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HIV PATHOGENESIS AND TREATMENT (AL LANDAY AND NS UTAY, SECTION EDITORS)

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Solid Organ Transplantation in HIV-Infected Recipients: History, Progress, and Frontiers

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Abstract

Purpose of Review End-stage organ disease prevalence is increasing among HIV-infected (HIV+) individuals. Trial and registry data confirm that solid organ transplantation (SOT) is efficacious in this population. Optimizing access to transplant and decreasing complications represent active frontiers.

Recent Findings HIV+ recipients historically experienced 2–4-fold higher rejection. Integrase strand transferase inhibitors (INSTIs) minimize drug interactions and may reduce rejection along with lymphodepleting induction immunosuppression. Hepatitis C virus (HCV) coinfection has been associated with inferior outcomes, yet direct-acting antivirals (DAAs) may mitigate this. Experience in South Africa and the US HIV Organ Policy Equity (HOPE) Act support HIV+ donor to HIV+ recipient (HIV D+/R+) transplantation.

Summary SOT is the optimal treatment for end-stage organ disease in HIV+ individuals. Recent advances include use of INSTIs and DAAs in transplant recipients; however, strategies to improve access to transplant are needed. HIV D+/R+ transplantation is under investigation and may improve access and provide insights for HIV cure and pathogenesis research.

Keywords HIV · Transplantation · Kidney · Liver · Hepatitis C · Rejection · Immunosuppression

Introduction

Nearly 37 million persons worldwide, including 1.1 million in the USA, are HIV-infected (HIV+) [1, 2]. Due to effective antiretroviral therapy (ART), life expectancy for HIV+ individuals has improved dramatically [3, 4]. End-stage organ disease is now a major contributor to morbidity and mortality, while AIDS-related deaths have declined [5]. For organ failure, solid organ transplantation (SOT) is the treatment of choice with a clear survival benefit in the general population [6]. Although initially contraindicated in HIV+ individuals, multicenter trials in the USA and Europe have established SOT as safe and efficacious for HIV+ patients, yet access to transplant is inadequate due to organ shortage. With pioneering efforts in South Africa and now in the USA via the HIV Organ Policy Equity (HOPE) Act, investigators are studying HIV+ donor to HIV+ recipient (HIV D+/R+) transplantation as a strategy to expand the donor pool.

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Burden of End-Stage Organ Disease

HIV+ individuals comprise 0.5–1.5% of the end-stage renal disease (ESRD) population across varied settings [7] with a higher incidence than in HIV-uninfected (HIV−) patients [8]. HIV and ART are unique contributors, in addition to traditional risk factors such as diabetes and hypertension. Moreover, those of African ancestry endure increased rates of glomerulopathy, including HIV-associated nephropathy (HIVAN), mediated in part by APOL1 gene polymorphisms selected to protect against the parasite *Trypanasoma brucei rhodesiense* [9, 10]. While the incidence of ESRD has decreased, prevalence continues to rise. Recent data indicate 2 to 4-fold higher ESRD risk for those infected with HIV [11–13]. Mortality on dialysis is higher for HIV+ individuals [14] compared with HIV-uninfected controls [15] due in part to longer times on dialysis and inadequate access to transplant [16]. One study showed up to 8.7% of HIV+ ESRD patients died per year, nearly twice that of HIV− controls. Transplantation reduces this mortality by nearly 80% [17••].

End-stage liver disease (ESLD) consistently accounts for about 10% of deaths among HIV+ adults [5, 18, 19]. Multiple factors contribute, including coinfection with hepatitis B virus (HBV) and hepatitis C virus (HCV) which occurs in 10% and > 30% of the HIV+ population, respectively [20], as well as drug-induced hepatopathy and alcoholic and non-alcoholic fatty liver disease. HIV+ patients with decompensated cirrhosis, including those awaiting liver transplant (LT), have higher mortality than HIV− patients [21]. This holds true when comparing survival between HIV+/HCV+ coinfected and HCV+ monoinfected patients [22]; a recent intention-to-treat analysis noted 7-fold greater mortality on the transplant waitlist (35% vs 5%) between these groups [23]. In the USA, HIV+ persons with ESLD face limited access to transplantation, and prospective studies demonstrate poor 1-year survival on the waitlist, > 50% in one series [24, 25].

Cardiovascular disease (CVD) ranging from HIV-associated cardiomyopathies to pulmonary hypertension and accelerated coronary artery disease contribute to thoracic organ failure syndromes in HIV+ patients with poor prognoses [26, 27]. ART improves aspects of these conditions, e.g., reducing systolic heart failure, but some antiretrovirals, particularly protease inhibitors (PIs), contribute to metabolic risk [28]. CVD and heart failure incidences are increasing [29] and sudden cardiac death [30] remains common. Transplantation is an emerging treatment for HIV+ individuals with end-stage heart and lung disease, though comparative and outcome data remain limited.

