donor derived and/or opportunistic infections.
4. HIV infection of allograft leading to organ dysfunction.
5. Increased allograft rejection due to HIV infection of allografts.

HIV superinfection, that is, acquisition of a second HIV viral strain from a donor (31), could be a clinical concern if the donor-derived virus proves to be resistant and difficult to treat with standard ART. Transmission of an X4 tropic viral strain might also cause loss of HIV control if the recipient's ART relies on a CCR5 inhibitor, which is only active against R5 tropic virus (32). The risk of ART-resistant virus in the donor is likely different between the South African experience and the United States. In South Africa, where there is lower access to ART, the majority of donors have been ART naïve (33). Also, the overall prevalence of transmitted drug resistance is <5% in South Africa compared to 10–18% observed in the United States (34).

Fortunately, emerging data with regard to superinfection have been reassuring. A study including 25 HIV D+/R+ kidney transplants from South Africa showed that although donor virus was detected transiently in 32% (8/25) of recipients at an early timepoint, there were no cases of HIV breakthrough or longer-term detection of donor virus (35). Moreover, a recent study in the United States of 17 HIV D+/R+ kidney and liver transplants demonstrated similarly reassuring results with no evidence of sustained donor-derived HIV superinfection (36).

The risk of HIV-associated disease in the allograft has also been considered. It is controversial whether the kidney is a reservoir for HIV (37, 38). In a single-center study of 19 HIV D–/R+ kidney recipients with undetectable plasma HIV RNA, allograft biopsies showed HIV in tubular cells ($n = 7$) or podocytes ($n = 5$), and in recipients where the virus was detected in podocytes, there was a decline of allograft function (39). This phenomenon has not been reported in other cohorts of HIV+ kidney transplant recipients (9, 35). If the kidney is a clinically significant reservoir for HIV, this could be relevant with an HIV+ kidney donor. In a recent HIV D+/R+ kidney transplant case report in the United States, phylogenetic analysis of HIV from renal tubular cells in urine early post-transplant showed two distinct viral lineages, one of which was genetically related to donor virus (40). Whether this donor virus will impact kidney function and whether it can enter the long-term viral reservoir in memory CD4 T cells of the recipient is unknown.

Another risk faced by HIV+ kidney transplant recipients is allograft rejection. Studies have shown that rejection is approximately 2–5 times higher in HIV+ recipients than in HIV– controls (9, 41–45). The reasons for this are not fully understood and likely multifactorial. HIV-associated immune dysregulation and difficulties with drug interactions are thought to contribute. Theoretically, the risk of rejection might be higher with HIV D+/R+ transplantation. In the South African cohort, rates of rejection were 25% at 1 year, 39% at 3 years, and 44% at 5 years, but there were no HIV D–/R+ transplant recipient controls for comparison (33).

EARLY HOPE EXPERIENCE

One of the first findings after HOPE Act implementation was the unexpected discovery of another novel donor pool: donors with false-positive HIV screening tests. All deceased donors in the United States must be tested with both an HIV antibody and an HIV nucleic acid test. These assays have a false-positive rate of 0.1–0.5%. Confirmatory testing for potential donors with discordant HIV assay results is not defined, required, or reported by the OPTN (46). In the past, organs from donors with discordant test results were discarded due to challenges of obtaining timely confirmatory testing, fear that the donor might be a true positive, or liability concerns. In the context of HOPE Act studies, it has been feasible to allocate these organs to HIV+ candidates who have consented to receive an HIV+ donor organ (47). It is estimated, based on false-positive

rates of screening assays and >20,000 eligible donors screened annually, that an additional 50–100 HIV false-positive donors could be added to the donor pool yearly (47).

The clinical trial data have not yet been published, but the OPTN reported trends in the first two years of HOPE (48). The number of transplant centers participating in the HOPE protocol has gradually increased. As of March 2019, 32 transplant centers had a HOPE Act research protocol; 75% of centers indicated capacity to transplant under a HOPE protocol by listing at least one candidate, and 47% of centers had already performed an HIV D+/R+ kidney or liver transplant. From November 2013 through December 2018, 56 deceased donors were recovered under the HOPE Act, and 102 organs were transplanted (71 kidneys and 31 livers). Additionally, the OPTN reported that HIV D+/R+ 1-year patient and graft survival did not deviate from that observed after HIV D–/R+ transplant (48); however, this analysis was limited, as the OPTN cannot distinguish between HIV+ donors and HIV– donors with false-positive tests (49). The HOPE in Action trials will be able to provide transplant outcomes linked to true HIV donor status (49). Outside South Africa, a small handful of successful HIV D+/R+ transplants have been reported internationally (50–54).

