Kidney Transplantation in a HIV-Positive Recipient

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Introduction
HIV infection is a risk factor for kidney disease. Kidney transplantation is an accepted therapy for ESKD in this population. HIV-positive candidates face barriers to waitlisting but can achieve good post-transplant outcomes. Drug–drug interactions and comorbid illnesses present unique challenges in this population.

Case
A 56 year-old man with ESKD attributed to HIV-associated nephropathy presents for his first transplant evaluation. On hemodialysis for 4 years, his other medical comorbidities include anemia, hypertension, and hyperparathyroidism. His CD4 count is 344 cells/m3 and his viral load undetectable; he has taken a regimen of ritonavir-boosted darunavir with abacavir and lamivudine for >10 years and reports perfect adherence. He had Pneumocystis pneumonia at his initial HIV diagnosis but no other opportunistic infections.

Which HIV-Positive Patients Are Appropriate for Kidney Transplantation?
HIV infection was once a relative contraindication to transplantation; however, the National Institutes of Health–sponsored, multicenter trial (1) of kidney transplantation in patients with HIV infection (Solid Organ Transplantation in HIV: Multi-Site Study [HIV-TR study]) clearly demonstrated safety in this patient population. Three-year patient (88.2%) and allograft (73.7%) survival were similar to those observed in older HIV-negative recipients and progression of HIV disease was not observed despite maintenance immunosuppression. To qualify for transplantation, HIV-positive candidates must meet the transplant center’s general medical and surgical criteria in addition to HIV-specific metrics. Although most centers generally adhere to the patient selection criteria outlined in the HIV-TR study (absence of active infection or malignancy, undetectable viral load, CD4 count >200 cells/m3, on a stable antiretroviral regimen and no history of progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, central nervous system lymphoma or Kaposi sarcoma), some centers will consider patients with a CD4 count <200 cells/m3 if the HIV viral load is undetectable. Although the HIV-TR study specified a 16-week time frame for viral loads and CD4 counts, many centers will accept 3 months of stability.

Timely referral for kidney transplantation is crucial for HIV-positive transplant candidates because their transplant evaluation process is lengthier and more complex. In addition to the standard evaluation performed by the nephrologist and surgeon, which includes cardiac risk stratification and general health maintenance screenings, HIV-positive candidates require a careful assessment of their social support and substance abuse history; active substance abuse issues are a common reason HIV-positive candidates fail to achieve waitlisting (2). Additionally, as many are coinfected with hepatitis C (HCV) or hepatitis B, evaluation by a hepatologist is often necessary. A transplant infectious disease specialist must review their HIV disease and antiretroviral treatment history, medication adherence, and vaccinations; past tuberculosis exposure or risk factors also require assessment. Despite the added complexities of their transplant evaluation, HIV-positive kidney transplant recipients have better survival with transplantation (3) and every effort should be made to facilitate their access to the waiting list. Notwithstanding the clear benefit of preemptive transplantation only 11.4% of HIV-positive candidates were evaluated preemptively (2).

Case, Continued
His evaluation reveals he is HCV-positive with genotype 1a infection; he is referred to hepatology and his liver biopsy demonstrated minimal fibrosis (Metavir stage F0-F1). He has a normal chest x-ray and exercise stress test. He is blood group O and his partner has expressed interest in donating.

What Type of Donor Is Best?
Living donor kidney transplantation is associated with a shorter time to transplantation and superior outcomes, including for recipients with HIV. However, HIV-positive transplant candidates may perceive their HIV status as a barrier to discussing living donation, and may be less willing to pursue this option (4); as a result, they have a 47% lower rate of living donor transplantation (5). Interventions, such as the living donor navigator program...
at University of Alabama at Birmingham, are being explored to narrow this disparity. For patients without a living donor option, registry data has demonstrated better outcomes for recipients of kidneys with fewer HLA mismatches.

HIV-positive transplant candidates are also eligible to consider HIV-positive organs in a research setting. Although the total number of HIV-positive deceased donors utilized thus far is small, patient and allograft outcomes have been acceptable (6), although a high rate of acute rejection was observed in HIV-positive deceased donor recipients induced with basiliximab. To date, no one has served as an HIV-positive living donor; given the association between HIV infection and the development of CKD, there are reasonable concerns about the safety of this practice.

HIV/HCV coinfected recipients also have the option of accepting an HCV nucleic acid test-positive organ. Use of HCV-positive donors has been associated with a shorter time to transplantation in the HCV-monoinfected population; HIV/HCV coinfected transplant candidates should be encouraged to defer HCV therapy to preserve this transplant option. Although inclusion criteria for the HIV-positive donor study permits the use of HIV/HCV coinfected donors, currently no published data regarding the use or outcomes from such transplants is available.