Early HIV SOT Experience and Attitudes

In the 1980s, transplantation among HIV+ adults was principally unintentional with poor outcomes. Six-month mortality for kidney and liver recipients approached 50% [31] and more than 30% of recipients died from AIDS [32]. Concurrently, in 1988, US legal code was amended to prohibit transplantation of tissues from HIV+ donors. From 1987 to 1997, only 32 HIV+ kidney transplants were reported in the USA, with poor patient and graft survival [33]. A survey of US transplant centers in 1997 indicated nearly 90% of providers would not refer an HIV+ individual for kidney transplant, citing concern for infection, death, and inappropriate allocation of a scarce resource [34]. Even with effective ART, a subsequent survey in 2003 revealed only 33% support among transplant surgeons for HIV+ SOT, compared with 70% support for HBV+ and HCV+ candidates [35].

HIV SOT in the Era of ART

With the impressive reductions in opportunistic infections (OIs) and mortality afforded by ART in the late 1990s, investigators received NIH funding for the HIV Transplant Recipient (HIVTR) Study. This landmark study was conducted from 2003 to 2009 at 19 US centers, enrolled 150 kidney and 125 liver recipients, and demonstrated the safety and feasibility of HIV-uninfected donor to HIV+ recipient (HIV D −/R+) transplant.

HIVTR inclusion criteria, which continue to guide clinical care, were designed to reduce OI risk. For kidney candidates, CD4+ T cells ≥ 200/ml^3 with suppressed HIV RNA on ART was required. For liver candidates, CD4+ T cells ≥ 100/ml^3, a lower threshold to account for sequestration due to hypersplenism was required. Viremia was also permitted if ART was hepatotoxic, assuming suppression was expected post-transplant (Fig. 1). Exclusions for prior OIs included chronic cryptosporidiosis, visceral Kaposi's sarcoma, and progressive multifocal leukoencephalopathy. The protocol permitted any induction immunosuppression, including anti-thymocyte globulin (ATG), a lymphocyte-depleting agent. Additional OI prophylaxis included lifelong Pneumocystis prophylaxis and secondary prophylaxis for prior OIs 1 month post-transplant or post-rejection; if cytopenia occurred during immunosuppression, standard CD4-directed OI prophylaxis was instituted.

Preliminary HIV D−/R+ Outcomes

An interim report of the HIVTR demonstrated 94% 3-year survival for 18 kidney recipients, but 64% 3-year survival among 11 liver recipients [36]. Mortality in liver recipients was primarily due to HCV or hepatocellular carcinoma recurrence. Rejection occurred in 67% of kidney recipients, more common than reported in HIV− cohorts [36]. Similarly, 39% of 89 HIV+/HCV+ liver recipients in a later HIVTR analysis experienced rejection [37]. In both groups, HIV-specific complications such as sustained HIV viremia or OIs were rare.

These early findings were reassuring and HIVTR contributed to a significant increase in HIV+ transplants performed nationally: kidney transplants rose from 43 between 1997 and 2001 to 208 between 2001 and 2006 [38]. The results also revealed the following challenges: (i) increased rejection, (ii) drug-drug interactions, and (iii) inferior outcomes for HIV+/HCV+ recipients.

Immunosuppression and Allograft Rejection

The final HIVTR analysis ($n = 150$ kidney recipients, median follow-up 1.7 years) confirmed excellent 1- and 3-year graft survival, 90% and 74%, respectively, similar to survival in older HIV− adults in the national registry. Rejection was

