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

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Abstract

a) Purpose of review: What is the goal of your paper? What questions did you seek to answer—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.

b) Recent findings: Summarize the latest research on your topic.—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.

c) Summary: What answers did you find? What are the major takeaways/ conclusions of your examination? What's the impact on future research?—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

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Conflict of Interest

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

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

INTRODUCTION

Nearly 37 million persons worldwide, including 1.1 million in the United States, 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 US 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 United States 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.

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 *Trypanosoma 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 to 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+ coinfecting 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 US, HIV+ persons with ESLD face limited access to transplantation and prospective studies demonstrate poor one-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 incidence 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 & 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 1987-1997, only 32 HIV+ kidney transplants were reported in the US, 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 2003-2009 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 $200/\text{ml}^3$ with suppressed HIV RNA on ART was required. For liver candidates, CD4+ T-cells $100/\text{ml}^3$, a lower threshold to account for sequestration due to hypersplenism. Viremia was also permitted if ART was hepatotoxic, assuming suppression was expected post-transplant (Figure 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 one 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 HIVTR demonstrated 94% 3-year survival for 18 kidney recipients, but 64% 3-year 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 1997-2001 to 208 between 2001-2006(38). The results also revealed challenges: (i) increased rejection, (ii) drug-drug interactions, and (iii) inferior outcomes for HIV+/HCV+ recipients.

Immunosuppression & 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 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 US and Europe observed kidney rejection in 20-40% of recipients(16, 40, 41) (Table 1). Liver rejection varied from 10-50%(36, 42), similar to that of HIV-recipients in some series(43), 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(44), 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(45). Selection of induction immunosuppression remains controversial, particularly the use of ATG, which is recommended for kidney recipients at high risk of rejection(46), yet leads to prolonged CD4 and CD8 lymphopenias regardless of HIV status(47, 48). In 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 2000-2014 of 189 HIV+ kidney recipients who received ATG reported a 40% reduction in acute rejection and 50% higher graft survival compared to those who received no induction(50). This study also showed a low incidence of OIs (6 total non-CMV, non-candida esophagitis events among 830 SOT recipients). Drug-interactions between PIs and maintenance immunosuppression have also been implicated in rejection(51). Among the calcineurin inhibitors (CNIs), tacrolimus appears to be more effective than 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(52).

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(53). 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(54). 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(55), while 6/43 had nonspecific cellular infiltrates on biopsy. The significance of these findings and relation to rejection remain unclear.

Pharmacologic considerations & 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(51, 56, 57). 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(58). 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(59, 60). 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(56), 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(61, 62). Dolutegravir is predicted to be safe, with successful case reports, though it is a P450 substrate and lower levels might occur post-transplant(63). Additionally, dolutegravir impairs creatinine excretion leading to artifactual increase in serum values that may be mistaken for renal pathology, necessitating transplant provider education(64, 65). Limited data demonstrate few interactions for the CCR5 inhibitor maraviroc(66). Few interactions are anticipated with new agents such as doravirine and bictegravir, though data is 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 pre- and post-transplant(22, 24, 67, 68). In contrast, HIV+/HBV+ liver recipients have excellent survival (>80% at 5 years), without significant hepatitis recurrence (69). Multiple mechanisms for inferior outcomes in HIV+/HCV+ coinfection are proposed, including immune dysregulation from HIV and increased microbial gut translocation(70, 71). Early transplant experience showed that HCV recurrence in HIV+ liver recipients was common and morbid, despite HIV control(42, 72). 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, 73). Rejection was 1.5-fold higher in the coinfecting 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 (43, 74, 75). 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)(76). Sustained virologic response (SVR)

with interferon and ribavirin were poor (10-20%) and incurred significant toxicity including rejection(77, 78).

Direct acting antivirals (DAAs) have revolutionized treatment of HCV among SOT recipients, including those with HIV co-infection. The multicenter European CUPILT group reported excellent results among HCV+ liver and liver-kidney recipients, with SVR rates of 93-98% using diverse regimens(79, 80). 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(81, 82). Another HIV+/HCV+ CULPIT study of 29 patients (multiple genotypes, 35% advanced fibrosis), reported 97% SVR including 100% in 6 FCH patients(83). 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(84).

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 US are associated with significantly shorter wait-times(85, 86). Current HCV guidelines also reference successful studies of non-SOF based DAA combinations in HIV+/HCV+ recipients(87). Generally, NRTIs, INSTIs, rilpivirine, and maraviroc do not exhibit relevant interactions with first-line DAAs though tenofovir disoproxil fumarate 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 US 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, 43, 49, 50, 88-95). Cytomegalovirus (CMV) viremia has been reported in up to 25% of HIV+ recipients, yet tissue-invasive disease was <5% across series(89, 90, 93). Prophylaxis practices (e.g. HSV prophylaxis) differed which likely impacted OI incidence(93). "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 coinfecting patients(39, 73). 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 (Figure 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(55).

This experience inspired the US 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 US estimated 2164 HIV+ deceased donor referrals per year (102). This exceeds the estimated 727 HIV+ persons who were listed for kidney transplantation between 2009-2012(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 (Figure 1). Living donation for HIV+ individuals is also permitted in donors with a CD4 ≥ 500 cells/ml³ 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](https://clinicaltrials.gov/ct2/show/study/NCT03500315) 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 & 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 are not reported(55). Notably, community-level ART resistance in South Africa is lower than that in the US(112). Only 2/25 donors were ART-experienced, reducing the probability of resistant virus transmission(55). 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 two 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 cases reports of HIV D+/R+ liver and kidney transplant in Europe and North America have been published without major complications or breakthrough viremia(63, 116-118).

