Kidney Disease in HIV: Moving beyond HIV-Associated Nephropathy

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ABSTRACT

In developed countries, remarkable advances in antiretroviral therapy have transformed HIV infection into a chronic condition. As a result, HIV-associated nephropathy, the classic HIV-driven kidney lesion among individuals of African descent, has largely disappeared in these regions. However, HIV-positive blacks continue to have much higher rates of ESRD than HIV-negative whites, which could be attributed to the APOL1 renal risk variants. Additionally, HIV-positive individuals face adverse consequences beyond HIV itself, including traditional risk factors for CKD and nephrotoxic effects of antiretroviral therapy. Concerns for nephrotoxicity also extend to HIV-negative individuals using tenofovir disoproxil fumarate–based pre-exposure prophylaxis for the prevention of HIV infection. Therefore, CKD remains an important comorbid condition in the HIV-positive population and an emerging concern among HIV-negative persons receiving pre-exposure prophylaxis. With the improved longevity of HIV-positive individuals, a kidney transplant has become a viable option for many who have progressed to ESRD. Herein, we review the growing knowledge regarding the APOL1 renal risk variants in the context of HIV infection, antiretroviral therapy–related nephrotoxicity, and developments in kidney transplantation among HIV-positive individuals.

With effective antiretroviral therapy (ART), the life expectancies of HIV-positive individuals may now approximate those of the general population.1 However, for a growing number of HIV-positive individuals, aging is accompanied by accumulation of noncommunicable diseases, including CKD.2,3 Among HIV-positive individuals in North America, CKD incidence increases by 11-fold among those ages 60–69 years old compared with those ages <40 years old.2 Moreover, the CKD incidence rate remains disproportionately higher in blacks versus nonblacks. This disparity extends to trends in ESRD incidence. Among HIV-positive individuals in North America, the rates of ESRD have declined; however, HIV-positive blacks continue to have substantially higher ESRD incidence rates compared with HIV-positive nonblacks.4 This racial difference may be partially driven by the APOL1 risk variants, which are strongly associated with HIV-associated nephropathy (HIVAN) and CKD progression among individuals of African descent.5–8 CKD among HIV-positive individuals may also be attributed to the rise of other comorbid conditions, such as diabetes, as well as nephrotoxicity from ART. In particular, tenofovir disoproxil fumarate (TDF), which is the most widely used agent for HIV treatment and prophylaxis, has been associated with several forms of kidney disorders and increased CKD risk.9–15 Although the new tenofovir formulation, tenofovir alafenamide (TAF), promises an improved safety profile,16–18 long-term studies are currently nonexistent. In addition, monitoring of kidney health in treated HIV-positive patients is often complicated by drug-related effects on renal tubular creatinine secretion. For many HIV-positive individuals who have progressed to ESRD, kidney transplantation yields favorable outcomes; however, early experiences have raised several issues to be tackled, such as the optimal ART and immunosuppressive regimens. This review focuses on recent advances issues regarding CKD among HIV-positive individuals.

APOL1 RISK VARIANTS AND HIV-RELATED KIDNEY DISEASE

HIVAN mouse models support the existence of host susceptibility genetic variants, which interact with HIV to cause collapsing glomerulopathy and tubulocystic changes characteristic of HIVAN.19–21 In humans, genetic susceptibility has been linked to the APOL1 G1 (composed of
rs73885319 [S342G] and rs60910145 [I348M]) and G2 variants (rs71785313, a 6-bp deletion).22,23 In HIV-positive blacks who underwent clinical kidney biopsies, the high-risk APOL1 genotypes (two copies) were associated with a 29- to 89-fold higher odds of HIVAN compared with the low-risk genotypes (zero of one copy).6,7 The strength of these associations far exceeds the associations of these variants with kidney diseases in HIV-negative populations.6,8,24 Moreover, the magnitude of these associations vary by region, with the most robust associations among HIV-positive blacks residing in sub-Saharan Africa.6,7 Interestingly, the APOL1 risk variants are not required for HIVAN development. Among individuals with biopsy-confirmed HIVAN, 20%–30% do not carry a high-risk genotype, and 5%–8% carry no risk variant, suggesting that other genetic susceptibility factors may contribute to HIVAN pathogenesis.7,25

