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Overcoming barriers and stigma: new frontiers in solid organ transplantation for people with HIV

K. Storm,[1] **C. M. Durand**[1]

AUTHOR AFFILIATION See affiliation list on p. 11.

SUMMARY There is a growing need for solid organ transplantation (SOT) for people living with human immunodeficiency virus (HIV). With the advent of antiretroviral therapy, people living with HIV are experiencing increased life expectancies and are, therefore, developing more comorbidities, including end-stage organ disease. In cases of advanced organ failure, SOT is often the best therapeutic option to improve quality of life and overall survival. As organ shortages persist, transplantation of organs from donors with HIV to recipients with HIV has become a potential therapeutic option. This article first reviews the current state of organ transplantation from donors without HIV to recipients with HIV (HIV D−/R+) by organ and discusses key lessons learned from these transplant trials, including those about drug-drug interactions, rejection, and opportunistic infections. It then explores transplantation from donors with HIV to recipients with HIV (HIV D+/R+), a new frontier. Finally, it investigates challenges of implementation, including public awareness and regulatory requirements, and explores future directions for SOT in people living with HIV.

Editor Graeme N. Forrest, Rush University, Chicago, Illinois, USA

Address correspondence to C. M. Durand, christinedurand@jhmi.edu.

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INTRODUCTION

With the advent of antiretroviral therapy (ART), people living with human immunodeficiency virus (HIV) are experiencing increased life expectancies. As they age, they are developing more comorbidities, including end-stage organ disease (1). When people with organ failure reach a critical stage, solid organ transplantation (SOT) is often the best therapeutic option to improve quality of life and overall survival (1–4). Trial and registry data have demonstrated the efficacy of SOT for people living with HIV (PLWH) with end-stage organ disease (5). Consequently, it is crucial to ensure optimal access to transplantation for PLWH. However, the number of available donors falls significantly below the need, resulting in numerous deaths on the transplant waitlist (6). Indeed, in 2021, over 100,000 people were on the waitlist for a SOT, but only 44,600 transplants were performed (7). As organ shortages persist, transplantation of organs from donors with HIV to recipients with HIV has become a potential therapeutic option.

In this article, we will first review the current state of organ transplantation from donors without HIV to recipients with HIV (HIV D−/R+) by organ and will discuss key lessons learned from these transplant trials, including those about drug-drug interactions, rejection, and opportunistic infections. We will then focus on transplantation from donors with HIV to recipients with HIV (HIV D+/R+), a new frontier. Finally, we will investigate challenges of implementation, including public awareness and regulatory requirements, and future directions for SOT in PLWH.

HIV D−/R+ TRANSPLANTATION BY ORGAN

Kidney

One of the largest studies of HIV D−/R+ kidney transplantation in the United States was the NIH HIV Transplant Recipient (HIV TR) Study, a multicenter trial that included 150 HIV D−/R+ kidney transplants from November 2003 to June 2009 (8). Eligible candidates had pre-transplant CD4+ T cell counts of at least 200 cells/mL and suppressed plasma HIV type 1 (HIV-1) RNA levels on stable ART. Post-transplant, immunosuppressive therapy varied at the discretion of the provider and typically included induction therapy with an interleukin-2–receptor blocker (IL2RB) and/or antithymocyte globulin (ATG) and maintenance therapy with glucocorticoids, cyclosporine or tacrolimus, and mycophenolate mofetil (8).

Patient survival rates at 1 year and 3 years were 94.6% and 88.2%, respectively (8). Graft survival rates were 90.4% at 1 year and 73.7% at 3 years. Patient and graft survival rates were generally between those reported in the Scientific Registry of Transplant Recipients (SRTR) for all kidney transplant recipients and kidney transplant recipients ≥65 years old during similar timeframes (8).

HIV infection remained well controlled throughout the study (8). The median change in the CD4+ T cell count from baseline to 1 year after transplantation was significantly greater in patients who received ATG than in those who did not (−238 vs −135 cells per cubic millimeter, $P < 0.001$), but by 3 years, it was similar between groups. The main finding of concern was unexpectedly higher rejection rates (by a factor of 2.5) in the HIV D−/R+ recipients as compared to adult kidney transplant recipients in SRTR over the same time period. Indeed, the cumulative incidence of rejection at 1 year was 31% [95% confidence interval (CI), 24–40] for HIV D−/R+ recipients in comparison to 12.3% (95% CI, 11.9–12.7) for recipients without HIV (8, 9).

During the 4 years of follow-up, there were a total of 17 (11.3%) deaths among HIV D−/R+ kidney recipients, which was similar to mortality in a group of matched HIV D−/R− recipients (9). These results were reassuring, and the excellent outcomes and survival benefit were replicated outside of the clinical trial in several registry studies using real-world data of recipients with HIV (10, 11). As a result, kidney transplantation

became considered standard of care for people with well-controlled HIV and end-stage renal disease (9).