Coreceptor expression & 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. Animals 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 CCR5 $\Delta 32$ 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](https://clinicaltrials.gov/ct2/show/study/NCT02990312) 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 four-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 to 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. An 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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References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). (2018). Global HIV & AIDS statistics - 2018 fact sheet. Available: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. Accessed: 5 August, 2018.
2. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2010–2015. HIV Surveillance Supplemental Report. 2018;23(1).
3. Teeraananchai S, Kerr SJ, Amin J, Ruxruntham K, Law MG. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. *HIV Med.* 2017;18(4): 256–66. [PubMed: 27578404]
4. Wandeler G, Johnson LF, Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. *Curr Opin HIV AIDS.* 2016;11(5): 492–500. [PubMed: 27254748]
5. Smith CJ, Ryom L, Weber R, Morlat P, Pradier C, Reiss P, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet.* 2014;384(9939):241–8. [PubMed: 25042234]
6. Rana A, Gruessner A, Agopian VG, Khalpey Z, Riaz IB, Kaplan B, et al. Survival benefit of solid-organ transplant in the United States. *JAMA Surg.* 2015;150(3):252–9. [PubMed: 25629390]
7. Boyle SM, Lee DH, Wyatt CM. HIV in the dialysis population: Current issues and future directions. *Semin Dial.* 2017;30(5):430–7. [PubMed: 28608994]
8. Mallipattu SK, Wyatt CM, He JC. The New Epidemiology of HIV-Related Kidney Disease. *J AIDS Clin Res.* 2012;Suppl 4:001.
9. Freedman BI. APOL1 and nephropathy progression in populations of African ancestry. *Semin Nephrol.* 2013;33(5):425–32. [PubMed: 24119848]
10. Kruzell-Davila E, Wasser WG, Aviram S, Skorecki K. APOL1 nephropathy: from gene to mechanisms of kidney injury. *Nephrol Dial Transplant.* 2016;31(3):349–58. [PubMed: 25561578]
11. Abraham AG, Althoff KN, Jing Y, Estrella MM, Kitahata MM, Wester CW, et al. End-stage renal disease among HIV-infected adults in North America. *Clin Infect Dis.* 2015;60(6):941–9. [PubMed: 25409471]

12. Gathogo E, Jose S, Jones R, Levy JB, Mackie NE, Booth J, et al. End-stage kidney disease and kidney transplantation in HIV-positive patients: an observational cohort study. *J Acquir Immune Defic Syndr*. 2014;67(2):177–80. [PubMed: 25072607]
13. Saracho R, Martin Escobar E, Comas Farnes J, Arcos E, Mazuecos Blanca A, Gentil Govantes MA, et al. Clinical evolution of chronic renal patients with HIV infection in replacement therapy. *Nefrologia*. 2015;35(5):457–64. [PubMed: 26409500]
14. Bickel M, Marben W, Betz C, Khaykin P, Stephan C, Gute P, et al. End-stage renal disease and dialysis in HIV-positive patients: observations from a long-term cohort study with a follow-up of 22 years. *HIV Med*. 2013;14(3):127–35. [PubMed: 22994610]
15. Rasch MG, Helleberg M, Feldt-Rasmussen B, Kronborg G, Larsen CS, Pedersen C, et al. Increased risk of dialysis and end-stage renal disease among HIV patients in Denmark compared with the background population. *Nephrol Dial Transplant*. 2014;29(6):1232–8. [PubMed: 23975841]
16. Trullas JC, Cofan F, Barril G, Martinez-Castelao A, Jofre R, Rivera M, et al. Outcome and prognostic factors in HIV-1-infected patients on dialysis in the cART era: a GESIDA/SEN cohort study. *J Acquir Immune Defic Syndr*. 2011;57(4):276–83. [PubMed: 21623213]
- 17*. Locke JE, Gustafson S, Mehta S, Reed RD, Shelton B, MacLennan PA, et al. Survival Benefit of Kidney Transplantation in HIV-infected Patients. *Ann Surg*. 2017;265(3):604–8. [PubMed: 27768622] US registry study of 1431 HIV-infected renal failure patients demonstrating significantly improved 1-year survival among waitlisted HIV+ patients with renal failure who achieved kidney transplantation (3.1% vs 8.7%). A 79% reduction in adjusted relative risk of mortality was seen at 5 years, supporting a durable survival benefit of SOT in HIV+ persons.
18. Cowell A, Sheno SV, Kyriakides TC, Friedland G, Barakat LA. Trends in hospital deaths among human immunodeficiency virus-infected patients during the antiretroviral therapy era, 1995 to 2011. *J Hosp Med*. 2015;10(9):608–14. [PubMed: 26130520]
19. Farahani M, Mulinder H, Farahani A, Marlink R. Prevalence and distribution of non-AIDS causes of death among HIV-infected individuals receiving antiretroviral therapy: a systematic review and meta-analysis. *Int J STD AIDS*. 2017;28(7):636–50. [PubMed: 26868158]
20. Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. Increasing burden of liver disease in patients with HIV infection. *Lancet*. 2011;377(9772):1198–209. [PubMed: 21459211]
21. Ragni MV, Eghtesad B, Schlesinger KW, Dvorchik I, Fung JJ. Pretransplant survival is shorter in HIV-positive than HIV-negative subjects with end-stage liver disease. *Liver Transpl*. 2005;11(11):1425–30. [PubMed: 16237709]
22. Pineda JA, Romero-Gomez M, Diaz-Garcia F, Giron-Gonzalez JA, Montero JL, Torre-Cisneros J, et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. *Hepatology*. 2005;41(4):779–89. [PubMed: 15800956]
23. Araiz JJ, Serrano MT, Garcia-Gil FA, Lacruz EM, Lorente S, Sanchez JJ, et al. Intention-to-treat survival analysis of hepatitis C virus/human immunodeficiency virus coinfecting liver transplant: Is it the waiting list? *Liver Transpl*. 2016;22(9):1186–96. [PubMed: 27114030]
24. Subramanian A, Sulkowski M, Barin B, Stablein D, Curry M, Nissen N, et al. MELD score is an important predictor of pretransplantation mortality in HIV-infected liver transplant candidates. *Gastroenterology*. 2010;138(1):159–64. [PubMed: 19800334]
25. Murillas J, Rimola A, Laguno M, de Lazzari E, Rascon J, Aguero F, et al. The model for end-stage liver disease score is the best prognostic factor in human immunodeficiency virus 1-infected patients with end-stage liver disease: a prospective cohort study. *Liver Transpl*. 2009;15(9):1133–41. [PubMed: 19718643]
26. Jarrett H, Barnett C. HIV-associated pulmonary hypertension. *Current Opinion in Hiv and Aids*. 2017;12(6):566–71. [PubMed: 28902721]
27. Remick J, Georgiopolou V, Marti C, Ofotokun I, Kalogeropoulos A, Lewis W, et al. Heart failure in patients with human immunodeficiency virus infection: epidemiology, pathophysiology, treatment, and future research. *Circulation*. 2014;129(17):1781–9. [PubMed: 24778120]
28. Alvi RM, Neilan AM, Tariq N, Awadalla M, Afshar M, Banerji D, et al. Protease Inhibitors and Cardiovascular Outcomes in Patients With HIV and Heart Failure. *J Am Coll Cardiol*. 2018;72(5):518–30. [PubMed: 30049313]