With global rollout of ART, the incidence of HIVAN has declined substantially. However, the APOL1 risk variants are associated with elevated CKD risk, even among ART-treated HIV-positive blacks. Among 1285 HIV-positive black women, those with high- versus low-risk genotypes were fivefold more likely to have proteinuria, independent of kidney function.26 Among HIV-positive blacks with non-HIVAN kidney disease, those with high-risk genotypes had a threefold higher risk of progressing to ESRD compared with those with low-risk genotypes.5 Similar associations were observed in HIV-positive children, in whom the high-risk genotypes were associated with 3.5-fold odds of CKD.27

The mechanisms by which these variants contribute to CKD are not fully elucidated. In a cohort of HIV-positive women, the APOL1 risk variants were associated with albuminuria but were not associated with urine biomarkers of tubular injury, including IL-18 and kidney injury molecule-1.28 These results suggest that the variants specifically affect the glomeruli and are supported by the predominant expression of apoL1 in podocytes and endothelial cells.29,30 In vitro studies have also shown that apoL1 may allow HIV to persist within IL-1β-primed podocytes, further augmenting endogenous apoL1 production31; in turn, apoL1 overexpression leads to cellular demise.32 Furthermore, in an APOL1 transgenic mouse model, podocyte-specific expression of aberrant apoL1 dose dependently recapitulated global and segmental glomerulosclerosis with tubulointerstitial fibrosis, whereas tubular expression of these proteins did not result in histopathologic changes.33 Interestingly, in this model, aberrant apoL1 expression leads to inflammatory cell death, a similar process induced by HIV infection.34 Collectively, these studies may explain the synergistic effect of APOL1 risk variants and HIV infection on HIVAN and the correlation of ART implementation with diminished HIVAN incidence.

HIV viremia increases levels of proinflammatory cytokines,35 which augment apoL1 production in vitro.36 However, in a case-control study of HIV-positive blacks with or without CKD, proinflammatory cytokines did not correlate with plasma apoL1 levels, and plasma apoL1 levels were similar by CKD status.37 These results along with experiments showing characteristic histopathologic changes with glomerular expression of aberrant apoL1 suggest that intrarenal rather than plasma apoL1 is important in the pathogenesis of APOL1-related kidney diseases.

ART NEPHROTOXICITY

Although ART mitigates HIVAN risk, certain antiretrovirals may be nephrotoxic via direct renal tubular toxicity, crystal-induced obstruction, or interstitial nephritis.13,15,38–41 Table 1 lists the generic names and available formulations of contemporary antiretroviral drugs associated with CKD.14,42–44 In the EuroSIDA Study of HIV-positive persons, each additional year of TDF, atazanavir, and ritonavir-boosted lopinavir was associated with 16%, 21%, and 8% higher incidence of CKD, respectively.45 Similar findings were observed among individuals without baseline CKD in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study over a median follow-up of 7.2 years.52,44 Surveillance for nephrotoxicity in the context of HIV treatment, however, is confounded by the effect of several antiretrovirals and pharmacoenhancers on renal tubular creatinine secretion (Figure 1).45–48 These medications may reduce the serum creatinine-based eGFR within the first 4 weeks of drug initiation, but the decline is typically nonprogressive. Because cystatin C seems to be reabsorbed and then metabolized within renal tubular cells,49,50 serum cystatin C may be a useful alternative biomarker of kidney function, and urine biomarkers may detect ongoing kidney injury.45