Liver

The NIH HIV TR study also included HIV D−/R+ liver transplantation trials for PLWH who had end-stage liver disease from either hepatitis C virus (12) or hepatitis B virus (13). The first study compared 89 recipients coinfected with HIV and HCV and a control group of 235 recipients with HCV mono-infection (12). The 3-year post-transplant patient and graft survival rates were 60% and 53% for recipients with HIV/HCV but 79% and 74% for the recipients with HCV ($P < 0.001$ for both). HIV infection was significantly associated with lower patient and graft survival rates. The incidence of acute rejection was 1.6-fold higher at 3 years post transplant for the recipients with HIV/HCV compared to recipients with HCV (39% vs 24%, log rank $P = 0.02$). Cumulative rates of severe HCV disease at 3 years post transplant were not significantly different between the groups (12). In concordance with the kidney study, there was no evidence of HIV breakthrough with stable CD4+ T cell counts and suppression of HIV viremia (8, 12).

The second liver study followed 22 liver recipients coinfected with HIV and hepatitis B virus (HBV) and a control group of 20 recipients with HBV mono-infection (13). The recipients were treated with hepatitis B immune globulin and nucleos(t)ide analogs. There was no clinical evidence of HBV flares, but low-level HBV DNA was detectable in approximately 50% of recipients in both groups. The recipients with HIV/HBV had similar patient and graft survival rates in comparison with recipients with HBV: both were 85% for recipients with HIV/HBV, and both were 100% for recipients with HBV (log rank $P = 0.08$). Overall, this study demonstrated excellent short-term outcomes for recipients with HIV and HBV (13).

Recipients from both liver studies (total of 125) were followed for a median of 3.5 years with a patient survival rate of 64%, compared to the 62% 5-year post-transplant survival rate among liver transplant recipients ≥65 years old in SRTR (9). Moreover, a survival benefit of transplantation was confirmed for candidates with pre-transplant Model for End-Stage Liver Disease scores greater than 15 in both studies (9).

These promising outcomes have only improved with the advent of interferon-free direct-acting antivirals (DAAs) for HCV in 2014. Indeed, a registry study using data from all liver transplant recipients in the United Network for Organ Sharing (UNOS) and Organ Procurement and Transplantation Network (OPTN) found that by the period 2014–2018, there were no longer differences in graft and patient survival by HIV status (3-year patient survival was 81.2% with HIV vs 86.4% without HIV, $P = 0.34$) (14). These reassuring survival rates support liver transplant becoming standard of care for patients with end-stage liver disease, regardless of HIV or HCV status (14).

Pancreas

HIV D−/R+ simultaneous pancreas/kidney transplants have been performed less commonly. The first HIV D−/R+ simultaneous pancreas/kidney transplant performed in a patient with HIV in Spain was reported in a case study in 2010 (15). Although the recipient's HIV infection was adequately controlled on raltegravir-based ART, the pancreas graft failed at 2 weeks due to venous thrombosis, and the patient died at 9 months due to a *Pseudomonas aeruginosa* infection (15). Four other HIV D−/R+ pancreas/kidney transplants were performed between 2006 and 2009 and reported in 2012 (16). All four recipients survived with median follow-up of 45 months and had suppressed HIV RNA and CD4+ T cell counts >300 cells/mL (16). Additionally, a report on transplantation in PLWH in Italy between 2002 and December 2014 reported five combined kidney-pancreas transplants (17). The report states that at the time of analysis in 2015, three of these recipients were alive and two were dead but that causes of death were not recorded (17).

In the United States, a long-term follow-up study of 10 islet or pancreas transplant recipients who were living with HIV and who had received a kidney transplant either

concurrently or prior to the pancreas transplant found that patient survival rates and graft survival rates were 100% and 100% at 1 year post transplant and 80% and 100% at 5 years post transplant (18). There were four opportunistic infections observed, all of which were BK viremia. In all patients, CD4 counts remained stable, and HIV remained undetectable throughout the follow-up (18). The lack of HIV breakthrough in these reports is encouraging and lends support to future investigations of pancreas transplants for recipients with HIV.

Lung

A European multicenter retrospective study published in 2022 identified 22 HIV D−/R+ lung transplant recipients across 25 transplant centers from 2007 to 2021 (19). The mean pre-transplant CD4+ T cell count was 514 (range, 351–670) cells/mL with suppressed HIV RNA in all patients. Immunosuppression was given according to local protocols, with IL2RB or ATG induction in seven (32%) recipients. During the first year post transplant, there were seven (37%) cases of acute cellular rejection, two (11%) instances of antibody-mediated rejection, and eight (40%) infections requiring hospitalization. During a median follow-up of 25 months (range, 0.1–172), 26% of patients developed chronic lung allograft dysfunction, and 14% developed malignancy. Post-transplant survival rates were 79% at 1, 3, and 5 years. While early infection rates were high, patient survival and graft survival were similar to HIV D−/R− liver transplant recipients. Given the high mortality for people on in need of lung transplant, these results suggest that lung HIV D−/R+ transplants can be of great clinical benefit for patients with HIV (19).