29. Feinstein MJ, Bahiru E, Achenbach C, Longenecker CT, Hsue P, So-Armah K, et al. Patterns of Cardiovascular Mortality for HIV-Infected Adults in the United States: 1999 to 2013. *Am J Cardiol.* 2016;117(2):214–20. [PubMed: 26639041]
30. Tseng ZH, Secemsky EA, Dowdy D, Vittinghoff E, Moyers B, Wong JK, et al. Sudden cardiac death in patients with human immunodeficiency virus infection. *J Am Coll Cardiol.* 2012;59(21):1891–6. [PubMed: 22595409]
31. Dummer JS, Erb S, Breinig MK, Ho M, Rinaldo CR Jr., Gupta P, et al. Infection with human immunodeficiency virus in the Pittsburgh transplant population. A study of 583 donors and 1043 recipients, 1981–1986. *Transplantation.* 1989;47(1):134–40. [PubMed: 2911869]
32. Tzakis AG, Cooper MH, Dummer JS, Ragni M, Ward JW, Starzl TE. Transplantation in HIV+ patients. *Transplantation.* 1990;49(2):354–8. [PubMed: 2305465]
33. Swanson SJ, Kirk AD, Ko CW, Jones CA, Agodoa LY, Abbott KC. Impact of HIV seropositivity on graft and patient survival after cadaveric renal transplantation in the United States in the pre highly active antiretroviral therapy (HAART) era: an historical cohort analysis of the United States Renal Data System. *Transpl Infect Dis.* 2002;4(3):144–7. [PubMed: 12421459]
34. Spital A. Should all human immunodeficiency virus-infected patients with end-stage renal disease be excluded from transplantation? The views of U.S. transplant centers. *Transplantation.* 1998;65(9):1187–91. [PubMed: 9603166]
35. Halpern SD, Asch DA, Shaked A, Stock PG, Blumberg E. Determinants of transplant surgeons' willingness to provide organs to patients infected with HBV, HCV or HIV. *Am J Transplant.* 2005;5(6):1319–25. [PubMed: 15888036]
36. Roland ME, Barin B, Carlson L, Frassetto LA, Terrault NA, Hirose R, et al. HIV-infected liver and kidney transplant recipients: 1- and 3-year outcomes. *Am J Transplant.* 2008;8(2):355–65. [PubMed: 18093266]
37. Terrault NA, Roland ME, Schiano T, Dove L, Wong MT, Poordad F, et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. *Liver Transpl.* 2012;18(6):716–26. [PubMed: 22328294]
38. Yoon SC, Hurst FP, Jindal RM, George SA, Neff RT, Agodoa LY, et al. Trends in renal transplantation in patients with human immunodeficiency virus infection: an analysis of the United States renal data system. *Transplantation.* 2011;91(8):864–8. [PubMed: 21301399]
39. Stock PG, Barin B, Murphy B, Hanto D, Diego JM, Light J, et al. Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med.* 2010;363(21):2004–14. [PubMed: 21083386]
40. Landin L, Rodriguez-Perez JC, Garcia-Bello MA, Cavadas PC, Thione A, Nthumba P, et al. Kidney transplants in HIV-positive recipients under HAART. A comprehensive review and meta-analysis of 12 series. *Nephrol Dial Transplant.* 2010;25(9):3106–15. [PubMed: 20228071]
41. Malat GE, Ranganna KM, Sikalas N, Liu L, Jindal RM, Doyle A. High frequency of rejections in HIV-positive recipients of kidney transplantation: a single center prospective trial. *Transplantation.* 2012;94(10):1020–4. [PubMed: 23169224]
42. Ragni MV, Belle SH, Im K, Neff G, Roland M, Stock P, et al. Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis.* 2003;188(10):1412–20. [PubMed: 14624365]
43. Locke JE, Durand C, Reed RD, MacLennan PA, Mehta S, Massie A, et al. Long-term Outcomes After Liver Transplantation Among Human Immunodeficiency Virus-Infected Recipients. *Transplantation.* 2016;100(1):141–6. [PubMed: 26177090]
44. Paiardini M, Muller-Trutwin M. HIV-associated chronic immune activation. *Immunol Rev.* 2013;254(1):78–101. [PubMed: 23772616]
45. Lorio MA, Rosa R, Suarez JF, Ruiz P, Ciancio G, Burke GW, et al. Influence of immune activation on the risk of allograft rejection in human immunodeficiency virus-infected kidney transplant recipients. *Transpl Immunol.* 2016;38:40–3. [PubMed: 27297667]
46. Kidney Disease: Improving Global Outcomes Transplant Work G. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant.* 2009;9 Suppl 3:S1–155.