TDF

TDF is included in several first-line ART regimens.51,52 Its active metabolite, tenofovir, is renally eliminated through glomerular filtration and proximal tubular secretion (Figure 2A).53 Tenofovir’s accumulation within tubular cells has been hypothesized to cause mitochondrial injury through inhibition of the mitochondrial DNA polymerase-γ,54,55 manifesting pathologically as mitochondrial swelling and depletion.13,56,57 Although clinical trials have reported minimal nephrotoxicity,53,58 observational studies have shown that TDF is associated with higher risks of AKI, proteinuria, nephrogenic diabetes insipidus, and CKD.14,15,59–66 Among 10,841 HIV-positive United States veterans, each year of TDF exposure was associated with a 34% higher risk of proteinuria, a 33% higher risk of CKD, and an 11% higher risk of rapid kidney function decline.64 A subsequent meta-analysis of 17 studies reported faster kidney function decline (−3.9 ml/min) and slightly increased risk of AKI (risk difference of 0.7%) among TDF versus non-TDF users.67 The risk of nephrotoxicity may be higher among TDF users with concomitant use of ritonavir-boosted protease inhibitors.68 One study reported faster decline in creatinine clearance over 24 weeks among TDF users receiving ritonavir-boosted protease inhibitors compared with non-nucleoside reverse transcription inhibitors (−14.7 versus −4.5 ml/min per 1.73 m² per year).65 Ritonavir-boosted
lopinavir, in particular, may enhance TDF-induced nephrotoxicity by increasing plasma tenofovir concentrations. In a trial of HIV-positive women initiating TDF, those randomized to also receive ritonavir-boosted lopinavir versus nevirapine had a 3.1-fold odds of experiencing a creatinine rise to $2 \text{ mg/dl}$ or creatinine clearance $50 \text{ ml/min}$, causing interruption or discontinuation of TDF. Concurrent use of ritonavir-boosted lopinavir was also associated with a 16.4-fold odds of Fanconi syndrome among HIV-positive TDF users. This drug interaction may occur through inhibition of tenofovir efflux into urine by protease inhibitors or enhanced intestinal absorption of tenofovir. Recovery from TDF-induced nephrotoxicity can be incomplete, particularly among persons with lower eGFR at the time of TDF discontinuation. Therefore, early recognition of TDF nephrotoxicity is critical. TDF-induced nephrotoxicity is characterized by Fanconi syndrome, manifesting as low molecular weight proteinuria, phosphaturia, uricosuria, normoglycemic glucosuria, and metabolic acidosis; however, the full syndrome is seen only in a minority of TDF users, with a reported incidence of 0.4% over a median duration of 44 months. However, milder forms of tubular damage occur commonly among TDF users. Among ART-naive patients, those who initiated TDF versus non-TDF regimens had a 5.2-fold higher risk of developing proximal tubular dysfunction after 2 years of follow-up. Additionally, TDF has been associated with higher urine biomarkers of proximal tubular dysfunction and injury. In two randomized trials, urine levels of $\alpha_1$-microglobulin and $\beta_2$-microglobulin were 50% higher after 48 weeks among TDF versus non-TDF users. Furthermore, among HIV-positive men initiated on TDF, each year of exposure was associated with incrementally higher urine levels of $\alpha_1$-microglobulin, IL-18, kidney injury molecule-1, and procollagen type 3 N-terminal propeptide. These markers are prognostic for CKD and mortality risk in HIV-positive populations and may be useful in early detection of TDF-induced nephrotoxicity in the future. Meanwhile, to assess the renal risks of TDF, two CKD risk scores have been developed using the D:A:D Study and the Veterans Health Administration HIV cohorts (Table 2).

### Table 1. Generic and brand names of commonly used antiretroviral medications and potential nephrotoxicities

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Names</th>
<th>Associated Kidney Diseases</th>
</tr>
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<tbody>
<tr>
<td>TDF</td>
<td>Viread (TDF)</td>
<td>Proximal tubulopathy</td>
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<tr>
<td></td>
<td>Truvada (TDF, emtricitabine)</td>
<td>Low molecular weight proteinuria</td>
</tr>
<tr>
<td></td>
<td>Atripla (rilpivirine, TDF, emtricitabine)</td>
<td>AKI</td>
</tr>
<tr>
<td></td>
<td>Complera (efavirenz, TDF, emtricitabine)</td>
<td>Nephrogenic diabetes insipidus</td>
</tr>
<tr>
<td></td>
<td>Striobl (elvitegravir/cobicistat, TDF, emtricitabine)</td>
<td>CKD</td>
</tr>
<tr>
<td>TAF</td>
<td>Descovy (TAF, emtricitabine)</td>
<td>None reported</td>
</tr>
<tr>
<td></td>
<td>Odefsey (rilpivirine, TAF, emtricitabine)</td>
<td>Crystalluria</td>
</tr>
<tr>
<td></td>
<td>Genvoya (elvitegravir/cobicistat, TAF, emtricitabine)</td>
<td>Urolithiasis</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Reyataz (atazanavir)</td>
<td>Tubulointerstitial nephritis</td>
</tr>
<tr>
<td></td>
<td>Evotaz (atazanavir/cobicistat)</td>
<td>CKD</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>Kaletra (lopinavir/ritonavir)</td>
<td>Albuminuria</td>
</tr>
<tr>
<td></td>
<td>Odefsey (rilpivirine, TAF, emtricitabine)</td>
<td>Low molecular weight proteinuria</td>
</tr>
<tr>
<td></td>
<td>Genvoya (elvitegravir/cobicistat, TAF, emtricitabine)</td>
<td>CKD</td>
</tr>
</tbody>
</table>