HIV LIVING DONOR TRANSPLANTATION

The HOPE Act also allows HIV+ living donor transplantation. HIV+ kidney transplant candidates have a 47% lower rate of living donor transplantation than their HIV– counterparts on the waitlist (55). Allowing consideration of HIV+ donors might increase these candidates' likelihood of identifying potential donors among their social network. However, there have been concerns that HIV+ donors might face a higher risk of ESRD after donation. To better estimate this risk, Muzaale et al. (56) compared the cumulative incidence of ESRD in individuals with well-controlled HIV and without diabetes, hypertension, or hepatitis C in the North American AIDS Cohort Collaboration on Research and Design to matched HIV– individuals within the National Health and Nutrition Examination III cohort study. They found a slightly increased risk of ESRD in those with HIV; however, this risk was low (2.5 versus 1.1 per 10,000 among white women, 3.0 versus 1.3 per 10,000 among white men, 13.2 versus 3.6 among black women, and 15.8 versus 4.4 among black men) and comparable to other risk factors, such as tobacco use, which are not contraindications to donation (56). A prospective clinical trial of living HIV+ kidney donors was opened in 2018 (NCT03408106), and the first living donation in the United States was performed in March 2019 followed by the second of its kind in September 2019 with favorable clinical outcomes (57, 58).

The first ever living donor liver transplant was conducted in South Africa in 2017. This also happens to be the first intentional HIV D+/R– liver transplant: An HIV+ mother donated to her 13-month-old child on the waitlist with progressive liver failure from biliary atresia. This controlled HIV D+/R– liver transplant had a favorable short-term surgical outcome in the donor and recipient; more than 1 year post transplant, HIV is undetectable in the recipient, who remains on ART. This groundbreaking case has the potential to expand the living liver donor pool and provide new insights into HIV transmission and cure (59).

HOPE IN ACTION—BARRIERS AND PROGRESS

Significant milestones in HIV transplantation have been achieved (**Figure 1**); yet, in order to realize the full potential of the HOPE Act, continued progress is needed. Remaining challenges can be conceptualized at the community level, at the organ procurement organization (OPO) level, and at the transplant center level (**Figure 2**).

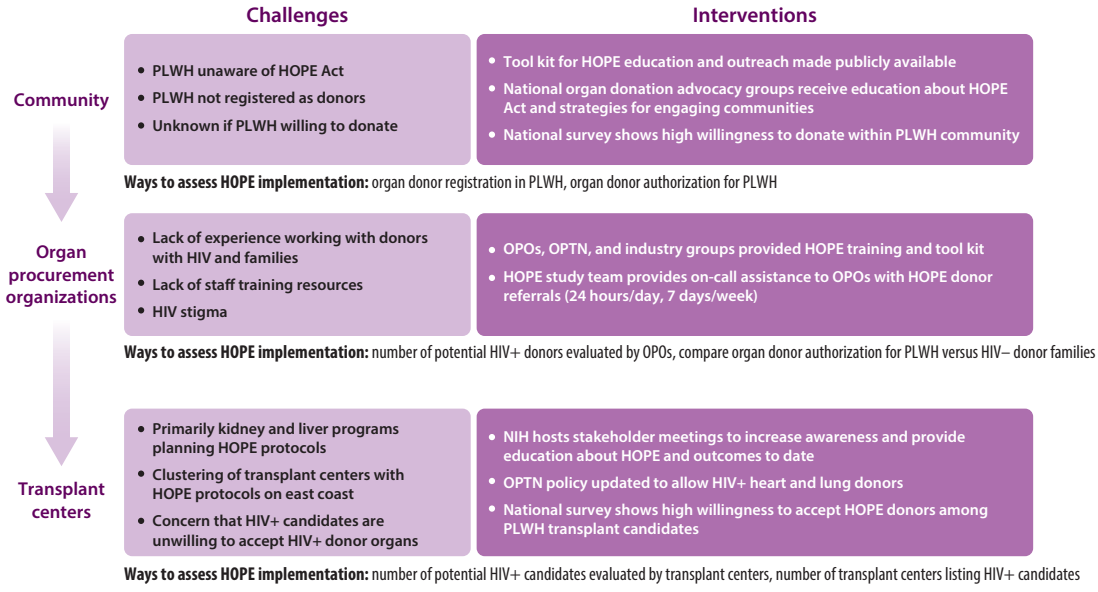

Figure 2

Challenges to realizing the full potential of the HOPE Act exist at three levels: the community, organ procurement organizations, and transplant centers. Progress has been made at each level with a number of interventions by the HOPE study team, the NIH, and national organizations involved in donation and transplantation. Abbreviations: HOPE, HIV Organ Policy Equity; NIH, National Institutes of Health; OPO, organ procurement organization; OPTN, Organ Procurement and Transplantation Network; PLWH, people living with HIV.