47. Carter JT, Melcher ML, Carlson LL, Roland ME, Stock PG. Thymoglobulin-associated Cd4+ T-cell depletion and infection risk in HIV-infected renal transplant recipients. *Am J Transplant*. 2006;6(4):753–60. [PubMed: 16539632]
48. Fernandez-Ruiz M, Lopez-Medrano F, Allende LM, Andres A, Garcia-Reyne A, Lumberras C, et al. Kinetics of peripheral blood lymphocyte subpopulations predicts the occurrence of opportunistic infection after kidney transplantation. *Transpl Int*. 2014;27(7):674–85. [PubMed: 24650360]
- 49*. Roland ME, Barin B, Huprikar S, Murphy B, Hanto DW, Blumberg E, et al. Survival in HIV-positive transplant recipients compared with transplant candidates and with HIV-negative controls. *AIDS*. 2016;30(3):435–44. [PubMed: 26765937] 125 HIV+ liver and 150 kidney transplant recipients in the HIVTR were compared to risk-matched waitlisted HIV+ patients and HIV-negative controls. Survival benefit was seen with HIV+ liver transplant if MELD 15, though absolute graft loss was 6.7% higher than in HIV-negative controls. Kidney graft failure (31% vs 29%) and patient mortality (11.3 vs 12.7%) were similar. Predictors of mortality at > 4 years of median follow up included older age as well as HCV infection in HIV+ liver SOT and lower BMI in HIV+ kidney SOT, relevant to recipient selection.
- 50**. Kucirka LM, Durand CM, Bae S, Avery RK, Locke JE, Orandi BJ, et al. Induction Immunosuppression and Clinical Outcomes in Kidney Transplant Recipients Infected With Human Immunodeficiency Virus. *Am J Transplant*. 2016;16(8):2368–76. [PubMed: 27111897] US registry study of 830 HIV+ kidney transplants comparing rates of rejection and infection by type of induction immunosuppression. Use of ATG demonstrated favorable rates of rejection (41% lower) and no increase in infections versus no induction, supporting safety of lymphodepleting agents.
51. Frassetto LA, Browne M, Cheng A, Wolfe AR, Roland ME, Stock PG, et al. Immunosuppressant pharmacokinetics and dosing modifications in HIV-1 infected liver and kidney transplant recipients. *Am J Transplant*. 2007;7(12):2816–20. [PubMed: 17949460]
52. Gathogo E, Harber M, Bhagani S, Levy J, Jones R, Hilton R, et al. Impact of Tacrolimus Compared With Cyclosporin on the Incidence of Acute Allograft Rejection in Human Immunodeficiency Virus-Positive Kidney Transplant Recipients. *Transplantation*. 2016;100(4):871–8. [PubMed: 26413990]
53. Canaud G, Dejucq-Rainsford N, Avettand-Fenoel V, Viard JP, Anglicheau D, Bienaime F, et al. The kidney as a reservoir for HIV-1 after renal transplantation. *J Am Soc Nephrol*. 2014;25(2):407–19. [PubMed: 24309185]
54. Avettand-Fenoel V, Rouzioux C, Legendre C, Canaud G. HIV Infection in the Native and Allograft Kidney: Implications for Management, Diagnosis, and Transplantation. *Transplantation*. 2017;101(9):2003–8. [PubMed: 28196049]
55. Muller E, Barday Z. HIV-Positive Kidney Donor Selection for HIV-Positive Transplant Recipients. *J Am Soc Nephrol*. 2018;29(4):1090–5. [PubMed: 29330339]
56. Primeggia J, Timponi JG Jr., Kumar PN. Pharmacologic issues of antiretroviral agents and immunosuppressive regimens in HIV-infected solid organ transplant recipients. *Infect Dis Clin North Am*. 2013;27(2):473–86. [PubMed: 23714350]
57. Han Z, Kane BM, Petty LA, Josephson MA, Sutor J, Pursell KJ. Cobicistat Significantly Increases Tacrolimus Serum Concentrations in a Renal Transplant Recipient with Human Immunodeficiency Virus Infection. *Pharmacotherapy*. 2016;36(6):e50–e3. [PubMed: 27041642]
58. Jain AK, Venkataramanan R, Fridell JA, Gadomski M, Shaw LM, Ragni M, et al. Nelfinavir, a protease inhibitor, increases sirolimus levels in a liver transplantation patient: a case report. *Liver Transpl*. 2002;8(9):838–40. [PubMed: 12200787]
59. Rosa R, Suarez JF, Lorio MA, Morris MI, Abbo LM, Simkins J, et al. Impact of antiretroviral therapy on clinical outcomes in HIV (+) kidney transplant recipients: Review of 58 cases. *F1000Res*. 2016;5:2893. [PubMed: 28299182]
60. Sawinski D, Shelton BA, Mehta S, Reed RD, MacLennan PA, Gustafson S, et al. Impact of Protease Inhibitor-Based Anti-Retroviral Therapy on Outcomes for HIV+ Kidney Transplant Recipients. *Am J Transplant*. 2017;17(12):3114–22. [PubMed: 28696079]

61. Tricot L, Teicher E, Peytavin G, Zucman D, Conti F, Calmus Y, et al. Safety and efficacy of raltegravir in HIV-infected transplant patients cotreated with immunosuppressive drugs. *Am J Transplant.* 2009;9(8):1946–52. [PubMed: 19519819]
62. Azar MM, Malinis MF, Moss J, Formica RN, Villanueva MS. Integrase strand transferase inhibitors: the preferred antiretroviral regimen in HIV-positive renal transplantation. *Int J STD AIDS.* 2017;28(5):447–58. [PubMed: 27193421]
63. Calmy A, van Delden C, Giostra E, Junet C, Rubbia Brandt L, Yerly S, et al. HIV-Positive-to-HIV-Positive Liver Transplantation. *Am J Transplant.* 2016;16(8):2473–8. [PubMed: 27109874]
64. Lee DH, Malat GE, Bias TE, Harhay MN, Ranganna K, Doyle AM. Serum creatinine elevation after switch to dolutegravir in a human immunodeficiency virus-positive kidney transplant recipient. *Transpl Infect Dis.* 2016;18(4):625–7. [PubMed: 27159656]
65. Milburn J, Jones R, Levy JB. Renal effects of novel antiretroviral drugs. *Nephrol Dial Transplant.* 2017;32(3):434–9. [PubMed: 27190354]
66. Righi E, Londero A, Pea F, Bonora S, Nasta P, Della Siega P, et al. Antiretroviral blood levels in HIV/HCV-coinfected patients with cirrhosis after liver transplant: a report of three cases. *Transpl Infect Dis.* 2015;17(1):147–53. [PubMed: 25620392]
67. Limketkai BN, Mehta SH, Sutcliffe CG, Higgins YM, Torbenson MS, Brinkley SC, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfecting with HIV/HCV. *JAMA.* 2012;308(4):370–8. [PubMed: 22820790]
68. Kirk GD, Mehta SH, Astemborski J, Galai N, Washington J, Higgins Y, et al. HIV, age, and the severity of hepatitis C virus-related liver disease: a cohort study. *Ann Intern Med.* 2013;158(9):658–66. [PubMed: 23440167]
69. Coffin CS, Stock PG, Dove LM, Berg CL, Nissen NN, Curry MP, et al. Virologic and clinical outcomes of hepatitis B virus infection in HIV-HBV coinfecting transplant recipients. *Am J Transplant.* 2010;10(5):1268–75. [PubMed: 20346065]
70. de Oca Arjona MM, Marquez M, Soto MJ, Rodriguez-Ramos C, Terron A, Vergara A, et al. Bacterial translocation in HIV-infected patients with HCV cirrhosis: implication in hemodynamic alterations and mortality. *J Acquir Immune Defic Syndr.* 2011;56(5):420–7. [PubMed: 21266909]
71. Mastroianni CM, Lichtner M, Mascia C, Zuccala P, Vullo V. Molecular mechanisms of liver fibrosis in HIV/HCV coinfection. *Int J Mol Sci.* 2014;15(6):9184–208. [PubMed: 24865485]
72. Prachalias AA, Pozniak A, Taylor C, Srinivasan P, Muiesan P, Wendon J, et al. Liver transplantation in adults coinfecting with HIV. *Transplantation.* 2001;72(10):1684–8. [PubMed: 11726833]
73. Miro JM, Montejo M, Castells L, Rafecas A, Moreno S, Aguero F, et al. Outcome of HCV/HIV-coinfecting liver transplant recipients: a prospective and multicenter cohort study. *Am J Transplant.* 2012;12(7):1866–76. [PubMed: 22471341]
- 74*. Sawinski D, Goldberg DS, Blumberg E, Abt PL, Bloom RD, Forde KA. Beyond the NIH Multicenter HIV Transplant Trial Experience: Outcomes of HIV+ Liver Transplant Recipients Compared to HCV+ or HIV+/HCV+ Coinfecting Recipients in the United States. *Clin Infect Dis.* 2015;61(7):1054–62. [PubMed: 26082506] Registry study comparing graft and patient survival post liver transplant by viral serostatus among 72 HIV+/HCV–, 160 HIV+/HCV+, 20829 HIV–/HCV+, and 22926 HCV–/HIV– controls. No difference in survival seen between HIV+/HCV– and reference HIV–/HCV– patients, though higher mortality was seen in HIV–/HCV+ (1.5-fold) and HIV+/HCV+ (2.6-fold) recipients, identifying HCV as an important driver of poorer outcomes.
75. Stock PG, Terrault NA. Human immunodeficiency virus and liver transplantation: Hepatitis C is the last hurdle. *Hepatology.* 2015;61(5):1747–54. [PubMed: 25292153]
76. Antonini TM, Sebach M, Roque-Afonso AM, Teicher E, Roche B, Sobesky R, et al. Fibrosing cholestatic hepatitis in HIV/HCV co-infected transplant patients-usefulness of early markers after liver transplantation. *Am J Transplant.* 2011;11(8):1686–95. [PubMed: 21749638]
77. Duclos-Vallee JC, Feray C, Sebach M, Teicher E, Roque-Afonso AM, Roche B, et al. Survival and recurrence of hepatitis C after liver transplantation in patients coinfecting with human immunodeficiency virus and hepatitis C virus. *Hepatology.* 2008;47(2):407–17. [PubMed: 18098295]