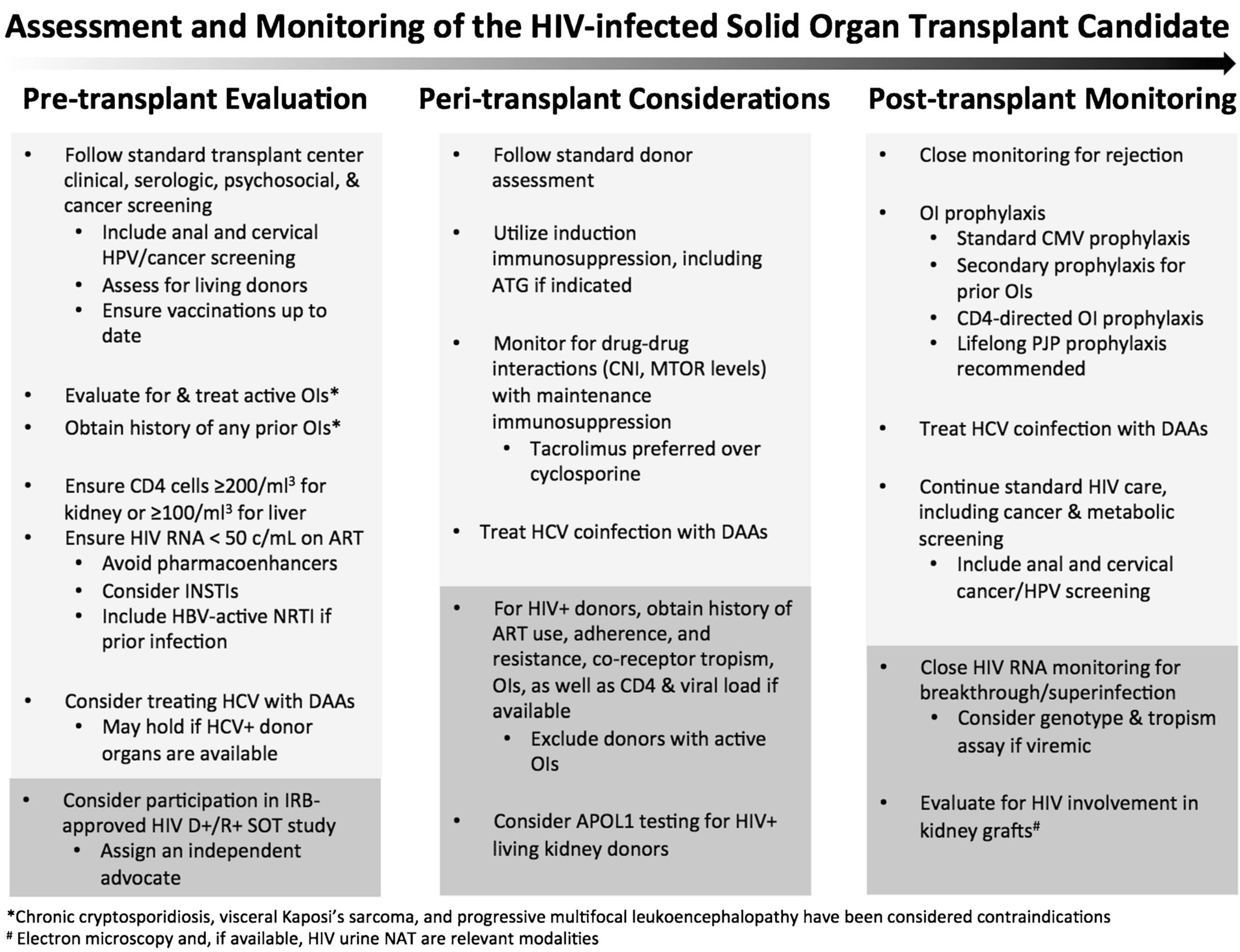

Fig. 1 Assessment and monitoring of the HIV-infected solid organ transplant candidate
This figure presents an abridged approach to pre-transplant risk stratification and management of HIV+ SOT patients, including immunosuppression and prophylaxis considerations. Light gray boxes denote standard HIV+ SOT practices whereas the darker gray boxes pertain to HIV D+/R+ SOT and other investigational protocols.
APOL1 apolipoprotein L1, ATG anti-thymocyte globulin, c/ml copies/ml, CMV cytomegalovirus, CNI calcineurin inhibitor, D+/R+ donor and recipient positive, DAA direct-acting antiviral, HBV hepatitis B virus, HCV hepatitis C virus, HPV human papilloma virus, INSTI integrase strand transfer inhibitor, MTOR mammalian target of rapamycin, NAT nucleic acid test, OI opportunistic infection, PJP *Pneumocystis jirovecii*, SOT solid organ transplant

2.5-fold higher than in the HIV− population, occurring in 31% and 41% by 1 and 3 years, respectively. This was primarily T cell mediated and associated with 2.8-fold increased risk of graft loss [39]. Other studies in the USA and Europe observed kidney rejection in 20–40% of recipients [16, 40, 41] (Table 1). Liver rejection varied from 10 to 50% [36, 53], similar to that of HIV− recipients in some series [51], yet consistently higher for HIV+/HCV+ recipients [37].

Proposed rationale for increased rejection includes host and drug-related factors. Immune activation is elevated in HIV [54], including an expanded, possibly alloreactive memory T cell population. Precise mechanisms and significance remain unclear, as elevated levels of CD3+HLA-DR+ cells in HIV+ kidney recipients have not been definitively linked to rejection [55]. Selection of induction immunosuppression remains controversial, particularly the use of ATG, which is recommended for kidney recipients at high risk of rejection [56], yet leads to prolonged CD4 and CD8 lymphopenias regardless of HIV status [57, 58]. In the HIVTR, a paradoxical association with ATG induction and rejection was observed, accompanied by a 2-fold increase in infections requiring hospitalization and a 3.5-fold increase (CI 1.3, 9.1; $p < 0.01$) in mortality [49•]. In contrast, a larger registry study from 2000 to 2014 of 189 HIV+ kidney recipients who received ATG reported a 40% reduction in acute rejection and 50% higher graft survival compared with those who received no induction [45••]. This study also showed a low incidence of OIs (6 total non-CMV, non-candida esophagitis events among 308 SOT recipients with available infection data). Drug interactions between PIs and maintenance immunosuppression have also been implicated in rejection [59]. Among the calcineurin inhibitors (CNIs), tacrolimus appears to be more effective than