Heart

From 1999 to 2004, the SRTR database reported 20 HIV D−/R+ heart transplants (20). Post-transplant survival at 1 year and 3 years were comparable to those observed HIV D−/R− heart transplant recipients (20). A later analysis of UNOS data included 41 HIV D−/R+ heart transplant recipients from January 2004 to March 2017 and was published in 2019 (21). It found that HIV D−/R+ heart transplant recipients have excellent post-transplant survival (Kaplan-Meier analysis estimates 86% at 1 year and 77% at 5 years), including those who had bridge-to-transplant ventricular-assist devices. During follow-up, rates of cardiac allograft vasculopathy (32%) and malignancy (19%) were similar to those seen in heart transplant recipients without HIV in the International Society for Heart and Lung Transplantation (ISHLT) registry (29.3% and 15.9%, respectively). However, as with the studies of other solid organ transplants, a higher risk of acute rejection was identified in HIV D−/R+ heart recipients (39.3%) compared to HIV D−/R− heart recipients (generally ≤20% depending on the era). Despite increased rejection rates, the analysis supports the notion that patients with HIV derive similar benefit from heart transplantation as those without HIV (21).

LESSONS LEARNED FROM HIV D−/R+ TRANSPLANTS

Drug-drug interactions

Understanding and mitigating drug-drug interactions between ART and immunosuppressant medications is crucial to prevent adverse outcomes in SOT recipients with HIV. Protease inhibitors (PIs) can inhibit the metabolism of calcineurin inhibitors (CNIs), such as cyclosporine and tacrolimus, as well as mTOR inhibitors, such as sirolimus and everolimus, increasing their blood levels (Table 1) (22). This occurs because PIs strongly inhibit the cytochrome P450 3A (CYP3A) enzyme system that is responsible for the metabolism of CNIs and mTOR inhibitors. Increased CNI and mTOR inhibitor blood levels may increase the risk of nephrotoxicity (22). One study in liver transplant recipients found that on average, participants on ART required a 16-fold lower tacrolimus dose in comparison to patients not on ART (23).

Conversely, potent non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as efavirenz and nevirapine, induce the metabolism of CNIs (Table 1). This can result in

TABLE 1 Antiretrovirals with significant interactions with tacrolimus and cyclosporine

	Impact on CYP3A4	Expected effect on levels and dosing
Non-nucleoside reverse- transcriptase inhibitors:	CYP3A4 inducer	Decrease in tacrolimus levels, requiring higher dosing.
Efavirenz		Decrease in cyclosporine levels, requiring higher dosing.
Etravirine		
Nevirapine		
Protease inhibitors:	CYP3A4 inhibitor	Increase in tacrolimus levels, requiring lower, less frequent dosing.
Atazanavir		May increase cyclosporine levels, requiring monitoring and potentially lower, less frequent dosing.
Darunavir		
Lopinavir/ritonavir		
Capsid inhibitor:	Moderate CYP3A4 inhibitor	Its effect on tacrolimus is not fully known, requiring monitoring.
Lenacapavir[a]		May increase cyclosporine levels, requiring monitoring and potentially lower, less frequent dosing.
Pharmacoenhancer (booster):	CYP3A4 inhibitor	Increase in tacrolimus levels, requiring substantially lower, less frequent dosing.
Cobicistat		May increase cyclosporine levels, requiring monitoring and potentially lower dosing.
Ritonavir		

[a]Injectable ART. Pharmacokinetic interactions between antiretrovirals and immunosuppressive agents based on www.hiv-druginteractions.org (University of Liverpool).

lower blood levels of CNIs, leading to reduced immunosuppressive effects and increased risk of organ rejection (24).

Expert guidelines recommend that, when feasible, integrase strand transfer inhibitor (INSTI)-based antiretroviral regimens should be preferred to PI- and NNRTI-based regimens (25). INSTIs have no interactions with CNI or mTOR inhibitors. INSTIs also do not interact with DAAs for HCV (26). Supporting this notion, one study of 58 HIV D−/R+ kidney transplants with different immunosuppression combinations found that INSTI-containing regimens had excellent patient survival (96%) and graft survival (100%) at 3 years (26).