78. Terrault N, Reddy KR, Poordad F, Curry M, Schiano T, Juhl J, et al. Peginterferon and ribavirin for treatment of recurrent hepatitis C disease in HCV-HIV coinfecting liver transplant recipients. *Am J Transplant.* 2014;14(5):1129–35. [PubMed: 24636466]
79. Dharancy S, Coilly A, Fougerou-Leurent C, Duvoux C, Kamar N, Leroy V, et al. Direct-acting antiviral agent-based regimen for HCV recurrence after combined liver-kidney transplantation: Results from the ANRS CO23 CUPILT study. *Am J Transplant.* 2017;17(11):2869–78. [PubMed: 28898563]
80. Houssel-Debry P, Coilly A, Fougerou-Leurent C, Jezequel C, Duvoux C, De Ledinghen V, et al. 12 weeks of a Ribavirin-free Sofosbuvir and NS5A inhibitor regimen is enough to treat recurrence of hepatitis C after liver transplantation. *Hepatology.* 2018.
81. Leroy V, Dumortier J, Coilly A, Sebah M, Fougerou-Leurent C, Radenne S, et al. Efficacy of Sofosbuvir and Daclatasvir in Patients With Fibrosing Cholestatic Hepatitis C After Liver Transplantation. *Clin Gastroenterol Hepatol.* 2015;13(11):1993–2001 e1–2. [PubMed: 26044317]
82. Morales AL, Liriano-Ward L, Tierney A, Sang M, Lalos A, Hassan M, et al. Ledipasvir/sofosbuvir is effective and well tolerated in postkidney transplant patients with chronic hepatitis C virus. *Clin Transplant.* 2017;31(5).
83. Antonini TM, Coilly A, Rossignol E, Fougerou-Leurent C, Dumortier J, Leroy V, et al. Sofosbuvir-Based Regimens in HIV/HCV Coinfected Patients After Liver Transplantation: Results From the ANRS CO23 CUPILT Study. *Transplantation.* 2018;102(1):119–26. [PubMed: 28846559]
- 84*. Manzardo C, Londono MC, Castells L, Testillano M, Luis Montero J, Penafiel J, et al. Direct-acting antivirals are effective and safe in HCV/HIV-coinfecting liver transplant recipients who experience recurrence of hepatitis C: A prospective nationwide cohort study. *Am J Transplant.* 2018;Spanish multicenter prospective cohort study comparing 47 HIV-HCV coinfecting patients with recurrent HCV, treated with DAAs, versus 148 matched HCV mono-infected liver recipients; SVR rates were 94 vs 95% respectively. There was no evidence of rejection or loss of HIV viral control among coinfecting patients post SOT, confirming the safety and efficacy of DAAs in this population
85. Terrault NA, Berenguer M, Strasser SI, Gadano A, Lilly L, Samuel D, et al. International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Recipients. *Transplantation.* 2017;101(5):956–67. [PubMed: 28437388]
86. Terrault N Hepatitis C in Patients With Renal Disease: A Deeper Dive Into the KDIGO Guideline. *Hepatology.* 2018;68(5):2035–8. [PubMed: 29672896]
87. AASLD-IDSA. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Patients Who Develop Recurrent HCV Infection Post Liver Transplantation. <https://www.hcvguidelines.org/unique-populations/post-liver-transplant>. Accessed: 22 August, 2018.
88. Locke JE, Mehta S, Reed RD, MacLennan P, Massie A, Nellore A, et al. A National Study of Outcomes among HIV-Infected Kidney Transplant Recipients. *J Am Soc Nephrol.* 2015;26(9):2222–9. [PubMed: 25791727]
89. Gathogo EN, Hamzah L, Hilton R, Marshall N, Ashley C, Harber M, et al. Kidney transplantation in HIV-positive adults: the UK experience. *Int J STD AIDS.* 2014;25(1):57–66. [PubMed: 23970634]
90. Suarez JF, Rosa R, Lorio MA, Morris MI, Abbo LM, Simkins J, et al. Pretransplant CD4 Count Influences Immune Reconstitution and Risk of Infectious Complications in Human Immunodeficiency Virus-Infected Kidney Allograft Recipients. *Am J Transplant.* 2016;16(8):2463–72. [PubMed: 26953224]
- 91*. Muller E, Barday Z, Mendelson M, Kahn D. HIV-positive-to-HIV-positive kidney transplantation--results at 3 to 5 years. *N Engl J Med.* 2015;372(7):613–20. [PubMed: 25671253] South African series of 27 HIV D+/R+ SOT patients demonstrating 5-year death-censored graft survival (84% vs 75%) and patient survival (75% vs 85%) similar to that of HIV-controls. HIV viral control was excellent, while only one HIV-associated OI (tuberculosis) was detected during the study period, supporting the safety of this novel practice.
92. Cristelli MP, Cofan F, Tedesco-Silva H, Trullas JC, Santos D, Manzardo C, et al. Regional differences in the management and outcome of kidney transplantation in patients with human immunodeficiency virus infection: A 3-year retrospective cohort study. *Transpl Infect Dis.* 2017;19(4).