Table 1 HIV+ SOT representative series: infection, rejection, and survival rates. This table details important HIV+ transplantation studies, some of which have overlapping study populations, including several analyses of the HIVTR and the US national Scientific Registry of Transplant Recipients. Liver and kidney transplant series are listed separately.

Kidney Transplantation Trial (ref) Year, country	Study period	Study design	Organ (N)	HCV+ %	ATG induction %	Rejection % (period)	Severe infection[1] %	Bacteremia %	Invasive fungal infection Process (N)	Viral OI[2] Process (N)	Other HIV-associated OI[3] Process (N)	Patient survival 1, 3, 5-Year (%)
Stock et al. [39] 2010, USA	2003–2009	Prospective Multicenter (HIVTR)	Kidney (150)	19	32	31 (1 yr) 41 (3 yrs)	38	7	0	BKV (5)	Candida esoph (1) KS (2) Cryptosporidiosis (1)	95, 88, ND
Locke et al. [42] 2015, USA	2002–2011	Registry	Kidney (510)	24	28	18 (1 yr)	ND	ND	ND	ND	ND	95, 88, 84
Gathogo et al. [43] 2013, UK	2005–2011	Retrospective Multicenter	Kidney (35)	3	0	44 (1 yr)[a] 47 (1 yr)	54	ND	0	CMV (13) BKV (5) HSV (1)	KS (1) Candida esoph (1)	91, 91, ND
Suarez et al. [44] 2016, USA	2006–2013	Retrospective Single-center	Kidney (35) Kidney-Pancreas (2) Liver-Kidney (1)	13	100	15 (1 yr) 27 (3 yrs)	32	13	Candidemia (1) Aspergillosis (3)	CMV (2) BKV (2)	KS (1) Candida esoph (1)	87, 91, ND
Kucirka et al. [45••] 2014, USA	2000–2014	Registry	Kidney (830)[b]	22	44	ND	15	ND	Coccidiomycosis (1)	CMV (22)	Candida esoph (8) PJP (3) TB (1) KS (1)	95, ND, ND[c]
Muller et al. [46••] 2015, South Africa	2008–2014	Prospective Single-center	Kidney (27)	0	100	8 (1 yr)[a] 22 (3 yrs)[a]	33	7	Aspergillosis (1)	ND	TB (1)	84, 84, 74
Cristelli et al. [47] 2017, Brazil/Spain	2005–2015	Retrospective Multicenter	Kidney (54)	11	31	22 (1 yr)[a]	ND	ND	0	CMV (8) VZV (6)	CE (5)	94, 94, ND

Table 1 (continued)

Liver Transplantation Trial (ref)	Study period	Study design	Organ	HCV+	Rejection	Severe infection[1]	Bacteremia	Invasive fungal infection	Viral OI[2]	Other HIV-associated OI[3]	Patient survival
Year, country			(*N*)	%	% (follow-up)	%	%	Process (*N*)	Process (*N*)	Process (N)	1, 3, 5-Year (%)
Moreno et al. [48] 2012, Spain	2002–2009	Prospective Multicenter	Liver (84)	100	38 (median 2.6 yrs)	43	10	Candidemia (2) Aspergillosis (1) Zygomycosis (2)	CMV (21) HSV (13) VZV (1)	PJP (2) TB (2) Candida esoph (1)	85, 48, 34[c]
Roland et al. [49•] 2016, USA	2003–2010	Prospective Multicenter (HIVTR)	Liver (116) Liver-Kidney (9)	71	ND	55	11	ND	ND	Candida esoph (4) KS (2) Candida bronchi (1) PJP (1)	ND, ND, ND
Terrault et al. [37] 2012, USA	2003–2010	Prospective Multicenter (HIVTR)	Liver (81) Liver-Kidney (8)	100	39 (3yrs)	ND	ND	ND	ND	Candida esoph (3) KS (1) Candida bronchi (1) PJP (1)	76, 60, ND
Di Benedetto et al. [50••] 2011, Italy	2003–2010	Retrospective Single-center	Liver (23)	83	35 (median 2 yrs)	ND	ND	Aspergillosis (1)	EBV (13) CMV (4)	KS (1)	57, 50, 50[c]
Locke et al. [51] 2016, USA	2002–2011	Registry	Liver (180)	65	16 (median 1.8 yrs)	ND	ND	ND	ND	ND	77, 62, 56
Teicher et al. [52] 2015, France	1990–2012	Retrospective Single-center	Liver (109)	79	41 (median 3.8yrs)	37[d]	26	Candidemia (2) Aspergillosis (3)	CMV (5)	Candida esoph (2) NTM (1) TB (1)	83, 77, 61

