Human Immunodeficiency Virus in Kidney Transplantation

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Summary: Patients infected with human immunodeficiency virus (HIV) are living longer, healthier lives on highly active antiretroviral therapy and, as a result, interest in kidney transplantation for HIV-infected patients with end-stage renal disease has increased. HIV is no longer considered a contraindication to solid-organ transplantation and the number of kidney transplants performed in HIV-infected patients each year is increasing steadily. HIV-infected kidney transplant recipients have had excellent outcomes overall, but there are still significant challenges, including high rates of acute rejection, drug–drug interactions, and poor outcomes in patients co-infected with hepatitis C virus. The gap between supply and demand for organs remains a challenge but new developments in HIV-positive to HIV-positive kidney transplantation may help bridge this gap.

Semin Nephrol 36:405-416

Keywords: Human immunodeficiency virus (HIV), kidney transplant, drug interactions, highly active antiretroviral therapy (HAART), HIV-infected deceased donors (HIVDD)

After the introduction of highly active antiretroviral therapy (HAART) in 1996, rates of opportunistic infections (OIs) and death from acquired immune deficiency syndrome have decreased significantly and chronic diseases, including end-stage renal disease (ESRD), are now increasingly common causes of morbidity and mortality in human immunodeficiency virus (HIV)-infected patients.[1] HIV-infected patients who develop chronic kidney disease (CKD) that progresses to ESRD may develop it as a direct complication of HIV infection, as a result of nephrotoxic HIV therapies, or as a result of comorbid conditions and infections.[2]

Kidney diseases resulting from a direct HIV effect on the kidney include HIV-associated nephropathy (HIVAN), immune complex diseases, and thrombotic microangiopathy.[3] Biopsy specimens from patients with HIVAN have shown that HIV directly infects renal epithelial cells, leading to podocyte and tubular dysfunction and, ultimately, collapsing focal segmental glomerulosclerosis.[4] HIVAN occurs in an estimated 10% of HIV-infected patients and can result in rapid progression to ESRD over weeks to months.[3] HIV immune complex kidney disease involves the deposition of HIV-1 antigens, reactive antibodies, and activation of complement in the kidney, which leads to a robust inflammatory response and kidney damage.[5] The high level of polyclonal antibodies that often is seen in HIV-infected patients may predispose these patients to immune-complex deposition.[5]

There are also well-known associations between certain antiretrovirals (ARVs) and renal dysfunction. Tenofovir disoproxil fumarate (TDF) (Viread; Gilead, Foster City, CA) is the most commonly implicated drug and is thought to cause nephrotoxicity by accumulating and causing mitochondrial damage in proximal renal tubular cells.[6] A study of almost 24,000 HIV-positive individuals with normal baseline renal function found that use of either TDF, ritonavir-boosted atazanavir, or ritonavir-boosted lopinavir was associated with an increasing incidence of CKD over time, suggesting cumulative nephrotoxicity by these drugs.[7] The toxicities of TDF prompted the recent development of a newer formulation: tenofovir alafenamide (Gilead, Foster City, CA), which has an improved renal safety profile.[8]

Finally, HIV-infected patients on HAART now are surviving long enough to experience cardiovascular disease and HAART-induced metabolic alterations, leading to a possible increasing incidence of nephrosclerosis and diabetic nephropathy in this population.[1]

EPIDEMIOLOGY OF HIV IN RENAL DISEASE

HIV-infected patients are significantly more likely to develop ESRD than HIV-uninfected patients, with an estimated 2- to 20-fold higher risk.[9] Approximately 1% to 1.5% of US patients on dialysis are HIV positive.[10,11] An estimated 900 HIV-positive patients start dialysis each year in the United States.[12]

There is a large racial disparity in the risk of ESRD, with black HIV-infected patients having an estimated six-fold higher risk of developing ESRD compared with white HIV-infected patients, even after

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Financial disclosure and conflict of interest statements: none