93. Moreno A, Cervera C, Fortun J, Blanes M, Montejo E, Abradelo M, et al. Epidemiology and outcome of infections in human immunodeficiency virus/hepatitis C virus-coinfected liver transplant recipients: a FIPSE/GESIDA prospective cohort study. *Liver Transpl.* 2012;18(1):70–81. [PubMed: 21898772]
94. Teicher E, Boufassa F, Vittecoq D, Antonini TM, Tateo MG, Coilly A, et al. Infectious complications after liver transplantation in human immunodeficiency virus-infected recipients. *Transpl Infect Dis.* 2015;17(5):662–70. [PubMed: 26192379]
95. Di Benedetto F, Tarantino G, De Ruvo N, Cautero N, Montalti R, Guerrini GP, et al. University of Modena experience in HIV-positive patients undergoing liver transplantation. *Transplant Proc.* 2011;43(4):1114–8. [PubMed: 21620066]
96. Hernandez Mdel P, Martin P, Simkins J. Infectious Complications After Liver Transplantation. *Gastroenterol Hepatol (N Y).* 2015;11(11):741–53. [PubMed: 27134589]
97. Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol.* 2012;7(12):2058–70. [PubMed: 22977217]
98. Muller E, Kahn D, Mendelson M. Renal transplantation between HIV-positive donors and recipients. *N Engl J Med.* 2010;362(24):2336–7. [PubMed: 20554994]
99. Muller E, Barday Z, Kahn D. HIV-positive-to-HIV-positive kidney transplantation. *N Engl J Med.* 2015;372(21):2070–1.
100. Boyarsky BJ, Hall EC, Singer AL, Montgomery RA, Gebo KA, Segev DL. Estimating the potential pool of HIV-infected deceased organ donors in the United States. *Am J Transplant.* 2011;11(6):1209–17. [PubMed: 21443677]
101. Richterman A, Sawinski D, Reese PP, Lee DH, Clauss H, Hasz RD, et al. An Assessment of HIV-Infected Patients Dying in Care for Deceased Organ Donation in a United States Urban Center. *Am J Transplant.* 2015;15(8):2105–16. [PubMed: 25976241]
102. Cash A, Luo X, Chow EKH, Bowring MG, Shaffer AA, Doby B, et al. HIV+ deceased donor referrals: A national survey of organ procurement organizations. *Clin Transplant.* 2018;32(2).
103. Locke JE, Mehta S, Sawinski D, Gustafson S, Shelton BA, Reed RD, et al. Access to Kidney Transplantation among HIV-Infected Waitlist Candidates. *Clin J Am Soc Nephrol.* 2017;12(3):467–75. [PubMed: 28232406]
104. Doby BL, Tobian AAR, Segev DL, Durand CM. Moving from the HIV Organ Policy Equity Act to HIV Organ Policy Equity in action: changing practice and challenging stigma. *Curr Opin Organ Transplant.* 2018;23(2):271–8. [PubMed: 29432254]
105. Boyarsky BJ, Segev DL. From Bench to Bill: How a Transplant Nuance Became 1 of Only 57 Laws Passed in 2013. *Ann Surg.* 2016;263(3):430–3. [PubMed: 26575282]
106. Malani P. HIV and Transplantation: New Reasons for HOPE. *JAMA.* 2016;316(2):136–8. [PubMed: 27404170]
107. Organ Procurement & Transplantation Network, US Department of Health and Human Services. HOPE Act. Available: <https://optn.transplant.hrsa.gov/learn/professional-education/hope-act/>. Accessed: 28 October, 2018.
108. Durand CM, Halpern SE, Bowring MG, Bismut GA, Kusemiju OT, Doby B, et al. Organs from deceased donors with false-positive HIV screening tests: An unexpected benefit of the HOPE act. *Am J Transplant.* 2018.
109. Redd AD, Quinn TC, Tobian AA. Frequency and implications of HIV superinfection. *Lancet Infect Dis.* 2013;13(7):622–8. [PubMed: 23726798]
110. Gottlieb GS, Nickle DC, Jensen MA, Wong KG, Kaslow RA, Shepherd JC, et al. HIV type 1 superinfection with a dual-tropic virus and rapid progression to AIDS: a case report. *Clin Infect Dis.* 2007;45(4):501–9. [PubMed: 17638203]
111. Smith DM, Wong JK, Hightower GK, Ignacio CC, Koelsch KK, Daar ES, et al. Incidence of HIV superinfection following primary infection. *JAMA.* 2004;292(10):1177–8. [PubMed: 15353529]
112. Nwobegahay J, Selabe G, Ndjeka NO, Manhaeve C, Bessong PO. Low prevalence of transmitted genetic drug resistance in a cohort of HIV infected naive patients entering antiretroviral treatment programs at two sites in northern South Africa. *J Med Virol.* 2012;84(12):1839–43. [PubMed: 23080485]