[1] Severe infection was variably defined by study but most often refers to non-opportunistic infections requiring hospitalization. See specific studies for details

[2] Any non-HHV8 herpesvirus infection including all CMV viremia (any disease severity), as well as BK viremia or nephropathy

[3] Adapted from standard CDC criteria: candida infection of esophagus or airways, pneumocystosis, cryptosporidiosis, tuberculosis, non-tuberculous mycobacteria, progressive multifocal leukoencephalopathy, toxoplasmosis, and Kaposi's sarcoma

[a] Biopsy-proven rejection

[b] Includes 308 patients with available infection data. CMV rates calculated from provided graphs

[c] Survival calculated from Kaplan-Meier curves

[d] Reported any infection

BKV BK virus, *Candida bronchi* candidiasis of the bronchus, *Candida esoph* candida esophagitis, *CMV* cytomegalovirus, *ND* no data, *EBV* Epstein-Barr virus, *HSV* herpes simplex virus, *KS* Kaposi's sarcoma, *NTM* non-tuberculous mycobacteria, *PJP Pneumocystis jirovecii*, *TB* tuberculosis, *VZV* varicella zoster virus cyclosporine, demonstrating a protective effect in HIVTR as well as in a UK series of 125 HIV+ kidney recipients where use was associated with 73% lower 1-year rejection and less herpesvirus reactivation [60].

Role of HIV in Graft Function

Canaud et al. (2014) introduced a novel potential mechanism of HIV-related kidney injury post-transplant by identifying HIV in recipient biopsies despite undetectable HIV plasma RNA [61]. In the single-center French series, electron microscopy identified HIV infection of podocytes in 5/19 recipients, associated with nephrotic-range proteinuria and graft dysfunction reminiscent of HIVAN. In 8/19 recipients, viral infiltration of tubular cells was observed, with features of subclinical acute cellular rejection and minimal graft dysfunction. This small cohort suggests that HIV infiltration of the kidney allograft may contribute to—or perhaps be mistaken for—rejection [62]. Notably, HIVTR documented HIVAN in only 3/150 recipients [49•]. More recently, in the HIV D+/R+ kidney experience in South Africa, pathologic signs of HIVAN were found in 3/43 patients with two late graft losses [63], while 6/43 had non-specific cellular infiltrates on biopsy. The significance of these findings and relation to rejection remain unclear.

Pharmacologic Considerations and ART Selection

HIV+ SOT involves complicated drug-drug interactions, side effects, and toxicity, most relevant with interactions between pharmacoenhancers, such as the PI ritonavir or cobicistat, and calcineurin inhibitors (CNIs). Pharmacoenhancers inhibit cytochrome P-450 3A4 markedly raising CNI exposure, necessitating > 4-fold dose reductions and large increases in dosing intervals [59, 64, 65]. Sirolimus, a mammalian target of rapamycin (MTOR) inhibitor, is less studied, but is also processed via both the cytochrome and P-glycoprotein systems and may be increased by PIs [66]. Both single-center and national studies have reported an association between PI use and graft loss (1.2–1.8-fold) and mortality (1.8–12.1-fold) among kidney transplant patients [67, 68]. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) display varying CYP effects; efavirenz and nevirapine are potent inducers and lower CNI/MTOR inhibitor levels, while etravirine and rilpivirine exhibit little effect. Nucleoside reverse transcriptase inhibitors (NRTIs) do not display major CYP interactions [64], and tenofovir and lamivudine provide benefit for HBV coinfection and HBV+ donors.

Integrase strand transfer inhibitors (INSTIs) have simplified ART for HIV+ recipients, given excellent tolerability and minimal drug-interactions. Multiple series, mostly with raltegravir, have demonstrated safety with CNIs [69, 70]. Dolutegravir is predicted to be safe, with successful case reports, though it is a P450 substrate and lower levels might occur post-transplant [71]. Additionally, dolutegravir impairs creatinine excretion leading to artifactual increase in serum values that may be mistaken for renal pathology, necessitating transplant provider education [72, 73]. Limited data demonstrate few interactions for the CCR5 inhibitor maraviroc [74]. Few interactions are anticipated with new agents such as doravirine and bictegravir, though data are sparse.