In the community, early challenges included uncertainty about the attitudes toward organ donation and HIV+ donor organ acceptance in PLWH. In two cross-sectional surveys, one in 2012 in the United Kingdom ($n = 206$) and the other in 2016 in Taiwan ($n = 1{,}010$), 62% and 72% of PLWH, respectively, were willing to be donors (60, 61). After the HOPE Act, the first US survey was conducted with 114 respondents, predominantly African American, in care at the Johns Hopkins HIV clinic (62). The survey showed high willingness to donate (80%) but low knowledge regarding the HOPE Act (25%) and low donor registration rates (21%). These data highlighted a need for community-based education to ensure that PLWH know that they are legally allowed to donate and that the process to register as an organ donor is the same. Such efforts have been implemented at both local (63) and national levels (64–66) (**Figure 2**).

OPOs are responsible for evaluating deceased donor referrals, making organ offers to transplant centers, and recovering organs; as such, they play a critical role in realizing the full potential of the HOPE Act. A national survey of all 58 OPOs estimated that more than 1,450 HIV+ donor referrals were received per year (67). However, it was not known how many of these referrals were medically suitable donors, as many OPOs do not collect thorough clinical data on initial referrals (68, 69). Other OPO challenges include low awareness among hospital providers, which could lead to missed or delayed HIV+ donor referrals (69). Before the HOPE Act, OPO screening was designed to exclude HIV+ donors, and there was limited clinical experience or training in working with HIV (70). To address these barriers, the HOPE study team and national societies involving donation and transplantation have created and disseminated educational materials about working with HIV+ deceased donors (65, 66).

HIV-related stigma within healthcare settings is a well-documented phenomenon (71), which presents another challenge. The perceptions and attitudes of OPO staff toward PLWH have

not yet been reported, so the impact of HIV-related stigma on OPO practice is currently unknown. Each OPO independently defines its clinical evaluation criteria for potential deceased organ donors (72). Since criteria are not standardized and there is no policy prohibiting the exclusion of potential HIV+ deceased donors from evaluation, OPO recovery of HIV+ organ donors is currently optional and discretionary. In healthcare settings where stigma can influence practice, prohibiting discrimination and enforcing nondiscriminatory policies have been key interventions to reduce suboptimal treatment for patients (73). National transplant policy that defines OPO discrimination against HIV+ potential deceased organ donors could be a valuable tool in decreasing HIV-related stigma in OPO settings.

There have also been barriers to full HOPE implementation at the transplant center level (**Figure 2**). A national survey of 114 US centers reported that less than half (44%) were planning to perform HIV D+/R+ transplants. These were almost exclusively kidney and liver programs and the majority were clustered along the east coast (74). The OPTN has also announced that it will update policy to allow HIV D+/R+ heart and lung transplants in 2020 (75), yet even so, if a significant number of transplant programs in the western and middle United States do not use HIV+ donors, OPOs in those areas could be less likely to evaluate potential HIV+ donors. Recent changes to organ allocation policy seek to reduce inter-region preference for local transplant centers and locally recovered organs, specifically kidneys and livers (76). Under this policy, local center participation in HIV D+/R+ transplantation may have less influence on OPO decisions to pursue HIV+ donors, as abdominal organs experience broader allocation (77). In addition to geographical limitations, 50% of transplant centers anticipated that at least half of their HIV+ waitlist candidates would be unwilling to accept HIV+ deceased donor organs, and these centers were less likely to plan an HIV D+/R+ transplantation protocol (72). However, this belief appears to be a misperception. A recent survey of 116 HIV+ transplant candidates at nine centers indicated that 84% would be willing to accept HIV+ deceased donor organs (78).

CONCLUSION

Passage of the HOPE Act provides an opportunity to alleviate the organ shortage crisis by expanding the donor pool. It also provides a more equitable opportunity for transplant for a vulnerable population of PLWH who face higher waitlist mortality and decreased access to transplant. The numbers of HIV D+/R+ solid organ transplants in the United States have been increasing steadily under the established research protocols. The clinical and scientific data with regard to outcomes and safety of HIV D+/R+ transplantation from multiple ongoing HOPE in Action studies will further extend the frontiers of knowledge in this field.

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