113. Smith DM, May SJ, Tweeten S, Drumright L, Pacold ME, Kosakovsky Pond SL, et al. A public health model for the molecular surveillance of HIV transmission in San Diego, California. *AIDS*. 2009;23(2):225–32. [PubMed: 19098493]
114. Truong HM, Kellogg TA, McFarland W, Louie B, Klausner JD, Philip SS, et al. Sentinel surveillance of HIV-1 transmitted drug resistance, acute infection and recent infection. *PLoS One*. 2011;6(10):e25281. [PubMed: 22046237]
115. Hathorn E, Smit E, Elsharkawy AM, Bramhall SR, Bufton SA, Allan S, et al. HIV-Positive-to-HIV-Positive Liver Transplantation. *N Engl J Med*. 2016;375(18):1807–9.
116. Ambaraghassi G, Cardinal H, Corsilli D, Fortin C, Fortin MC, Martel-Laferriere V, et al. First Canadian Case Report of Kidney Transplantation From an HIV-Positive Donor to an HIV-Positive Recipient. *Can J Kidney Health Dis*. 2017;4:2054358117695792. [PubMed: 28321326]
117. Nolan E, Karydis N, Drage M, Hilton R. First UK case report of kidney transplantation from an HIV-infected deceased donor to two HIV-infected recipients. *Clin Kidney J*. 2018;11(2):289–91. [PubMed: 29644073]
118. Lauterio A, Moiola MC, Di Sandro S, Travi G, De Carlis R, Merli M, et al. HIV-positive to HIV-positive liver transplantation: To be continued. *J Hepatol*. 2018.
119. Naif HM. Pathogenesis of HIV Infection. *Infect Dis Rep*. 2013;5(Suppl 1):e6.
120. Nelson PJ, Krensky AM. Chemokines and allograft rejection: narrowing the list of suspects. *Transplantation*. 2001;72(7):1195–7. [PubMed: 11602841]
121. Connor RI, Sheridan KE, Ceradini D, Choe S, Landau NR. Change in coreceptor use correlates with disease progression in HIV-1--infected individuals. *J Exp Med*. 1997;185(4):621–8. [PubMed: 9034141]
122. Verheyen J, Thielen A, Lubke N, Dirks M, Widera M, Dittmer U, et al. Rapid rebound of a preexisting CXCR4-tropic HIV variant after allogeneic transplantation with CCR5 delta32 homozygous stem cells. *Clin Infect Dis*. 2018.
123. Schenk AD, Rosenblum JM, Fairchild RL. Chemokine-directed strategies to attenuate allograft rejection. *Clin Lab Med*. 2008;28(3):441–54, vii. [PubMed: 19028262]
124. Reshef R, Luger SM, Hexner EO, Loren AW, Frey NV, Nasta SD, et al. Blockade of lymphocyte chemotaxis in visceral graft-versus-host disease. *N Engl J Med*. 2012;367(2):135–45. [PubMed: 22784116]
125. Heidenhain C, Puhl G, Moench C, Lautem A, Neuhaus P. Chemokine receptor 5Delta32 mutation reduces the risk of acute rejection in liver transplantation. *Ann Transplant*. 2009;14(3):36–44. [PubMed: 19644158]
126. Fischereder M, Luckow B, Hoher B, Wuthrich RP, Rothenpieler U, Schneeberger H, et al. CC chemokine receptor 5 and renal-transplant survival. *Lancet*. 2001;357(9270):1758–61. [PubMed: 11403814]
127. Donia M, McCubrey JA, Bendtzen K, Nicoletti F. Potential use of rapamycin in HIV infection. *Br J Clin Pharmacol*. 2010;70(6):784–93. [PubMed: 21175433]
128. Stock PG, Barin B, Hatano H, Rogers RL, Roland ME, Lee TH, et al. Reduction of HIV persistence following transplantation in HIV-infected kidney transplant recipients. *Am J Transplant*. 2014;14(5):1136–41. [PubMed: 24698537]
129. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*. 2010;329(5993):841–5. [PubMed: 20647424]
130. Shah PB, Cooper JE, Lucia MS, Boils C, Larsen CP, Wiseman AC. APOL1 Polymorphisms in a Deceased Donor and Early Presentation of Collapsing Glomerulopathy and Focal Segmental Glomerulosclerosis in Two Recipients. *Am J Transplant*. 2016;16(6):1923–7. [PubMed: 26849829]
131. Reeves-Daniel AM, DePalma JA, Bleyer AJ, Rocco MV, Murea M, Adams PL, et al. The APOL1 gene and allograft survival after kidney transplantation. *Am J Transplant*. 2011;11(5):1025–30. [PubMed: 21486385]
- 132*. Freedman BI, Julian BA, Pastan SO, Israni AK, Schladt D, Gautreaux MD, et al. Apolipoprotein L1 gene variants in deceased organ donors are associated with renal allograft failure. *Am J Transplant*. 2015;15(6):1615–22. [PubMed: 25809272] Multicenter study of 675 patients

demonstrating association of donor APOL1 genotype (2.3-fold increased risk) and African American recipient ethnicity (1.6-fold increased risk) with long term kidney graft loss post HIV-negative SOT. This informs a potential strategy for risk stratifying donors and recipients in HIV D+/R+ SOT, particularly with respect to risk of HIVAN.

133. Lee BT, Kumar V, Williams TA, Abdi R, Bernhardt A, Dyer C, et al. The APOL1 genotype of African American kidney transplant recipients does not impact 5-year allograft survival. *Am J Transplant*. 2012;12(7):1924–8. [PubMed: 22487534]
134. Cohen DM, Mittalhenkle A, Scott DL, Young CJ, Norman DJ. African American living-kidney donors should be screened for APOL1 risk alleles. *Transplantation*. 2011;92(7):722–5. [PubMed: 21878839]
135. Gokool S, Fabian J, Venter WD, MacPhail C, Naicker S. HIV-positive kidney transplants for HIV-positive individuals: attitudes and concerns of South African patients and health care workers. *S Afr Med J*. 2010;100(2):96–8. [PubMed: 20459911]
136. Nguyen AQ, Anjum SK, Halpern SE, Kumar K, Van Pilsum Rasmussen SE, Doby B, et al. Willingness to Donate Organs Among People Living With HIV. *J Acquir Immune Defic Syndr*. 2018;79(1):e30–e6. [PubMed: 29781880]
137. Taha H, Newby K, Das A, Das S. Attitude of patients with HIV infection towards organ transplant between HIV patients. A cross-sectional questionnaire survey. *Int J STD AIDS*. 2016;27(1):13–8. [PubMed: 25614524]
138. Lee YC, Hung CC, Cheng A, Liu WC, Wu PY, Yang SP, et al. Willingness of human immunodeficiency virus-positive patients to donate their organs for transplantation in Taiwan: a cross-sectional questionnaire survey. *Transpl Infect Dis*. 2016;18(6):856–61. [PubMed: 27663143]