HIV+/HCV+ Coinfection

In HIV+/HCV+ patients, HCV follows a more virulent course with increased risk of fibrosis, decompensated liver disease, and death both in pre- and post-transplant [22, 24, 75, 76]. In contrast, HIV+/HBV+ liver recipients have excellent survival (> 80% at 5 years), without significant hepatitis recurrence [77]. Multiple mechanisms for inferior outcomes in HIV+/HCV+ coinfection are proposed, including immune dysregulation from HIV and increased microbial gut translocation [78, 79]. Early transplant experience showed that HCV recurrence in HIV+ liver recipients was common and morbid, despite HIV control [53, 80]. Both HIVTR and a Spanish series compared outcomes between HIV+/HCV+ and HCV+ liver recipients, finding coinfection was associated with a 2.2-fold increase in death [37, 81]. Rejection was 1.5-fold higher in the coinfected groups (38–39% vs 20–24%) with a trend toward significance. Registry studies confirmed these observations, with 5-year survival of 50–60% for HIV+/HCV+ liver recipients, without improvement over time, despite improvement for HIV monoinfected recipients [51, 82•, 83]. Lower patient and graft survival were related to HCV, including fibrosing cholestatic hepatitis (FCH), seen in 10–20% with a dismal prognosis (9/11 patients dying in one series) [84]. Sustained virologic response (SVR) with interferon and ribavirin was poor (10–20%) and incurred significant toxicity including rejection [85, 86].

Direct-acting antivirals (DAAs) have revolutionized treatment of HCV among SOT recipients, including those with HIV coinfection. The multicenter European CUPILT group reported excellent results among HCV+ liver and liver-kidney recipients, with SVR rates of 93–98% using diverse regimens [87, 88]. Smaller US and European studies demonstrated SVR rates near 90% with early sofosbuvir (SOF)-based regimens among HIV+/HCV+ recipients, including cure of 3/4 patients with FCH, without treatment-associated complications [89, 90]. Another HIV+/HCV+ CULPIT study of 29 patients (multiple genotypes, 35% advanced fibrosis), reported 97% SVR including 100% in 6 FCH patients [91]. HIV remained suppressed, CD4 increased, and there were no rejection episodes. A multicenter Spanish trial of 47 HIV+/HCV+ liver recipients, matched 1:3 to HCV+ recipients, treated with various DAA regimens reported no difference in SVR (94 vs 95%) between groups and no acute rejection [92•].

Thus, DAAs have been established in HIV+/HCV+ recipients as safe and effective, and are expected to improve long-term outcomes. Whether to treat before or immediately after SOT depends upon the candidate's severity of liver disease as well as local availability and center-level comfort with use of HCV+ donor organs which in the USA are associated with significantly shorter wait times [93, 94]. Current HCV guidelines also reference successful studies of non-SOF-based DAA combinations in HIV+/HCV+ recipients [95]. Generally, NRTIs, INSTIs, rilpivirine, and maraviroc do not exhibit relevant interactions with first-line DAAs though tenofovir disoproxil fumarate exposure may be increased with velpatasvir and ledipasvir; tenofovir alafenamide may be preferred. Pharmacoenhancers (ritonavir and cobicistat) and certain NNRTIs (efavirenz, etravirine, and nevirapine) should be avoided due to drug interactions.

Infection Risk Following HIV+ SOT

Despite initial concern, HIV+ kidney and liver transplantation series in the USA and Europe show low rates of OIs (Table 1). For example, only 6 cases each of pneumocystis and Kaposi's sarcoma were reported in over 1000 recipients, despite variable ATG use (0–100%) and 1-year rejection (8–47%) [37, 39, 42–44, 45••, 46••, 47, 48, 49•, 50••, 51, 52]. Cytomegalovirus (CMV) viremia has been reported in up to 25% of HIV+ recipients, yet tissue-invasive disease was < 5% across series [43, 44, 48]. Prophylaxis practices (e.g., HSV prophylaxis) differed which likely impacted OI incidence [48]. "Severe infection" which was heterogeneously defined and most often referred to bacterial infections requiring hospitalization, occurred in 15–55% of patients (Table 1). These rates appear similar to those seen in HIV-negative SOT [96, 97], though may be higher among HIV-HCV coinfected patients [39, 81]. This population is also at increased risk for virus-related malignancies, i.e., hepatocellular carcinoma (HBV, HCV), post-transplant lymphoproliferative disease (Epstein Barr virus), and HPV-related cervical and anal cancer; accordingly, screening and monitoring are critical (Fig. 1).

HIV D+/R+ Transplantation

Transplant surgeon Dr. Elmi Muller pioneered HIV D+/R+ kidney transplants in South Africa in 2010 [98]. The first 4 patients received ATG induction, maintenance immunosuppression including tacrolimus, and PI-based ART with no rejection, graft loss, or mortality in the first year. A 2015 update included 27 HIV D+/R+ kidney recipients (median follow-up 2.4 years) with 1- and 5-year survival similar to HIV− controls at the center (84% vs 91% and 74% vs 85%, respectively). Rejection occurred in 22% at 3 years. All recipients remained virologically suppressed, and there were no AIDS-defining OIs, though 3 recipients died of infection including one with aspergillosis [99]. Notably, 14 of the 15 HIV+ donors were untreated and CD4 counts were not available at transplant. Donors with active tuberculosis, sepsis, and proteinuria were excluded. As of 2018, Dr. Muller has performed 43 kidney transplants from 25 deceased donors [63].