Allograft rejection

Allograft rejection rates in HIV D−/R+ transplant recipients have consistently been higher than HIV D−/R− transplant recipients. In the HIV TR kidney transplant study, the incidence of rejection was 31% at 1 year post transplant and 41% at 3 years post transplant, which is unexpectedly higher compared to the 12.3% 1-year post-transplant rate of rejection seen in kidney recipients without HIV (8). Similarly, in a single-center study, Malat et al. reported an acute cellular rejection incidence of 28% at 1 month and 55% at 1 year post transplant in a study of 92 HIV D−/R+ kidney transplant recipients (27). The causes for these increased rejection rates are not fully understood.

One proposed cause is drug-drug interactions discussed above, which affect the normal metabolism of immunosuppressant medications. It is thought that through careful selection of ART and immunosuppressive regimens, the risk of rejection may be mitigated. Indeed, Rollins et al. reported biopsy-proven rejection rates that were significantly higher in kidney recipients on PI-containing ART compared to other ART regimens: 59% vs 24% (P = 0.029) at 1 year post transplant and 68% vs 24% (P = 0.01) at 3 years post transplant (28). In another study, Barday et al. found that 63% (12/19) of kidney recipients on PI-containing ART experienced rejection compared to 28% (8/29) of kidney recipients on an NNRTI-based regimen (24). In their regression analysis, there was a positive association between rejection and a PI-containing regimen, with an incidence rate ratio of 2.77 (95% confidence interval, 1.03–7.48) (24).

Another hypothesis is that increased rejection rates may result from the chronic inflammatory state from HIV or from immune dysregulation from chronic HIV infection (29). Immune dysregulation may explain why ATG, one of the most potent immunosuppression induction medications, has been associated with less rejection in some studies, such as the South African studies and pilot HOPE kidney study (29–33). The influence of immune dysregulation and inflammatory state due to HIV requires further investigation.

Opportunistic infections

While still a concern, there are relatively few reports of HIV-associated opportunistic infections after HIV D−/R+ transplantation (34). In the HIV TR kidney transplant study, there were two cases of newly diagnosed cutaneous Kaposi's sarcoma (KS) and one case each of candida esophagitis, presumptive *P. jirovecii* pneumonia, and cryptosporidiosis (8). Since transplant candidates with HIV are generally required to have CD4+ T cell counts >100 cells/mL and controlled HIV viral replication, it seems likely that the opportunistic infections are related to post-transplant immunosuppression medication rather than to HIV infection (35). Indeed, a number of HIV D−/R+ studies have identified increased rates of infections but limited numbers of opportunistic infections or those that are linked to HIV (8, 9, 12, 19).

Other chronic viral infections may increase the risk of opportunistic infections as well. Indeed, at least one study demonstrates that HCV coinfection was associated with higher rates of opportunistic infections. In a multicenter cohort in Spain of 84 liver transplant recipients with HIV/HCV, nine patients (11%) experienced opportunistic infections including zymogycosis (n = 2), invasive aspergillosis (n = 1), cytomegalovirus disease (n = 2), esophageal candidiasis (n = 1), tuberculosis (n = 2), and *Pneumocystis jirovecii* pneumonia (n = 1) (36). This cohort was compared with 105 liver transplant recipients with HIV monoinfection at a center in France in which five liver recipients (4.8%) developed opportunistic infections, including esophageal candidiasis (n = 2), tuberculosis (n = 1), cytomegalovirus colitis (n = 1), and atypical mycobacterial infection (n = 1) (37). In contrast, in the NIH TR study of liver transplant recipients with HIV/HCV compared to recipients with HCV, there were no difference opportunistic infections between groups (12). Further research into opportunistic infections and their relation to viral coinfections is needed.

Malignancy

Both PLWH and transplant recipients have abnormalities in cell-mediated immunity, which increase risk of cancer. One registry-based study found nearly parallel elevations in the incidence of virus-related cancers in PLWH without transplants and transplant recipients without HIV (38). The incidence was found to be strongly elevated for KS, which is caused by KS-associated herpesvirus, with a standardized incidence ratio of 3,640 for PLWH and 208 for transplant recipients (38). Increased incidence rates for anal cancer, which is caused by human papillomavirus, have also been observed in both PLWH and transplant recipients (39). However, it is still unclear how cancer risks are impacted for PLWH who receive a transplant and whether it is additive or multiplicative. Dedicated studies of cancer incidence in transplant recipients with HIV are needed.

MOTIVATION FOR HIV D+/R+ TRANSPLANTATION AND THE HOPE ACT

Despite the benefits of SOT for PLWH being well demonstrated, the availability of organs is limited, and PLWH face additional barriers to transplant. Indeed, one 2017 study found that candidates with HIV were 28% less likely to undergo kidney transplant compared with candidates without HIV (adjusted hazard ratio = 0.72, $P < 0.001$) (40). Similarly, despite positive findings from HIV D−/R+ cardiac transplants, a 2021 study found only a limited number of centers (<80%) in the United States offer cardiac transplant to patients with HIV (20).

