Kidney transplantation in patients with HIV

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Abstract

HIV+ individuals are at increased risk for end-stage renal disease (ESRD). Kidney transplantation is the best treatment for ESRD in the HIV+ population. Despite reduced access to transplantation, HIV+ patients have excellent outcomes and clearly benefit. Common posttransplant complications and management concerns, including the optimal antiretroviral regimen, immunosuppression protocols, infectious prophylaxis, Hepatitis C co-infection, metabolic complications and malignancy are all discussed.
Despite advances in HIV care, HIV infection remains associated with an increased risk of ESRD, especially among African American individuals. North American AIDS Cohort Collaboration on Research and Design (NAACORD) (1) demonstrated that the standardized incidence ratio (SIR) for ESRD among African Americans was 4.5 (95% CI 3.9-5.2) and 1.5 (95% CI 1.0-2.2) for Caucasians. Historically, survival on dialysis for HIV+ individuals was poor, but has improved with anti-retroviral therapy (ART). In analysis of United States Renal Data Systems (USRDS) data (2) spanning 1985-1999, Ahuja et al. demonstrated steady improvement in 1-year dialysis survival for HIV+ patients, from 56% in 1990 to 74% in 1999; however overall outcomes were inferior to a matched HIV- cohort. More recently an analysis (3) of contemporary HIV+ dialysis patients (2004-2013) examined the impact of race and HCV co-infection on dialysis survival. In multivariable models HIV mono-infection was not associated with an increased risk of mortality among Caucasians (aHR 1.03, 95% CI 0.91-1.16) but HIV/HCV co-infection was (aHR 1.48, 95% CI 1.18-1.87); likewise, both HIV infection (1.44, 95% CI 1.37-1.52) and HIV/HCV co-infection (1.71, 95% CI 1.60-1.84) were associated with an increased risk of death among Non-Caucasians. Thus ESRD is a frequent complication of HIV infection, disproportionately affecting African Americans, and associated with persistent racial differences in survival. In the pre-direct acting antiviral (DAA) era HCV co-infected patients had diminished dialysis survival and the effect of treating HCV on dialysis survival remains an open question.

**Summary**

- ESRD is a common complication of HIV infection
- African Americans are disproportionately affected
- Survival on dialysis has improved with ART but racial disparities persist

**Access to kidney transplantation**

Kidney transplantation is the ideal renal replacement therapy, yet HIV+ individuals face clear barriers to accessing kidney transplantation. A single center study (4) from New York City demonstrated that from 2000-2007 only 20% of HIV+ patients evaluated for transplant were listed, whereas 73% of HIV- patients achieved listing during the same time period. African American race, a history of substance abuse and uncontrolled HIV infection (CD4 count <200 or detectable viral load) were independently associated with failure to achieve waitlisting. A similar study (5) from Philadelphia largely confirmed these findings; while waitlisting rates had improved, the evaluation process was longer for HIV+ candidates and they spent more time inactive on the list. In their cohort of patients evaluated 2011-2015, incomplete work up, substance abuse and uncontrolled HIV infection remained the top three reasons patients were not listed. The authors identified integrated HIV care as a contributor to their improved wait-listing rates and clearly comprehensive care benefits complex patients such as those with HIV infection.

**Patient selection**

Patient selection criteria (6) for HIV+ candidates mirror those established for HIV- patients; they must meet all of a center’s general medical and psycho-social criteria in addition to HIV specific metrics. Patients must have an undetectable viral load, a CD4 count >200, and with the exception of elite controllers, be on a stable ART regimen. They cannot have active
opportunistic infections. All HIV+ candidates should be evaluated by a transplant infectious
disease specialist to review HIV and ART history, vaccinations and tuberculosis risk factors. Due to shared modes of transmission, many HIV+ individuals are co-infected with HCV or HBV; co-infected kidney transplant candidates also require an evaluation by Hepatology and assessment of degree of liver fibrosis, often via transient elastography or biopsy as indicated. The more lengthy and complex evaluation process can create additional barriers to waitlisting for HIV+ transplant candidates. Thus, pre-emptive referral for HIV+ patients with CKD stage IV is essential. Transplant centers should be sensitive to the complexities of navigating the evaluation process for HIV+ individuals and centralized care that involves coordination with subspecialists whenever possible helps overcome barriers for these patients.