*TAF is a new tenofovir formulation that may be less nephrotoxic than TDF.

**Figure 1.** Several antiretroviral drugs and pharmacoenhancers affect renal tubular secretion of creatinine (Cr). Cr transport through tubular cells is mediated on the basolateral side by organic cation transporter 2 (OCT-2) and OCT-3 and possibly organic anion transporter 2 (OAT-2) and OAT-3. On the apical side, Cr is secreted via multidrug and toxin extrusion transporter-1 (MATE-1). Dolutegravir and rilpivirine inhibit OCT2 and thus, impair Cr entry into the tubular cell. Conversely, ritonavir and cobicistat inhibit MATE-1 and inhibit Cr efflux into urine.
TAF is an alternative tenofovir prodrug recently approved for the treatment of HIV infection. TAF is expected to have an improved renal toxicity profile due to lower plasma tenofovir concentrations (Figure 2B). In a trial of HIV-positive ART-naïve persons with eGFR $\geq 50$ ml/min per $1.73$ m$^2$, the median change in estimated creatinine clearance over 96 weeks was significantly lower among TAF users ($-2.0$ ml/min) compared...
with TDF users (7.5 ml/min). Improved renal safety was also suggested by a study among virologically suppressed persons with eGFRs 50 ml/min per 1.73 m² who switched from TDF to TAF. In a single-arm, open label study, virologically suppressed persons with an eGFR of 30–69 ml/min per 1.73 m² were switched to elvitegravir/cobicistat/emtricitabine/TAF. Although there was no significant change in eGFR overall, including in the subgroup with eGFR < 50 ml/min per 1.73 m², total proteinuria, albuminuria, and low molecular weight proteinuria improved substantially over the 48-week follow-up. These data suggest that TAF may be a safer alternative to TDF among persons at risk for CKD. Of note, the trial participants were highly selected, and the short duration of follow-up could not assess TAF's long-term safety. As TAF use increases, postmarketing surveillance for nephrotoxicity will be imperative.

HIV Pre-Exposure Prophylaxis

Pre-exposure prophylaxis (PrEP) with TDF (200 mg/emtricitabine 300 mg) has become a global strategy for HIV prevention. In the Iniciativa Prophylaxis Pre-Exposicion (iPrEx) Study of HIV-negative men and transgender women, eGFR between the active and placebo arms differed by 4 weeks of therapy (mean change of 2.4 versus 1.1 ml/min, respectively). This difference persisted through the 144-week study and resolved after stopping PrEP. Similarly, in the Partners Pre-Exposure Prophylaxis (Partners PrEP) Randomized, Controlled Trial of heterosexual HIV-negative individuals, PrEP use was associated with a slight eGFR reduction (2.123 to 2.159 ml/min per 1.73 m²) versus placebo. Although there was no significant change in eGFR overall, including in the subgroup with eGFR < 50 ml/min per 1.73 m², total proteinuria, albuminuria, and low molecular weight proteinuria improved substantially over the 48-week follow-up.17 These data suggest that TAF may be a safer alternative to TDF among persons at risk for CKD. Of note, the trial participants were highly selected, and the short duration of follow-up could not assess TAF's long-term safety. As TAF use increases, postmarketing surveillance for nephrotoxicity will be imperative.