In South Africa, PLWH with end-stage kidney disease faced a much more dire situation where access to dialysis was severely limited. As such, kidney transplant surgeon Dr. Elmi Muller pioneered the practice of HIV D+/R+ kidney transplant in the early 2000s (32). She and her team performed four HIV D+/R+ kidney transplants in 2008 with promising outcomes and an additional 27 more HIV D+/R+ kidney transplants from 2008 to 2014, demonstrating the potential of this practice (33).

Initially, HIV D+/R+ transplants were not allowed in the United States due to a federal ban implemented in the 1980s. However, researchers began investigating the potential

of this practice and, using death registry data, found that there could be up to 500–600 suitable deceased donors with HIV per year (41). This analysis, along with promising data from HIV D+/R+ transplants in South Africa motivated the Congressional HIV Organ Policy Equity (HOPE) Act. The HOPE Act was signed into law in 2013, allowing HIV D+/R+ transplantation under research protocols in the United States (42). These transplants are currently regulated by the HOPE Act Safeguards and Research Guidelines, which were published in 2015 (43).

HIV D+/R+ TRANSPLANTATION

Kidney

The first four HIV D+/R+ kidney transplants were conducted in South Africa and reported in 2010 (32). The recipients had well-controlled HIV on ART, and the kidneys were from two deceased donors not on ART with normal renal biopsies. Recipients received induction immunosuppression with ATG induction and maintenance immunosuppression with tacrolimus or sirolimus, mycophenolate mofetil, and prednisone. At 1 year post transplant, there was no graft rejection and 100% graft survival (32).

In 2015, Muller et al. detailed 3 to 5 years of follow-up of 27 HIV D+/R+ kidney transplant recipients (33). Survival rates were 84% at 1 year and 74% at 5 years. Graft survival rates were 93% at 1 year and 84% at 5 years (Table 2). These outcomes were comparable to HIV D−/R− transplants conducted at the same time frame at the same center: patient survival was 91% at 1 year and 85% at 5 years, and graft survival rates were 88% at 1 year and 75% at 5 years (33). Additionally, there were relatively few opportunistic infections including extrapulmonary tuberculosis and pulmonary aspergillosis. Three patients died from infectious complications, including a case of pancreatitis, urinary tract infection complicated by sepsis, and pulmonary aspergillosis. As with HIV D−/R+ studies, rejection occurred at an increased rate, with acute rejection episodes in five (19%) recipients. Overall, the trial presented the potential for highly successful HIV D+/R+ transplantations and demonstrated encouraging outcomes (33).

After passage of the HOPE Act, the first HIV D+/R+ kidney transplant study in the United States was conducted at 14 transplant centers from March 2016 to July 2019 (29). There were 25 HIV D+/R+ kidney transplants compared to 50 HIV D−/R+ kidney transplants. There were no deaths and no differences in graft survival rates at 1 year (91% D+ vs 92% D−, $P = 0.9$) (Table 2). Encouragingly, there were no differences in HIV breakthrough (4% D+ vs 6% D−, $P > 0.99$), despite 70% of the US donors being ART experienced (in comparison to South Africa, where 92% of donors were ART naïve) (29, 45). Additionally, the rates of infections requiring hospitalization (28% D+ vs 26% D−, $P = 0.85$) and opportunistic infections (16% D+ vs 12% D−, $P = 0.72$) were similar (29).

TABLE 2 Summary of HIV D+/R+ transplant studies

Author	Center	Transplant recipients (*n*)	1-year survival rate (%)	1-year graft survival rate (%)	1-year rejection rate (%)	HIV breakthrough (%)	Recipients with an opportunistic infection (*n*, %)	Opportunistic infection episodes (*n*)
Muller et al. (32, 33)	University of Cape Town	Kidney D+/R+ (27)	84	93	8	0	2, 7%	Extrapulmonary tuberculosis (1), pulmonary aspergillosis (1)
		Kidney D−/R−	91	88				
Durand et al. (29)	Multicenter	Kidney D+/R+ (25)	100	91	50	4	4, 16%	Cytomegalovirus (3), *Bartonella* infection of liver (1)
		Kidney D−/R+ (50)	100 ($P > 0.99$)	92 ($P = 0.9$)	29 ($P = 0.13$)	6 ($P > 0.99$)	6, 12% ($P > 0.72$)	Cytomegalovirus (3), esophageal candidiasis (2), *Candida glabrata* fungemia (1)
Durand et al. (44)	Multicenter	Liver D+/R+ (24)	83.3	96	17	8	6, 25%	Cytomegalovirus (7), Kaposi's sarcoma (3), pulmonary aspergillosis (1)
		Liver D−/R+ (21)	100 ($P = 0.04$)	100 ($P > 0.99$)	19 ($P > 0.99$)	10 ($P > 0.99$)	3, 14% ($P = 0.47$)	Cytomegalovirus (2), *Candida* esophagitis (1)

Rejection rates at 1 year post transplant trended higher in HIV D+/R+ recipients (50%) compared to HIV D−/R+ recipients (29%) (hazard ratio [HR]: 1.83; 95% CI, 0.84–3.95; $P = 0.13$). Despite the possibility of increased rejection rates, the overall transplant and HIV outcomes were excellent, providing further support for the practice of HIV D+/R+ transplantation (29).