This experience inspired the USA to challenge the 1988 amendment to the US National Organ Transplant Act (NOTA) which prohibited donation from HIV+ individuals. In investigating the potential benefit of HIV D+/R+ transplantation, Boyarsky et al. (2011) estimated the number of HIV+ deceased donors using national registry data. Employing strict criteria (excluding those with missing data, detectable HIV, recent AIDS-defining illness, HCV+ liver donors), they estimated approximately 500 HIV+ deceased donors per year [100]. A 2015 Philadelphia study identified 4–5 local HIV+ deceased donors annually and projected 356 donors/year nationally [101]. Recently, a national survey of organ procurement organizations in the USA estimated 2164 HIV+ deceased donor referrals per year [102]. This exceeds the estimated 727 HIV+ persons who were listed for kidney transplantation between 2009 and 2012 [103], though a significant percentage of referrals would not be expected to be appropriate for donation due to medical and social factors [104].

Given the potential of HIV+ donors to increase access to transplant, the HIV Organ Policy Equity (HOPE) Act was introduced. This bill allowed for HIV D+/R+ transplantation within investigational protocols adhering to federally mandated research criteria. It passed with bipartisan support and was enacted in November 2013 [105]. In June 2015, federal law was amended and in November 2015, the Department of Health and Human Services published HOPE safeguards and research criteria. In light of the South African experience with viremic donors, HIV+ donors with any CD4 and viral load were permitted (at the discretion of the investigators), though donors with active OIs are excluded (Fig. 1). Living donation for HIV+ individuals is also permitted in donors with a CD4 ≥ 500 cells/ml^3 for 6 months, undetectable HIV RNA, and no active OIs. HOPE Safeguards primarily discuss liver and kidney transplantation, though there is no exclusive language regarding transplantation of other organs. Transplant teams must have experience with at least 5 HIV D−/R+ transplants of a specific organ type over 4 years before initiating an HIV D+/R+ protocol for that organ. HIV+ recipient criteria are identical to HIVTR inclusion criteria (i.e., suppressed viral load, CD4 ≥ 200 for kidney and ≥ 100 for liver candidates). Finally, an independent advocate is required for all HIV+ recipients under study as well as for potential HIV+ living donors.

The HOPE in Action study group is currently engaged in multicenter studies to study HIV D+/R+ kidney and liver transplantation (ClinicalTrials.gov Identifier: NCT03500315, NCT02602262) supported by the NIH. Within these studies, the first HIV D+/R+ kidney and liver transplants were performed in March 2016 [106]. As of November 2018, 25 US transplant centers have active HOPE Act research protocols [107].

An unexpected early benefit of the HOPE Act is the use of organs from deceased donors who have false-positive HIV screening tests, organs which previously would have been discarded. The first 10 false-positive donors were reported in 2018, resulting in 23 transplants for HIV+ recipients [108]. Annually, 50–100 such donors are estimated based on HIV test characteristics (0.1–0.3% false-positive rate) and > 20,000 eligible donors tested/year. This could benefit hundreds of HIV+ transplant candidates via the HOPE Act.

HIV Superinfection and Resistant Virus

The likelihood and consequence of HIV superinfection, i.e., acquisition of a second HIV strain to an individual via transplantation is unknown. The phenomenon is uncommon, yet well-described in HIV+ persons via injection drug use and sexual contact [109]. Superinfection can result in a new dominant strain, recombinant virus, or coexistence of multiple strains, with the potential for ART failure and disease progression [110, 111]. Possible factors influencing superinfection in HIV D+/R+ SOT include size of the viral inoculum, whether latent and/or resistant virus can be transmitted, and how immunosuppression and ART would modulate this. Reassuringly, in South Africa, there have been no cases of virologic failure in the HIV D+/R+ cohort, despite donor viremia, but archived/next-generation sequencing of the recipient virome is not reported [63]. Notably, community-level ART resistance in South Africa is lower than that in the USA [112]. Only 2/25 donors were ART-experienced, reducing the probability of resistant virus transmission [63]. This cannot be generalized to the US experience where primary resistance can reach 10–20% in some populations [113, 114]. Recipient eligibility criteria require viral suppression with ART, which should reduce the probability of superinfection, extrapolating from treatment-as-prevention data.