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0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2016.05.017

accounting for other risk factors.[9] This racial disparity is attributed at least in part to the relatively high prevalence of the *apolipoprotein L1* gene in the black U.S. population, which increases susceptibility to kidney disease and cardiovascular disease.[9] In African Americans, HIV-associated nephropathy is noted to be the third leading cause of ESRD.[11,13] Higher rates of ESRD are also seen in HIV-infected patients who are female, have a history of injection drug use, or have a history of hypertension or diabetes.[9] Lower CD4 T-cell counts and unsuppressed viral loads also are associated with the progression of kidney disease.[9]

Although most HIV-positive kidney transplant recipients have been diagnosed with HIV before transplant, there are rare cases of donor-derived HIV infection in kidney transplant recipients that result from failures in screening donors.[14,15] Kidney transplant recipients may acquire HIV in the post-transplant period as a result of exposures unrelated to the transplant; it is unknown how frequently this occurs but is thought to be extremely infrequent.[14]

CLINICAL MANIFESTATIONS ASSOCIATED WITH THE VIRUS

Unfortunately, the higher rate of ESRD in HIV-infected patients is compounded by worse outcomes while on dialysis compared with their uninfected counterparts. Trullas et al[16] analyzed outcomes in HIV-infected patients on dialysis and found that even after a competing risk analysis, HIV-infected ESRD patients on dialysis had lower survival rates compared with matched HIV-negative patients on dialysis—62.7% and 94.4%, respectively. Kidney transplantation is known to offer a significant survival advantage over dialysis in the HIV-negative ESRD population.[17–20] Initially, HIV was considered a contraindication to transplantation because of poor outcomes before HAART therapy as well as concerns about the theoretically increased risk of developing OIs, malignancy, and HIV progression as a result of the requisite post-transplant immunosuppressive therapies.[10] However, newer studies have shown improved survival in HIV-infected patients undergoing a renal transplant compared with remaining on dialysis.[21] The first HIV-positive kidney transplant recorded in the United Network for Organ Sharing data set was on October 3, 1987.[22] Since then, the number of HIV-infected patients undergoing kidney transplants in the United States has increased from 8 in 2003 to 93 in 2009.[13]

To mitigate the potential adverse impact of HIV on transplant outcomes, transplant centers require HIV-infected patients to meet certain criteria before undergoing transplantation. In general, HIV-positive patients should have well-controlled HIV, be on a stable HAART regimen, and have no evidence of active OIs or malignancy before transplant.[11] Suggested pre–kidney transplant criteria for HIV-infected patients are listed in Table 1 and reflect the inclusion and exclusion criteria used in the National Institutes of Health (NIH)-sponsored Solid Organ Transplantation in HIV: Multi-Site Study (HIV-TR study).[11,14,23] There are no data to support a minimum time period that HIV-infected patients must adhere to this criteria before transplantation, but the American Society of Transplant Infectious Diseases recommends at least 3 months and the HIV-TR study mandated a minimum of 16 weeks.[11,14]

Outcomes

Overall, the outcomes of kidney transplantation in HIV-infected patients have been very good. In 2010,

Table 1. Criteria for Kidney Transplantation in HIV-Infected Individuals[11,14,33]

Meet center-specific transplant listing criteria
CD4+ T-cell count $\geq$ 200 cells/mL^3 (during the 16 weeks before transplant)
Undetectable HIV viral load (during the 16 weeks before transplant)
Compliance with stable HAART regimen (for at least 3 months before transplant)
Absence of active malignancy
Absence of active opportunistic infection*
Absence of significant wasting
Willing to take indicated prophylaxis medications(against PCP, fungal infections, and so forth)
No history of progressive multifocal leukoencephalopathy, primary central nervous system lymphoma, visceral Kaposi's sarcoma, or chronic intestinal cryptosporidiosis
If hepatitis C and/or B co-infection, should have no evidence of cirrhosis; patients with hepatitis B should have an undetectable surface antigen while on antiviral therapy
Appropriate follow-up evaluation with healthcare providers with expertise in HIV management
Access to therapeutic drug monitoring for immunosuppressive medications

Abbreviations: PCP, *Pneumocystis carinii* pneumonia.

*A prior history of certain opportunistic infections (eg,*Mycobacterium tuberculosis*, *Pneumocystis carinii* pneumonia, and so forth), is allowed if the patient has received acute and maintenance therapy and has no evidence of active disease.