Liver

The first HIV D+/R+ liver transplant reported in the literature was performed in October 2015 in Switzerland (46). Both donor and recipient were on ART with suppressed HIV RNA and CD4+ T cell counts between 300 and 400 cells/mL. Both patients had a history of ART-resistant viruses, so the recipient's ART regimen was modified based on the donor's HIV genotype, and at 5 months post transplant, HIV RNA remained suppressed (46).

Another case report from the United Kingdom of an HIV D+/R+ liver transplant was reported in 2016 from a donor with HCV co-infection (47). In this case, the donor was not on ART and the recipient had ART held briefly at transplant. On day 2 post-transplant, HIV was detected in the recipient, and phenotypic analysis confirmed that this HIV was donor in origin. With restarting ART in the recipient, HIV was suppressed within a few weeks through the first 5 years post transplant. HCV treatment was administered on week 15 post-transplant, and a sustained virologic response was achieved (47).

Under the HOPE Act, the first pilot study of HIV D+/R+ liver transplants in the United States occurred from March 2016 to July 2019 and included 45 liver transplants, including eight simultaneous liver/kidney (SLK) transplants (44). Of these, 24 were HIV D+/R+, and 21 were D−/R+. The median follow-up time was 23 months (interquartile range [IQR]: 15.3–32.4), during which time there were eight deaths: six in the D+ group (1 SLK) and two in the D− group (0 SLK). One of the deaths in the D+ cohort, a fatal HHV8-associated lymphoma, was deemed possibly related to donor HIV status, but the others were deemed unrelated. Overall, in weighted population analysis, 1-year survival was 83.3% for D+ vs 100.0% for D− recipients, which were improved over historical D−/R+ cohorts (Table 2) (9, 12, 44). The reason for increased mortality in the D+ recipients is not fully understood and may be due to a difference in cancer incidence—longer term follow-up studies are needed. There were similar rates of one-year graft survival (96% for D+ vs 100% for D−), serious adverse events (68% vs 80%), infections requiring hospitalization (36% vs 25%), and opportunistic infections (25% vs 14%) (all $P > 0.05$) (44). Rejection was also similar between groups (17% D+ vs 19% D−), which was re-assuring, particularly given the trend toward higher rejection observed in the HIV D+/R+ kidney pilot trial (29, 44). HIV breakthrough occurred in two D+ and two D− recipients due to ART nonadherence, and suppression was reestablished with medications (44). One D+ recipient experienced high-level viremia after ART interruption, but there was no evidence of donor HIV superinfection, as only recipient viral sequences were detected in a phylogenetic analysis (44, 48).

Heart

The first HIV D+/R+ combined cardiac/renal transplant was published in March 2023 in a recipient with ischemic cardiomyopathy and focal segmental glomerulosclerosis (49). The recipient received both a heart and a kidney from a donor with a recent diagnosis of HIV, on ART with suppressed HIV RNA. Basiliximab was used for induction immunosuppression, and maintenance immunosuppression included tacrolimus, mycophenolate, and steroids. There were several infectious complications post transplant but no opportunistic infections, and the recipient's HIV RNA remained suppressed with stabilization of CD4 T cells counts after resolution of sepsis. The recipient was discharged home on post-transplant day 69 and doing well in clinic at post-transplant day 90 with no evidence of rejection and with normal biventricular function on echocardiography. While it remains to be seen whether opportunistic infections or rejection rates are increased with hearts from donors with HIV, neither were observed in this case study (49).

Risk of superinfection

Despite an initial concern for HIV superinfection, there have been no clinical complications from donor-derived HIV breakthrough reported in the South African or US HIV D+/R+ kidney and liver transplantation studies (29, 32, 33, 44). Additionally, an in-depth phylogenetic analysis of 14 HIV D+/R+ kidney transplant recipients and 8 HIV D+/R+ liver transplant recipients using a next-generation sequencing did not detect any HIV superinfection (48). As referenced earlier, this cohort included an HIV D+/R+ liver transplant recipient who experienced high-level HIV breakthrough (HIV RNA 2,080,000 copies/mL after ART interruption) who was found to have only recipient HIV viral sequences (44, 48). This suggests that if donor HIV virus was still present, it was not reactivated during temporary cessation of ART (48). With no clear evidence of clinically significant superinfection to date, it appears this may not be a major concern in HIV D+/R+ transplantation.