### Table 2. Existing risk scores for CKD among HIV-positive individuals

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV exposure</td>
<td>Intravenous drug use</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hepatitis C virus serostatus</td>
<td>Positive</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age, yr</td>
<td>≤35</td>
<td>0</td>
<td>19–39</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age, yr</td>
<td>&gt;35 to ≤50</td>
<td>4</td>
<td>40–49</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>&gt;50 to ≤60</td>
<td>7</td>
<td>50–59</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>&gt;60</td>
<td>10</td>
<td>60–90</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Women</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Plasma glucose &gt;140 mg/dl</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Systolic BP &gt;140 mmHg</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>&gt;90</td>
<td>−6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>&gt;70 to ≤90</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>&gt;60 to ≤70</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Proteinuria ≥30 mg/dl</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Plasma triglycerides &gt;200 mg/dl</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CD4+ cell count</td>
<td>Nadir &gt;200 cells per 1 mm[^3]</td>
<td>−1</td>
<td>&lt;200 cells per 1 mm[^3]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Yes</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

[^4]: D:A:D Study, Data Collection on Adverse Events of Anti-HIV Drugs Study VHA, Veterans Health Affairs.
PrEP users had an absolute increased risk of 0.6% for a 1.1- to 1.3-fold increase above the upper limit of normal for serum creatinine. Conversely, the absolute risk reduction for HIV infection was 2% (number needed to treat, 50). However, the overall adherence to TDF/emtricitabine was low in these trials. An open label extension of the iPrEx Study reported a linear relationship between tenofovir hair concentrations, which reflect drug adherence, and longitudinal eGFR decline over 18 months.106 Notably, whether the rise in serum creatinine with PrEP reflects a reduction of GFR and/or tubular creatinine secretion is unknown. In a Partners PrEP Randomized, Controlled Trial substudy, the incidence of proximal tubulopathy was low among PrEP users and did not differ from the placebo group over 24 months.107 However, tubular proteinuria (7.3% versus 4.0%), urine protein-to-creatinine ratio >200 mg/g (8.0% versus 4.4%), and uricosuria (3.5% versus 1.3%) occurred more frequently in the PrEP versus placebo group, respectively. By comparison, an iPrEx Study substudy found no significant differences in prevalence of proximal tubular abnormalities by study arm. With widespread dissemination of PrEP, studies are needed to characterize tenofovir’s effects on renal tubular function in HIV-negative individuals, identify persons at highest risk for toxicity, and provide guidance on the optimal monitoring strategy of these individuals.

**Atazanavir**

Atazanavir has been associated with crystalluria, urolithiasis, tubulointerstitial nephritis, and CKD.38–41,108,109 Kidney biopsies have shown granulomatous inflammation surrounding intrarenal deposits of atazanavir crystals.39,108,110 The risk of nephrolithiasis is higher among individuals with higher atazanavir plasma trough concentrations, individuals with alkaline urine pH, and those with underlying CKD.111,112 Continuation of atazanavir after the diagnosis of kidney stones is associated with high recurrence risk, with one study reporting 33% recurrence.113 Moreover, the risk of nephrolithiasis may persist after atazanavir discontinuation.111

Epidemiologic studies have reproduced a modestly increased risk of nephrotoxicity with atazanavir. In a large study of HIV-positive United States veterans, each year of exposure was associated with a 22% higher risk of rapid kidney function decline.114 Similarly, the D:A:D Study reported a 20% higher CKD incidence per year of exposure to ritonavir-boosted atazanavir among HIV-positive individuals with preserved kidney function at baseline.115 Although a recent analysis reported stabilization or improvement in kidney function after switching from ritonavir-boosted atazanavir to ritonavir-boosted darunavir,116 the findings were largely driven by changes in eGFR among TDF users. Further studies are needed to confirm whether switching from atazanavir to other protease inhibitors improves kidney function.