There is a case report of donor-to-recipient viral transfer in HIV D+/R+ liver transplant, though definitive superinfection was not established. In the UK, an HIV+/HCV+ recipient on ART received a liver transplant from an untreated donor [115]. HIV was detected in the recipient on postoperative day 2, peaking at 92309 copies/mL, and was virtually identical to donor virus. ART had been held in the recipient for 2 days but with reinstitution; viremia was suppressed without clinical consequence. Whether there was true donor-to-recipient superinfection (i.e., stable infection of recipient cells) versus transient donor viremia is unclear. Additional case reports of HIV D+/R+ liver and kidney transplant in Europe and North America have been published without major complications or breakthrough viremia [71, 116–118].

Coreceptor Expression and Viral Tropism

In addition to ART resistance, HIV chemokine coreceptor (CC) tropism and host expression may play a role in HIV D−/R+ and HIV D+/R+ transplantation through influence on cellular infection [119] and lymphocyte chemotaxis and inflammation [120]. In primary infection, HIV typically infects cells expressing the CCR5 receptor (R5 virus). Without ART, ≈ 50% of individuals shift toward CXCR4 tropism (X4 virus) over time, associated with CD4 decline and disease progression [119, 121, 122]. Transplantation from an X4-infected donor into an R5-infected recipient could lead to viral breakthrough if the recipient's ART includes a CCR5 inhibitor.

Host CC expression may also impact organ rejection and survival. Animal models and small human series of HIV− SOT grafts (heart, skin, kidney) have demonstrated that CCR5-expressing cells infiltrate grafts during rejection [123]. In stem cell transplantation, CCR5 inhibition with maraviroc reduces lymphocyte chemotaxis and associated graft-versus-host disease [124]. Homozygosity for the CCR5Δ32 allele leads to loss of expression of CCR5 and has been associated with lower rejection and long-term graft survival in HIV− kidney transplant [125, 126]. The MTOR inhibitors also downregulate CCR5 [127] and have been associated with lower HIV DNA levels post-transplant through unclear mechanisms [128]. Ongoing trials are investigating CCR5 blockade and sirolimus in HIV+ recipients (ClinicalTrials.gov Identifier: NCT02990312, NCT02741323).

APOL1 Risk Alleles

An estimated 10–13% of African Americans carry two APOL1 risk alleles, associated with a 7–10-fold increased risk of kidney disease including HIVAN [129]. The prevalence of these alleles among donors is assumed to be near 2% [130]. In a single-center study of HIV− recipients, organs from donors with two high-risk variants had nearly 4-fold higher graft failure [131]. A multicenter study ($n = 675$) estimated 2.3-fold higher graft loss from donors who had two high-risk alleles compared with donors with zero or one [131, 132•]. Donor APOL1 status seems relevant to HIV+ kidney transplantation given reports of post-transplant HIVAN and the donor kidney as a possible HIV reservoir and target after transplant. In contrast, recipient APOL1 status has not been correlated with kidney transplant survival, with similar 5-year graft failure for those with two vs. zero/one high-risk variants (22 vs 18%) [133]. Whether donors should be screened for APOL1 alleles is controversial [134] but might be considered for potential HIV+ living kidney donors both for donor and recipient safety.

Evolving Attitudes toward HIV SOT

Provider and patient attitudes regarding HIV+ transplantation have shifted over time. By 2009, healthcare workers in South Africa reported 90% support for transplantation in HIV+ recipients, while 68% of HIV− patients and > 90% HIV+ patients with kidney disease endorsed the practice [135]. In countries with lower endemicity, there is also support for HIV+ organ donation. A US HIV clinic-based survey reported 90% of patients felt HIV+ persons should be able to donate their organs to other HIV+ patients and 80% and 62% of respondents were personally interested in becoming deceased and living donors, respectively [136]. A UK survey reported 62% of HIV+ persons were willing to donate, whereas a Taiwanese study noted 72% willingness [137, 138]. Relevant themes among respondents included a need for more information about donation and registration.

Conclusion

International experience with over 1000 HIV+ SOTs indicate that this practice should be standard of care for HIV+ individuals with end-organ disease, with excellent survival outcomes, and low incidence of OIs. DAAs for HCV coinfection should further improve outcomes in this higher risk group. Rejection might be reduced with INSTI-based ART, use of lymphodepleting induction therapy, and perhaps CCR5 blockade. HIV D+/R+ transplantation is under investigation as a strategy to improve access to transplant for HIV+ candidates with ongoing multicenter studies that aim to better understand post-transplant outcomes, including the role of superinfection, implications on the HIV latent reservoir, and interplay with CCR5 and APOL1 haplotypes. With an aging HIV+ population, metabolic disease and cancer incidence are important long-term considerations. Efforts should continue to focus on improving access to transplant and education for both patients and providers.

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Compliance with Ethical Standards

Conflict of Interest Drs. William Werbel and Christine Durand declare that they have no conflicts of interest.

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