Case, Continued

His partner is ruled out because of diabetes. The patient agrees to accept HCV nucleic acid test-positive organs and is transplanted within 3 months of waitlist registration with a 23-year-old Public Health Service increased risk donor. His serum creatinine is 1.3 mg/dl on postoperative day 4 and his antiretroviral regimen is switched to abacavir, lamivudine, and dolutegravir. He was started on a 12-week course of ledipasvir-sofosbuvir at 3 months post-transplant and achieved cure.

What Type of Immunosuppression Should HIV-Positive Recipients Receive?

The HIV-TR study (1) demonstrated that HIV-positive recipients can safely receive calcineurin inhibitor (CNI)-based immunosuppression after induction without loss of HIV viral control. There was a significantly increased risk of acute rejection observed in this trial, which may have been because nearly two thirds of participants were induced with anti-IL2 receptor antibodies. Although steroid-free approaches have been described in the literature, we utilize standard tacrolimus-based triple immunosuppression (including an antimetabolite and steroid) in our HIV-positive recipients. In response to the higher acute rejection rates observed in this population, it is our practice to use rabbit antithymocyte globulin induction; consistent with registry-based studies (7), we have not observed excessive infectious complications associated with this induction strategy. However, as T cell depletion with rabbit antithymocyte globulin can be profound and take up to a year for CD4 counts to recover (1), some transplant centers prefer basiliximab induction.

Similar to their HIV-negative counterparts, HIV-positive patients require prophylaxis for opportunistic infections including *Pneumocystis jiroveci*, cytomegalovirus (CMV), and fungi. Transplant society guidelines (8) suggest that HIV-positive recipients should receive lifelong *Pneumocystis* prophylaxis. CMV prophylaxis should mirror transplant center practices for HIV-negative recipients. Clotrimazole or nystatin provide adequate antifungal coverage unless patients are from an area endemic for *Histoplasma* or *Coccidioidomycosis*, when fluconazole would be indicated. *Prophylaxis for Mycobacterium avium* complex is not usually necessary because of the CD4 count threshold required for transplant candidacy.

Is One Antiretroviral Regimen Preferable Over Another?

Protease inhibitors (PIs) are among the most potent inhibitors of cytochrome P450 3A4, the main metabolic pathway for CNIs. Concomitant administration of PIs and CNIs requires significant CNI dose reductions and sometimes nondaily dosing to achieve acceptable CNI troughs; this can complicate medication adherence for patients and potentially lead to subtherapeutic levels. In contrast, non-nucleoside reverse transcription inhibitors are generally potent inducers of cytochrome P450 3A4; patients will require significantly increased CNI doses to achieve trough targets. In recognition of these complex drug-drug interactions and adverse posttransplant outcomes reported for patients on PI-based regimens (9), we convert all patients to an integrase inhibitor-based regimen, ideally in the pre-transplant setting, whenever possible. We also advocate for the use of tenofovir alafenamide, rather than tenofovir disoproxil fumarate, because of the reduced nephrotoxicity of tenofovir alafenamide.

It is reasonable to transplant elite controllers off antiretrovirals but they require close monitoring of HIV viral loads and CD4 counts after transplantation, with a plan to institute therapy if persistent detectable HIV viremia occurs.

When to Treat HCV Coinfection?

HIV/HCV coinfected kidney transplant recipients have been shown in clinical trials (1) and registry data analyses to have reduced post-transplant survival and inferior allograft outcomes compared with patients with HIV infection alone; however, the availability of direct acting antivirals for the cure of HCV is expected to improve outcomes significantly. HCV can be treated in either the pre- or post-transplant setting. Economic decision analysis data (10) suggests that post-transplant treatment is preferred for most transplant candidates, unless they have advanced fibrosis or are in a very short waiting time area, as pretransplant treatment generally delays deceased donor transplantation. We advise our patients to accept posttransplant treatment unless they have a living kidney donor.

Post-transplant treatment of HCV in coinfected patients is complex, with drug-drug interactions between direct acting antivirals, antiretrovirals, and immunosuppression to be considered; additionally, post-transplant kidney function influences regimen selection if GFR is $< 30$ ml/min. Treatment should only be undertaken in consultation with transplant infectious disease, hepatology, and transplant nephrology. We usually wait until 1–3 months...
post-transplant before starting HCV therapy, to permit clinical stabilization of kidney function before adding another element to the patient’s regimen, but there is no objective evidence to support our practice.

Conclusions
Kidney transplantation is considered standard of care for patients with HIV and preemptive transplantation the ideal. Effect HCV therapies are expected to improve outcomes for HIV/HCV coinfected patients and use of HCV-positive organs should be encouraged.

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References

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