Living donation

Along with deceased donors, the HOPE Act allows for living organ donation. Studies suggest that PLWH have high willingness to donate. In a study at an urban academic HIV clinic in Baltimore, MD, 114 PLWH were surveyed about organ donation, and 79.8% were willing to be deceased donors and 62.3% were willing to be living donors. Of the respondents, only 21.1% were registered donors, compared to 55% of the US population (50).

Following this study, 20 respondents who stated they were "definitely" willing to be a living donor were contacted for a more in-depth interview to understand their perspectives (51). Several HIV-specific motivations, benefits, and concerns related to living organ donation were identified. Potential benefits cited were overcoming HIV-related stigma, conferring a sense of normalcy for PLWH, and contributing to HIV research. Concerns about living donation included a risk of lengthened recovery due to immune system issues, future organ failure due to HIV, and transmission of a different strain of HIV during transplant (51).

In practice, there have been three international case reports of HIV D+/R+ living kidney donation internationally (52–54) and most recently three cases in the United States under the HOPE Act (55). Internationally, there was a case of a successful HIV D+/R+ kidney transplant from a wife to her husband in Tel Aviv in 2012 (52). The couple was followed up for 7 years post transplant, during which time the donor exhibited stable kidney function and HIV status, with her only complication being progression of hypertension (52). The other two international cases occurred in Germany and Italy and similarly involved directed donations between spouses, with no serious complications related to nephrectomy reported (53, 54). Among the three donors under the HOPE Act, outcomes at 2–4 years were good, providing proof of concept for donation in PLWH (55). While one of these donors donated to a spouse, the other two were non-directed donors who shared that part of their motivation was to reduce HIV-related stigma and overcome systemic barriers to donation for PLWH (55). As HIV D+/R+ donation and transplantation knowledge and expertise expand over the coming years, living donation from PLWH may prove to be a vital resource of organs for PLWH who are on the organ waitlist.

Challenges in practice and implementation

One challenge to implementation is identifying and utilizing organs from donors with HIV. Several studies have used retrospective data to estimate the potential numbers of donors with HIV, with estimates ranging from 356 to 600 annually from donors with HIV (41, 56, 57). However, between March 2016 and March 2020, there were 92 donors who donated 177 organs (131 kidneys and 46 livers), an average of 23 donors per year (58). The disparity between projected donor numbers and those identified in practice is likely multifactorial and represents systemic issues, as donation and transplantation are a complex field of practice, with multiple stakeholders involved. The increase in

the number of D+ donors from 9 donors in 2016 to 36 donors in 2019 is encouraging, although clearly, there is more progress to be made (58).

As discussed, studies show that although PLWH are willing to donate, the proportion that are registered is low. A recent study by Haidar et al. demonstrated that education about donation and providing opportunities to register for PLWH can increase donor registration rates.(59) Between July 2018 and April 2019, information and registration cards were given to 1,528 PLWH at their HIV clinic and increased the registration rates from 11.4% to 46.7%, which was comparable to the local Department of Motor Vehicle-registered donor rates of 48.9% in the region (59).

Another theoretical challenge to implementation is that transplant candidates with HIV must be willing to receive an organ from a donor with HIV. In practice, this does not seem to be much of a barrier. In 2020, a survey study of 116 transplant candidates with HIV at nine US transplant centers explored this issue (60). Among interviewees, the majority were willing to accept organs from living donors with HIV (87%) and deceased donors with HIV (84%). One concern was HIV superinfection, which was shared by around 30% of interviewees. Even within those respondents, however, 71% were willing to accept an organ from a donor with HIV (60). From these responses, it appears that the majority of PLWH who are transplant candidates are willing to receive organs from donors with HIV.

Organ procurement organizations (OPOs) play an important role in the transplant process as the local organizations responsible for evaluating donor referrals and recovering and offering organs in partnership with UNOS. Thus, barriers at OPOs may share partial responsibility for the low numbers of HIV D+ with organs used for transplants to date. In a study of in-depth interviews with 20 OPO staff members about HIV D+/R+ transplantation in 2021, it was found that the staff members had high awareness about HOPE but that several barriers remained, including (i) challenges obtaining authorization for donation, (ii) fear of potentially disclosing HIV status to next of kin, and (iii) fear of HIV infection among staff members engaged in organ recovery (61). Furthermore, a related study to explore OPO staff decision making regarding donors with HIV revealed that number of potential organs recovered per donor was a key factor; since HIV D+/R+ transplantation is largely limited to kidney and liver at this time, this may decrease incentives for OPOs to pursue these donors (62). Similarly, some OPOs derive a large portion of their revenue from tissue recovery, and the lack of potential for tissue recovery at transplant centers may explain the preference for donors without HIV (61, 62).