Summary

- HIV+ individuals face significant barriers in accessing the kidney transplant waiting list
- Integrated multispecialty care can facilitate waitlist access
- HIV+ individuals must demonstrate adequate HIV control in addition to meeting general medical listing criteria

Waitlist outcomes

Due to data collection practices by the Organ Procurement and Transplantation Network (OPTN), where HIV and HCV serostatus information is not recorded as part of the transplant candidate registration form, it has been difficult to ascertain the number of HIV+ individuals waitlisted for transplantation. In order to overcome this limitation, Locke et al. (7) linked detailed pharmacy fill data to transplant registry data, identifying 1636 HIV+ candidates waitlisted for a kidney from 2001-2012. Like the HIV+ dialysis population they were predominantly young, male and African American. While waitlist mortality was similar to HIV- candidates, HIV+ candidates were significantly less likely to receive a living donor kidney transplant (aHR 0.53, 95% CI 0.44-0.64) or a transplant at all (0.72, 95% CI 0.64-0.82). Data from Europe confirms this trend; in a report of 255 HIV+ dialysis patients from the Renal Epidemiology and Information Network (REIN) registry (8), HIV+ candidates were 32% less likely to be waitlisted and 25% less likely to be transplanted. Even among those who are able to be waitlisted challenges remain; HIV+ candidates are 12% less likely (aHR 0.88, 95% CI 0.79-0.99) to receive a first position organ offer (9). Clearly, multiple barriers in access to transplantation for HIV+ individuals exist and registry on the waitlist does not guarantee transplantation.

Kidney transplant outcomes

Kidney transplantation is the best method of renal replacement therapy, and has been associated with a survival benefit over remaining on dialysis. The benefit associated with transplantation has been demonstrated in many high-risk patient populations and holds true for HIV+ candidates as well. Using Scientific Registry of Transplant Recipient (SRTR) data linked to pharmacy fill records, Locke et al. (10) showed that HIV+ patients achieved a survival benefit with transplantation after 194 days; for those co-infected with HCV the time to equivalent survival was a little longer at 392 days. This study underscores the importance of referring all HIV+ patients with advanced CKD or ESRD for transplant evaluation.

Contemporary outcomes for HIV+ patients transplanted on ART are excellent. An analysis of OPTN data (11) that encompassed HIV+ and HIV/HCV+ first kidney recipients transplanted from 1996-2013 demonstrated excellent patient (aHR 0.90, 95% CI 0.66-1.24) and allograft
survival (aHR 0.60, 95% CI 0.40-0.88) among those mono-infected with HIV; whereas outcomes were notably inferior among those co-infected with HCV (mortality aHR 2.26, 95% CI 1.45-3.52; graft loss aHR 2.59, 95% CI 1.60-4.19). Similar findings were reported in analyses employing SRTR data (12) or matched sampling strategies (13).

Summary

- HIV+ individuals are less likely to be transplanted than HIV- individuals
- Kidney transplantation confers a significant survival benefit in HIV+ patients
- Patient and allograft outcomes are excellent among HIV mono-infected recipients.

Unique transplant opportunities – HIV+ to HIV+ kidney transplantation

The most extensive experience in the use of HIV+ kidney donors comes from South Africa. To date they have transplanted 51 recipients of HIV+ donor kidneys (14); outcomes have been comparable to those observed in HIV+ recipients of HIV- donor organs, with 1-year patient survival of 87% and 1-year death-censored allograft survival of 96%. Of note, the South African experience is somewhat unique – the vast majority of HIV+ donors are young trauma victims and most are either not on ART or only first-line therapy. One concern with the use of HIV+ donor organs is the transmission of other HIV strains to the recipient, including potentially ART resistant ones. They performed viral deep sequencing on 25 patients and could only detect donor-derived virus in 1 recipient, which was transient. There have been no virologic failures reported in the South African cohort.

In response to the profound organ shortage in the United States there has been interest in exploring the use of HIV+ donors in the US; this was previously illegal due to provisions in the National Organ Transplantation Act but overturned by passage of the HIV Organ Policy Equity (HOPE) Act in 2013, which permits research in the area of HIV+ to HIV+ transplantation. The true number of potential HIV+ donors is unknown. Estimates from Boyarsky et al. (15), generated using data from the Nationwide Inpatient Sample, HIV Research Network and the OPTN, were as high as 500 potential HIV+ donors per year. A study (16) that explored the possibilities among HIV+ individuals “in care” in Philadelphia generated a much more modest estimate of 13 potential donors over a 5 year period; the authors noted that most had comorbidities such as diabetes, hypertension or HCV co-infection that would result in them being labeled as high kidney donor profile index organs and therefore less likely to be used for transplantation. The truth may actually be somewhere in between – in the nearly 2 years since the inception of a multicenter trial of HIV+ to HIV+ transplantation, there were 27 HIV+ donors utilized (17). While HIV+ donor utilization may have failed to achieve initial projections, research in this area has helped to reduce the stigma around HIV in transplantation and increase public awareness of transplantation as a treatment option for individuals living with HIV and end-organ failure.