**KIDNEY TRANSPLANTATION**

The number of kidney transplantations with HIV-positive recipients has increased tenfold since 2002.115 Of studies to date (Table 3),116–120 the largest series reported on 150 HIV-positive kidney transplant recipients who met stringent eligibility criteria (Table 4).120 During a median follow-up of 1.7 years post-transplant, the overall 1- and 3-year patient survival rates were 95% and 88%, respectively, falling between those reported for all United States kidney transplant recipients and those ages ≥65 years old. Similar trends were observed for allograft survival, with 1- and 3-year allograft survival rates of 90% and 74%, respectively. These favorable outcomes were tempered by approximately 30% incidence of acute rejection and profound immunosuppression among recipients who received thymoglobulin. Nearly one third developed serious infections, and five developed AIDS-defining conditions. A subsequent analysis of the Scientific Registry of Transplant Recipients data from 2002 to 2011 showed favorable trends in 5- and 10-year patient and allograft survivals among HIV-positive recipients.115 However, it also noted that recipients coinfected with hepatitis C had 57% and 38% increased risks of mortality and allograft failure, respectively, compared with those monoinfected with hepatitis C. Nonetheless, HIV-positive individuals who underwent kidney transplantation had greater survival, including those coinfected with hepatitis C, versus candidates who remained waitlisted.121

In sub-Saharan Africa, where a dual burden of HIV infection and CKD exists, the lack of affordable dialysis and potential donors led to the initial HIV-positive to HIV-positive kidney transplantations.122,123 In 2010, Muller et al.124 reported on four HIV-positive recipients whose allografts originated from HIV-positive donors who had no prior ART exposure, serious opportunistic conditions, or proteinuria and had normal kidney biopsies. By 1-year post-transplant, all recipients had functional allografts and no significant acute rejection. A subsequent report of 27 HIV-positive to HIV-positive transplantations showed 1- and 5-year patient survival rates of 84% and 74%, respectively, and 1- and 5-year allograft survival rates of 93% and 74%, respectively.119 Consequently, the US HIV Organ Policy Equity (HOPE) Act of 2013 was ratified,125 thereby reversing the ban on the use of organs from HIV-positive individuals.126

Several uncertainties surrounding kidney transplantation among HIV-positive individuals remain, including optimal immunosuppressive and ART regimens, management of viral hepatitis coinfections, and transmission of resistant viral strains from HIV-positive donors. Immunosuppression considerations encompass the need to prevent allograft rejection, minimize infection risk, and manage drug-drug interactions, particularly between immunosuppressive and antiretroviral medications. Induction therapy for patients at high risk of rejection has been largely made up of thymoglobulin and IL-2 receptor antagonists. Within the first year post-transplant, thymoglobulin has been associated with 61% risk reduction of acute rejection, whereas IL-2 receptor antagonists yield similar acute rejection rates as no induction.127 Unfortunately, thymoglobulin may lead to profound, prolonged immunosuppression, especially in recipients with low pretransplant...
Table 3. Summary of studies to date on HIV-positive kidney transplant recipients

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Length of Follow-up, yr</th>
<th>Antiretroviral Regimen</th>
<th>Immunosuppressive Regimen</th>
<th>Survival</th>
<th>Reported Major Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stock et al.</td>
<td>150 HIV+ recipients of allografts from HIV—deceased (68%) or living (32%) donors in the United States</td>
<td>Median: 1.7 (IQR, 7–3)</td>
<td>99% on cART</td>
<td>Induction: basiliximab/daciluzumab or thymoglobin</td>
<td>1- and 3-yr graft: 90.4% and 73.7%, respectively</td>
<td>Delayed graft function: 46% of recipients with deceased donors; 15% of recipients with living donors</td>
</tr>
<tr>
<td>Mazuecos et al.</td>
<td>36 HIV+ recipients of allografts from HIV—deceased (94%) or living (6%) donors in Spain</td>
<td>Median: 2.8 (IQR, 1.1–4.9)</td>
<td>Paper did not provide details on cART use</td>
<td>Induction: anti-IL-2R or thymoglobin</td>
<td>1- and 3-yr graft: 91.6% and 86.2%, respectively</td>
<td>Acute rejection: 33.9% at 3 yr post-transplant; Opportunistic condition: 45%; Malignancy: 11%</td>
</tr>
<tr>
<td>Bossini et al.</td>
<td>13 HIV+ recipients of allografts from HIV—deceased donors in the United States</td>
<td>Mean: 4.2±1.8</td>
<td>92% on cART</td>
<td>Induction: basilizimab + methylprednisolone</td>
<td>4-yr graft: 88.9%</td>
<td>Acute rejection: 61.5%</td>
</tr>
<tr>
<td>Gathogo et al.</td>
<td>35 HIV+ recipients of allografts from HIV—deceased donors in the United Kingdom</td>
<td>Median: 1.8 (IQR, 1.2–4.1)</td>
<td>100% on cART</td>
<td>Induction: basiliximab/daciluzumab or methylprednisolone</td>
<td>1- and 3-yr graft: 91.3% and 84.7%, respectively</td>
<td>Acute rejection: 44%; Opportunistic condition: 6%; Hospitalization due to infectious complication: 54%</td>
</tr>
<tr>
<td>Muller et al.</td>
<td>27 HIV+ recipients of allografts from HIV+ deceased donors in South Africa</td>
<td>Median: 2.4</td>
<td>100% on cART</td>
<td>Induction: thymoglobin</td>
<td>1-, 3-, and 5-yr graft: 93%, 84%, and 84%, respectively</td>
<td>Delayed graft function: 7.4%</td>
</tr>
</tbody>
</table>