Pre-transplant Evaluation	Peri-transplant Considerations	Post-transplant Monitoring
<ul style="list-style-type: none"> Follow standard transplant center clinical, serologic, psychosocial, & cancer screening <ul style="list-style-type: none"> Include anal and cervical HPV/cancer screening Assess for living donors Ensure vaccinations up to date Evaluate for & treat active OIs* Obtain history of any prior OIs* Ensure CD4 cells $\geq 200/\text{ml}^3$ for kidney or $\geq 100/\text{ml}^3$ for liver Ensure HIV RNA $< 50 \text{ c/mL}$ on ART <ul style="list-style-type: none"> Avoid pharmacoenhancers Consider INSTIs Include HBV-active NRTI if prior infection Consider treating HCV with DAAs <ul style="list-style-type: none"> May hold if HCV+ donor organs are available Consider participation in IRB-approved HIV D+/R+ SOT study <ul style="list-style-type: none"> Assign an independent advocate 	<ul style="list-style-type: none"> Follow standard donor assessment Utilize induction immunosuppression, including ATG if indicated Monitor for drug-drug interactions (CNI, MTOR levels) with maintenance immunosuppression <ul style="list-style-type: none"> Tacrolimus preferred over cyclosporine Treat HCV coinfection with DAAs For HIV+ donors, obtain history of ART use, adherence, and resistance, co-receptor tropism, OIs, as well as CD4 & viral load if available <ul style="list-style-type: none"> Exclude donors with active OIs Consider APOL1 testing for HIV+ living kidney donors 	<ul style="list-style-type: none"> Close monitoring for rejection OI prophylaxis <ul style="list-style-type: none"> Standard CMV prophylaxis Secondary prophylaxis for prior OIs CD4-directed OI prophylaxis Lifelong PJP prophylaxis recommended Treat HCV coinfection with DAAs Continue standard HIV care, including cancer & metabolic screening <ul style="list-style-type: none"> Include anal and cervical cancer/HPV screening Close HIV RNA monitoring for breakthrough/superinfection <ul style="list-style-type: none"> Consider genotype & tropism assay if viremic Evaluate for HIV involvement in kidney grafts[#]

*Chronic cryptosporidiosis, visceral Kaposi's sarcoma, and progressive multifocal leukoencephalopathy have been considered contraindications
[#] Electron microscopy and, if available, HIV urine NAT are relevant modalities

Figure 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 grey boxes denote standard HIV+ SOT practices whereas the darker grey boxes pertain to HIV D+/R+ SOT and other investigational protocols.

Abbreviations

APOL1 denotes apolipoprotein L1, ATG anti-thymocyte globulin, c/ml copies/milliliter, 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

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)	Study Period	Study Design	Organ	HCV+	ATG Induction	Rejection	Severe Infection	Bacteremia	Invasive Fungal Infection	Viral OT ²	Other HIV-Associated OT ³	Patient Survival
Year, Country			(N)	%	%	% (period)	%	%	Process (N)	Process (N)	Process (N)	1, 3, 5-Year (%)
Stock et al. (39) 2010, USA	2003-2009	Prospective Multicenter	Kidney (150)	19	32	31 (1 yr) 41 (3 yrs)	38	7	0	BKV (5)	Candida esoph (1) KS (2) Cryptosporidiosis (1) PJP (1)	95, 88, ND
Locke et al. (88) 2015, USA	2002-2011	Registry	Kidney (510)	24	28	18 (1 yr)	ND	ND	ND	ND	ND	95, 88, 84
Gadhago et al. (89) 2013, UK	2005-2011	Retrospective Multicenter	Kidney (35)	3	0	44 (1 yr) ^a 47 (1 yr)	54	ND	0	CMV (13) EBV (5) BKV (5) HSV (1)	KS (1) Candida esoph (1)	91, 91, ND
Suarez et al. (90) 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. (50) 2014, USA	2000-2014	Registry	Kidney (830)	22	44	ND	15	ND	Coccidiomycosis (1)	CMV (58) ^b	Candida esoph (8) PJP (3) TB (1) KS (1)	95, ND, ND ^c
Muller et al. (91) 2015, South Africa	2008-2014	Prospective Single-center	Kidney (27)	0	100	8 (1 yr) ^a 22 (3 yr) ^a	33	7	Aspergillosis (1)	ND	TB (1)	84, 84, 74
Cristelli et al. (92) 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
Liver Transplantation												

Kidney Transplantation												
Trial (Ref)	Study Period	Study Design	Organ	HCV+	ATG Induction	Rejection	Severe Infection ¹	Bacteremia	Invasive Fungal Infection	Viral OI ²	Other HIV-Associated OI ³	Patient Survival 1, 3, 5-Year (%)
Year, Country			(N)	%	%	% (period)	%	%	Process (N)	Process (N)	Process (N)	
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	1, 3, 5-Year (%)
Year, Country			(N)	%	% (follow-up)	%	%	Process (N)	Process (N)	Process (N)	Process (N)	
Moreno et al. (93) 2012, Spain	2002-2009	Prospective Multicenter	Liver (84)	100	38 (median 2.6 yr)	43	10	Candidemia (2) Aspergillosis (1) Zygomycosis (2)	CMV (21) HSV (13) VZV (1)	PIP (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) PIP (1)	ND, ND, ND	
Terrault et al. (37) 2012, USA	2003-2010	Prospective Multicenter (HIVTR)	Liver (81) Liver-Kidney (8)	100	39 (3 yrs)	ND	ND	ND	ND	Candida esoph (3) KS (1) Candida bronchi (1) PIP (1)	76, 60, ND	
Di Benedetto et al. (95) 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. (43) 2016, USA	2002-2011	Registry	Liver (180)	65	16 (median 1.8 yr)	ND	ND	ND	ND	ND	77, 62, 56	
Teicher et al. (94) 2015, France	1990-2012	Retrospective Single-center	Liver (109)	79	41 (median 3.8 yr)	37 ^d	26	Candidemia (2) Aspergillosis (3)	CMV (5)	Candida esoph (2) NTM (1) TB (1)	83, 77, 61	
Annotation												

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, cryptocosporidiosis, tuberculosis, nontuberculous mycobacteria, progressive multifocal leukoencephalopathy, toxoplasmosis and Kaposi's sarcoma.

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biopsy-proven rejection

q : CMV rates calculated from provided graphs

c : survival calculated from Kaplan-Meier curves

d : reported any infection

Abbreviations

BKV denotes BK virus, Candida bronchi candidiasis of bronchus, Candida esoph Candida esophagitis, CMV cytomegalovirus, ND no data, EBV Epstein barr virus, HSV herpes simplex virus, KS Kaposi's sarcoma, NTM nontuberculous mycobacteria, PJP Pneumocystis jirovecii, TB tuberculosis, VZV varicella zoster virus