Limited outcome data (18) suggest that short-term outcomes for recipients of HIV+ organs are similar to those observed in recipients of HIV- organs, but acute rejection rates are very high (43%), especially among those who did not receive antibody depleting induction. Loss of HIV viral control was only observed in one study participant and attributed to nonadherence. These data are encouraging but longer-term follow up is clearly needed.

The HOPE Act also contains provisions allowing for HIV+ living donors. In light of the association between HIV infection and CKD/ESRD, there has been significant concern in the
transplant community regarding the suitability of HIV+ individuals to serve as living kidney donors. While one study (19) suggested that the risk of ESRD among potential HIV+ living donors was low, there were many limitations to this work, which did not include any actual HIV+ donors, had short follow up, missing data and included individuals in the cohort who would not meet most transplant center standards for donation. To date, only one person has served as an HIV+ living donor and the true risks associated with the practice remain largely unknown.

Summary

- Transplantation with HIV+ donor kidneys is possible but remains limited to the research setting in the United States
- Available data do not suggest clinically significant transmission of donor virus
- The true number of HIV+ organ donors in the United States is unknown

Posttransplant management

HIV+ kidney transplant recipients face many of the same long-term challenges to transplant success as their HIV- counterparts (Figure 1). Post-transplant monitoring and risk factor modification is in many ways the same.

Virologic monitoring and control

In addition to routine posttransplant laboratory testing, HIV+ recipients should have their CD4 count and HIV viral load (VL) checked at 1 month posttransplant and every 2-3 months thereafter (20). Individuals with a CD4 count less than 200 cells/m³ will require reinstitution of opportunistic infection prophylaxis; those with detectable VL will require adherence assessment and potentially viral resistance testing. This testing and any changes in ART regimen should be coordinated with the patient’s infectious disease provider.

Available data clearly suggest that integrase inhibitor based ART, rather than protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimens, is preferred for HIV+ kidney transplant recipients. Protease inhibitors are among the most profound inhibitors of the CYP3A4 metabolic pathway for calcineurin inhibitors (CNIs); concomitant use of PIs and CNIs requires significant CNI dose reductions (21), often irregular dosing schedules and provides a lower area under the curve (AUC) of CNI exposure at similar trough levels (22). Together these can contribute to the increased rates of acute rejection observed in HIV+ recipients. Additionally, use of PI-based regimens has been associated with an increased risk of patient mortality (aHR 1.91, 95% CI 1.02-3.59) and diminished allograft survival (aHR 1.84, 95% CI 1.22-2.77) (23). NNRTIs have a more variable effect on CYP3A4 enzymes. When selecting an integrase inhibitor it bears noting that dolutegravir inhibits tubular secretion of creatinine, which can falsely elevate serum creatinine levels, and elvitegravir requires cobicistat boosting, which also induces CYP3A4. Therefore, many transplant recipients are on a raltegravir-based regimen.

Patients who are co-infected with hepatitis B (HBV) require 2 drugs with anti-HBV activity. For many this means a tenofovir containing regimen. While tenofovir can be nephrotoxic, one small study (24) did not find a difference in posttransplant graft survival on the basis of tenofovir use; however, the rate of graft loss at 3 years was high in both cohorts. More recently a less nephrotoxic version of tenofovir, tenofovir alafenamide, became available and this is the preferred agent for use in this population.
Addressing HCV co-infection

In the general transplant population, treatment of HCV infection has been associated with improved patient and allograft survival (25). One small study from Miami (26) suggests that the same is true among HIV/HCV co-infected transplant recipients. In a cohort of 13 HIV/HCV+ patients transplanted from 2007-2017, patient (100% vs 83%) and allograft (100% vs 67%) survival were significantly better in those treated with direct acting antivirals and cured of their HCV infection. Posttransplant treatment, while rendered complex by consideration of drug-drug interactions between immunosuppression, ART and DAAs, is essential. Data suggest (27) that for many patients, especially those with less severe fibrosis (Metavir stage F0-F1), transplantation with an HCV+ donor followed by posttransplant treatment is more cost-effective than pretransplant treatment; however for individuals with advanced liver disease, who are at risk of decompensation, or who are listed at centers that do not use HCV+ organs, pretransplant treatment may be preferred.