IQR, interquartile range; cART, combination antiretroviral therapy; NRTI, nucleoside reverse transcription inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcription inhibitor; II, integrase inhibitor; CNI, calcineurin inhibitor; MMF, mycophenolic acid.
Hepatology evaluation for patients coinfected with hepatitis B or hepatitis C virus

Effective HIV suppression for serious infections. These results suggest that thymoglobulin should be used carefully in HIV-positive recipients whose CD4+ counts are <350 cells per 1 mm³ at transplantation.

The optimal ART among HIV-positive recipients remains unclear. Protease inhibitors and to a lesser extent, non-nucleoside reverse transcriptase inhibitors inhibit the cytochrome-P450 and p-glycoprotein systems, leading to greater exposure to calcineurin inhibitors and mammalian target of rapamycin inhibitors. In addition, pharmacoenhancement with ritonavir or cobicistat increases calcineurin inhibitor exposure. Conversely, integrase inhibitors (e.g., raltegravir) and the chemokine receptor-5 antagonists (e.g., maraviroc) do not affect the cytochrome-P450 system and therefore, may be associated with lower risk of delayed allograft function or allograft rejection. In addition, experimental studies suggest that rapamycin may augment viral suppression by chemokine receptor-5 antagonists. However, clinical studies comparing long-term outcomes among various ART regimens are lacking. The ongoing multicenter trial created through the HOPE Act will help address these uncertainties.

CONCLUSIONS

Advances in HIV treatment have ushered in an era in which HIV-positive individuals can reach “old age.” With the transformation of HIV infection to a chronic condition, the underlying causes of CKD in HIV-positive persons have shifted from those driven by HIV to those from traditional risk factors and ART-related nephrotoxicity. A substantial racial disparity in ESRD risk among HIV-positive individuals remains; the growing understanding of APOL1 pathomechanisms will hopefully yield strategies to mitigate CKD risk in these patients. TDF, the most common antiretroviral currently used for treating HIV-infected adults, 2000-2013. Clin Infect Dis 64: 459–467, 2017

DISCLOSURES

None.

REFERENCES


Table 4. Selection criteria for candidate HIV-positive recipients

<table>
<thead>
<tr>
<th>Meets Standard Transplant Criteria Plus the Following</th>
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<tbody>
<tr>
<td>Effective HIV suppression for ≥6 mo before transplantation</td>
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<tr>
<td>HIV-1 RNA &lt;50 copies per 1 ml</td>
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<tr>
<td>CD4+ cell count &gt;200 cells per 1 mm³</td>
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<tr>
<td>No active opportunistic infections</td>
</tr>
<tr>
<td>No prior history of Progressive multifocal leukoencephalopathy Primary central nervous system lymphoma Pulmonary aspergillosis Visceral Kaposi sarcoma Coccidiomycosis</td>
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<tr>
<td>Chronic intestinal cryptosporidiosis ≥1 mo</td>
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<tr>
<td>Hepatolgy evaluation for patients coinfected with hepatitis B or hepatitis C virus</td>
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HIV and Kidney Disease


BRIEF REVIEW