Finally, there may be barriers to participation by the transplant centers. Indeed, as of 2022, only 35 transplant centers, which is roughly 10% of transplant centers across the United States, have a regulatory variance to perform these transplants (63). As of 2022, HIV D+/R+ transplantation must occur under research protocols, which required additional administrative and staff time, effort, and cost (63). In addition, current federal HOPE Act research regulations include program eligibility restrictions related to center-level experience, which limits how many centers can perform these transplants (63, 64). With few centers participating, this may further decrease OPO incentives to identify donors. Based on the favorable results of the first HOPE Act kidney and liver transplant trials (43), a federal advisory committee made a recommendation to the Secretary of Health and Human Services to (i) remove the research restriction for HIV D+/R+ kidney and liver transplants outside of research and (ii) to revise research restrictions for other organ types which may increase the scope of practice and identification of donors (65).

Regulations limiting practice

Despite the HOPE Act being passed in 2013, a number of legal barriers to HIV D+/R+ transplantation remain. Laws regarding donors with HIV differ by state, with some states enforcing rules that limit the practice and others offering no guidance (64). Certain states also have explicit HOPE Act exceptions for organ and tissue use from PLWH.

These differing state laws and ambiguous definitions might lead to legal confusion for medical professionals both within the OPOs and transplant centers and limit HIV D+/R+ transplants (64).

Another regulation is the requirement by the HOPE Act Safeguards and Research Criteria that an independent recipient advocate (HIRA) work directly with HIV D+/R+ recipients (66). The role of the HIRA was created to advocate for potential recipients and ensure they understand the risks, benefits, and voluntariness of accepting an organ from a donor with HIV. However, some HIRAs have expressed concern that they are adding yet another hurdle for potential recipients that are already well educated regarding HIV D+/R+ transplantation (66). Some HIRAs also propose that the session may inadvertently increase participants' fear in the research (66). Their thought is that the encounter may imply the study's risks are so large that the participant must provide a second consent for the procedure (66). This area indicates further investigation, particularly with regards to impressions of potential recipients (66).

As mentioned previously, current HOPE Act regulations stipulate that HIV D+/R+ transplants can only be performed as part of a research study, with an OPTN variance, and if the transplant team meets the combined experience of the transplant physician and HIV physician of five organ-specific cases over 4 years (43). A recent analysis showed that the experience criteria significantly limited transplant center eligibility, in particular for cardiothoracic programs, as only one cardiothoracic program currently meets criteria (67). As safety data accrue and regulations are appropriately modified, broader engagement and larger numbers of donors and transplants may ensue (43, 65, 67).

CONCLUSIONS

Solid organ transplantation has been shown to be of great therapeutic benefit for people living with HIV who experience end-stage organ disease or organ failure. Current literature shows the expansion of this practice to include organs from donors with HIV is effective and may be one way to mitigate the organ shortage and waitlist mortality. Current evidence supports kidney and liver transplantation from donors with HIV to recipients with HIV becoming clinical practice, with future studies necessary to determine long-term outcomes and reduce complications. Finally, recognition of the challenges associated with this practice and solutions are needed to fully realize the maximum benefit for people living with HIV and all transplant candidates on the waitlist.

AUTHOR AFFILIATION

[1]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

AUTHOR ORCIDs

K. Storm http://orcid.org/0000-0001-8911-2364
C. M. Durand http://orcid.org/0000-0003-2605-9257

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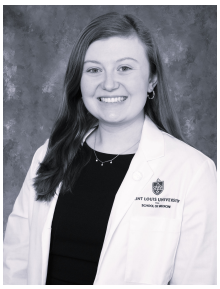

K. Storm is a medical student at Saint Louis University School of Medicine. Prior to medical school, she earned her B.S. in Biomedical Engineering at Johns Hopkins University (JHU), with a focus in immunoengineering. Post-graduation, Kaitlyn took on the role of Research Coordinator in the JHU Transplant Research Center (TRC), where she worked on the HOPE in Action and COVID Protection After Transplant (CPAT) clinical trials under direction of Dr. Christine Durand.

C. M. Durand, M.D., is an Associate Professor of Medicine and Oncology at Johns Hopkins University (JHU). Her clinical and research expertise include HIV and hepatitis in individuals who require transplant or cancer therapies. She is leading the first clinical trials of transplantation from donors with HIV to recipients with HIV under the HIV Organ Policy Equity (HOPE) Act in the United States. Finally, she directs the JHU Transplant Research Center (TRC), a multidisciplinary research group that aims to mitigate the organ shortage, improve outcomes after transplantation, and train leaders in the field.