Immune control and Immunosuppression

The HIV-TR Multi-Site trial (6) clearly demonstrated that despite relative immunodeficiency, HIV+ kidney transplant recipients are at increased risk of acute rejection; in that study, the 1-year cumulative risk of acute rejection was 30%, compared to 10-15% nationally among HIV-patients. There are aspects of this risk that are modifiable by clinical circumstances. Duration of viral control contributes; patients with undetectable VL for <2yrs pretransplant were 2.2-fold more likely to have rejection than those with longer periods of viral control (28). Immunosuppression choices are also relevant. Induction with rabbit anti-thymocyte globulin (rATG) has been associated with a 61% reduction in acute rejection (aRR 0.39, 95% CI 0.18-0.87) (29) and induction improves death censored graft loss (30). Use of tacrolimus-based maintenance immunosuppression reduces the risk of rejection, compared to cyclosporine-based regimens (31). Rapamycin, despite reducing the latent proviral reservoir (32), is associated with a >2-fold risk of rejection (29) and is generally to be avoided; likewise "steroid-free" immunosuppression protocols are associated with unacceptably high rates of rejection (33). Thus, for many patients rATG induction is preferred, along with tacrolimus-based, triple immunosuppression that includes steroids.

Interestingly, despite the increased risk of acute rejection observed in the HIV+ transplant population, current data do not suggest an increased frequency of de novo donor specific antibodies (DSA) (34). Some centers perform protocol biopsies in this patient cohort, however this is not universal practice.

Summary

- Integrase inhibitor based regimens are preferred in HIV+ transplant recipients
- HCV co-infected individuals benefit from DAA therapy to cure their HCV infection
- rATG induction and tacrolimus-based triple immunosuppression are associated with reduced rates of acute rejection

Infections

Infection is a frequent posttransplant complication among HIV+ recipients. In the HIV-TR Multi-Site trial (6) 38% of recipients had an infection necessitating hospitalization and more infections overall were observed in the group induced with rATG as well as in patients co-infected with
HCV. Of these infections the vast majority were bacterial (69%), with genito-urinary (26%), respiratory (20%) and bloodstream (19%) sources being the most common. Importantly, opportunistic infections were rare.

Excess infectious risk has been one of the concerns regarding use of rATG induction in HIV+ recipients. HIV+ patients induced with rATG have a more profound and longer lasting reduction in their CD4 count than those induced with anti-IL2 receptor antibodies (6); however this CD4 depletion mirrors what is observed in HIV- patients who receive rATG (35). There are some data to suggest that individuals with starting CD4 counts <350 are more greatly affected than those with higher CD4 counts at time of induction (36). Registry data (30) suggest that on a national level use of depleting induction is not associated with an increased risk of common posttransplant infections but does lead to lower delayed graft function rates, shorter hospital stays and reduced death censored graft loss.

Similar to HIV- recipients, HIV+ kidney transplant patients require prophylaxis for common posttransplant infections, including Pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV). Consensus guidelines (20) suggest at least 1 year of PJP prophylaxis, with some centers administering it life-long; trimethoprim-sulfamethoxazole is the preferred agent and also provides coverage for toxoplasma. CMV prophylaxis approaches vary, with some centers employing the same approach as in HIV- patients, while others use high dose valganciclovir (900mg daily, dosed for renal function) for 3-6 months depending on donor and recipient serostatus. Recipients require coverage for histoplasma and coccidiodomycosis if they live in endemic areas. All recipients should be screened for latent tuberculosis as a part of their transplant evaluation and those with known exposure require isoniazid treatment if not completed pretransplant.

BK virus is a frequent complication of kidney transplantation in general and thought to in part reflect a patient’s overall state of immunosuppression. Interestingly, even though HIV+ kidney transplant patients can be viewed as more immunocompromised than HIV- patients, no increase in BK viremia has been observed in this population (34). Posttransplant screening for BK in HIV+ recipients should follow general guidelines for kidney transplant recipient screening (37).

Summary

- Posttransplant infections are common, especially among HIV/HCV co-infected individuals
- Opportunistic infection prophylaxis strategies are similar to that employed in HIV-individuals but PJP prophylaxis is often extended

Metabolic complications

Cardiovascular disease is an important contributor to posttransplant mortality and HIV infection should be considered a coronary artery disease risk equivalent (38). Attention should be paid to hypertension as a modifiable risk factor and it is reasonable to extrapolate general targets for blood pressure control to this population (39). Dihydropyridine calcium channel blockers are preferred in transplant recipients due to a lack of drug-drug interactions with CNIs; they are also a reasonable first choice for HIV+ patients. Posttransplant diabetes is another target for intervention. HIV+ individuals are at increased risk for diabetes and there are multiple mechanisms by which HIV infection and its treatment contributes to this risk (40); a fasting
plasma glucose >125mg/dL or oral glucose tolerance test can make the diagnosis. When
initiating treatment it is important to consider drug-drug interactions between ART and diabetes
medications; dolutegravir increases metformin levels, PIs increase DPP-4, glitazone and
meglitinide levels, and patients on treatment require close monitoring. Dyslipidemia is common
in both the transplant and HIV+ populations. While a randomized trial (41) failed to show a
benefit of statins in the transplant population, meta-analytic data (42) suggests there is a trend
toward benefit and most transplant physicians recommend their use. Among people living with
HIV, statins are clearly beneficial and one meta-analysis (43) found a 33% reduction in all cause
mortality associated with their use. Drug interactions are a consideration with statins and ART;
lovastatin and simvastatin are contraindicated for use with PIs or integrase inhibitors, and all
HIV+ patients on a statin should be closely monitored for side effects.

Malignancy

Both transplant recipients and HIV+ individuals are at increased risk of cancer. Among
transplant recipients, virally-mediated cancers such as Kaposi’s sarcoma, liver and anogenital
cancers, are all significantly increased and many “common” cancers such as lung, kidney,
colon, skin and pancreas are also more prevalent (44). Among people living with HIV, AIDS-
defining malignancies are on the decline but a compensatory rise has been noted in other
malignancies (45); smoking is a major contributor to malignancy risk, dwarfing other factors
such as HIV viral control or hepatitis (46). A meta-analytic comparison (47) of published reports
of cancers in both the transplant and HIV+ populations noted that infection related cancers were
increased in both cohorts whereas epithelial cancers, such as breast, ovarian and prostate
cancers were not. Lung cancer was increased in both transplant recipients and HIV+
individuals. There are no cancer screening guidelines that specifically address HIV+ transplant
recipients, but in light of the available data it seems reasonable to suggest regular screening for
human papilloma virus-related malignancies (anal and cervical cancers) as well as lung cancer
screening among those with significant cigarette exposure. Additionally, any individuals who
are currently smoking should be strongly encouraged to quit.

Bone and mineral disease

Bone disease after kidney transplantation is complex; it can encompass low turnover states as
well as osteopenia/osteoporosis; use of steroids, CNIs and hyperparathyroidism all contribute to
risk (48). Transplant recipients at increased fracture risk benefit from DEXA screening, and
pharmacotherapy should be considered after contributing factors (such as hypovitaminosis D
and hypophosphatemia) have been corrected. HIV+ individuals are at increased risk for
osteoporosis and fracture; it has been estimated that almost 30% have osteoporosis and as
many as 50% have osteopenia (49). HIV infection contributes to bone loss in several ways. The
inflammatory state increases osteoclast activity and promotes osteoblast apoptosis while
increased TNFα levels increase bone resorption by osteoclasts (50). Initiation of tenofovir
containing regimens has been associated with a loss of bone mineral density of 2-6% (50).
DEXA should be considered in all HIV+ individuals who are over age 50 and pharmacotherapy
considered for those with T-scores less than 2.5, a history of fracture or low bone mass with
increased fracture risk; bisphosphonates are considered first line therapy in this population. All
patients benefit from weight bearing exercise and smoking cessation; consideration should be
given to switching ART to non-tenofovir containing regimens if possible.

Summary
• HIV+ transplant recipients should be screened for new onset diabetes after transplant
• Statin therapy should be considered in all HIV+ kidney transplant recipients
• Smoking cessation is important to reduce both posttransplant malignancy and posttransplant bone loss in this patient population

Summary

ESRD remains a common complication of HIV infection and people living with HIV clearly benefit from kidney transplantation. Perceived medical complexity should not be a barrier and comprehensive, multidisciplinary care can help patients achieve transplantation. Posttransplant outcomes are generally similar to those observed in HIV- individuals. HIV+ donor organs remain limited to the research domain. For most patients rATG induction with tacrolimus-based maintenance immunosuppression provides the best protection from rejection. Co-infected individuals benefit from prompt posttransplant treatment of HCV. Posttransplant care is largely similar to that of HIV- recipients, including infectious prophylaxis, laboratory monitoring, and cardiovascular disease risk modification. Aggressive screening for posttransplant malignancy is reasonable although guidelines specific for this population do not exist.

Author Contributions

D Sawinski: Writing - original draft; Writing - review and editing

Disclosures

D Sawinski has nothing to disclose.

References


42. Palmer SC, Navaneethan SD, Craig JC et al. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. Cochrane Database of Sytematic Reviews. 2014


Figure 1. There are many threats to long-term patient and allograft survival. The challenges faced by HIV+ kidney transplant recipients are largely shared by the HIV- transplant population.