

# End-Stage Renal Disease and Kidney Transplant in HIV-Infected Patients

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**Summary:** Chronic kidney and end-stage renal disease are important complications of HIV disease and treatment. African Americans with HIV infection are at significantly increased risk for development of chronic kidney disease and for progression to end-stage renal disease. Survival of HIV-positive patients on dialysis has improved dramatically since the introduction of combination antiretroviral therapy, with hemodialysis and peritoneal dialysis appearing to offer similar survival. Renal transplant has been shown to be successful in HIV-positive patients and emerging data suggest a survival benefit over remaining on dialysis, despite data indicating an increased incidence of acute rejection. Immunosuppression dosing is complicated by interactions with antiretroviral therapy, and drug levels must be followed closely. Experience to date suggests that HIV-positive transplant recipients are best cared for in academic institutions with multi-disciplinary teams devoted to their care.

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As of 2003, an estimated 1,039,000 to 1,185,000 people were living with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) in the United States, and more than 25% of them were undiagnosed or unaware of their infection.<sup>1</sup> Since the introduction of highly active antiretroviral therapy (ART) in the mid-1990s, survival among HIV/AIDS patients has increased dramatically. Improved survival has revealed new problems, in particular end organ damage resultant from the virus itself and the medications used to treat it. End-stage cardiac, liver, and kidney disease have replaced opportunistic infections as the major causes of morbidity and mortality among HIV-infected patients with access to ART.<sup>2,3</sup> HIV infection is no longer considered an absolute contraindication to solid organ transplant, and how best to treat this patient population has become an important question facing physicians across disciplines today.

## EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE IN HIV-INFECTED PATIENTS

Chronic kidney disease (CKD) is an important complication of HIV infection and treatment. Because patients are living longer and HIV infection is spreading most quickly among African Americans, it is projected that the number of patients at risk for HIV-related end-stage renal disease (ESRD) will increase. HIV-associated nephropathy has been identified as a leading cause of ESRD in African Americans.<sup>4</sup> The introduction of ART has decreased the incidence of HIV-associated nephropathy, but these medications themselves may have contributed to the CKD epidemic because of associated nephrotoxicity.<sup>5</sup> Although ESRD may affect only a small percentage of HIV-infected patients, proteinuria has been shown in nearly 30% of HIV-positive patients in some populations, indicating widespread occult kidney damage.<sup>6</sup> The overall incidence of HIV-related ESRD has stabilized, but the prevalence continues to increase as patients are living longer.<sup>7</sup>

In a large cohort of HIV-positive African Americans followed up in Baltimore over 15 years, the incidence of ESRD was 1% per year,

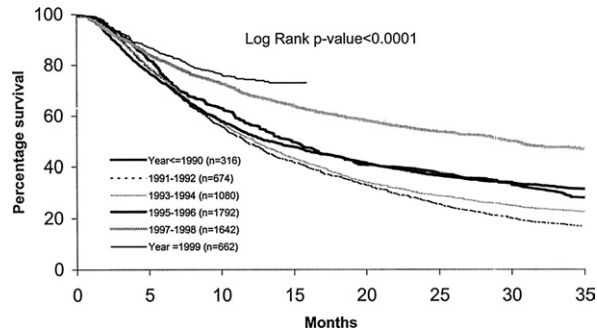
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**Figure 1.** Kaplan-Meier estimates of survival of HIV-infected dialysis patients, showing improved survival over time. Adapted with permission from Ahuja et al.<sup>13</sup>

representing a 10-fold higher risk than the general African American population. Over the lifetime of their study, the investigators failed to find a change in the incidence of ESRD among HIV-positive African Americans despite a decrease in the incidence of CKD after the introduction of ART.<sup>8</sup> Similar results were observed in a 4-year retrospective cohort study in the US Veterans Affairs system. HIV seropositivity was found to confer a risk of ESRD among African Americans that was equivalent to diabetes; when compared with HIV-negative, nondiabetic Caucasians the risk of ESRD among HIV-positive African Americans was 4- to 5-fold higher.<sup>9</sup>

In the general population, CKD has been recognized as a significant independent risk factor for mortality.<sup>10,11</sup> More recent studies have noted CKD to increase mortality significantly in HIV populations as well, regardless of race.<sup>12</sup> Among African American veterans, the combination of HIV infection and CKD conferred a risk of death greater than, and a risk of ESRD equivalent to, that observed in HIV-negative diabetic patients.<sup>12</sup> Mortality rates for HIV-positive patients on dialysis were initially quite high, approaching nearly 70% in 1991 and subsequently decreasing to 24% by 2002.<sup>7</sup> In a review of the United States Renal Database System, the 1-year survival of HIV-positive dialysis patients improved from 56% in 1990 to 74% in 1999, which was attributed to the use of ART (Fig. 1).<sup>13</sup> Race did not predict survival, and despite survival gains in the HIV-positive population, their outcomes were still inferior when compared with age-, sex-, and race-matched HIV-negative controls.<sup>13</sup>

Choice of dialysis modality does not appear to influence survival among HIV-infected ESRD patients. Among 6,053 patients with ESRD owing to HIV-associated nephropathy for whom dialysis modality was specified in the US Renal Database System from 1995 to 1999, there was no difference in survival between the hemodialysis and peritoneal dialysis groups.<sup>14</sup>

## TRANSPLANTATION

Given the growing numbers of HIV-positive ESRD patients and the improved survival rates observed with the use of ART, there has been increasing interest in providing renal transplantation for this patient population. Although the United Network for Organ Sharing does not consider HIV seropositivity a contraindication to transplantation, kidney transplant remains limited to specialized centers and is performed mostly in the setting of clinical trials. It has not yet been established whether the survival benefit observed with kidney transplantation over dialysis in the seronegative population extends to HIV-infected patients, although preliminary data are encouraging.<sup>15</sup>

Before the introduction of ART, data on renal transplantation in HIV-infected patients was limited to case reports and retrospective analyses. Most subjects were undiagnosed with HIV at the time of their transplant or acquired HIV in the peritransplant period; these patients generally had poor outcomes with rapid progression to AIDS.<sup>16</sup>

The widespread use of ART and improved patient survival has renewed interest in the feasibility of transplantation in this population, and several pilot studies have been conducted to address this question. In a prospective study from San Francisco, Stock et al<sup>17</sup> described 10 patients who received kidney transplants and were followed up for a mean of 480 days. Beyond the standard transplant criteria, inclusion criteria for the study included undetectable HIV viral load for 3 months, CD4+ T-cell count of at least 200 cells/mL for 6 months, and no history of opportunistic infection or malignancy. Patients received a standard cyclosporine-based triple immunosuppression regimen. Patient and allograft survival was 100% despite 5 episodes of biopsy-proven acute rejection. HIV viral

loads remained undetectable in all kidney transplant recipients, and no opportunistic infections occurred.<sup>17</sup> Further reports from a multicenter pilot study initiated by this group have been similarly favorable.<sup>18</sup> After following up 18 patients for a median of 4 years, they found 1- and 3- year recipient survival rates of 94%, and 1- and 3- year allograft survival rates of 83%. None of the 4 patient deaths observed were the result of HIV-related causes. Four renal allografts were lost within the first year, 2 because of chronic rejection, 1 because of acute rejection, and 1 because of vascular thrombosis. In total there were 17 documented episodes of renal allograft rejection, with a 1-year incidence of 52%. There was no progression of HIV disease observed.<sup>18</sup>

In a series of 40 HIV-positive ESRD patients transplanted in a single center in Philadelphia between 2001 and 2004, the mean follow-up time was 20.4 months, with a 1-year patient survival rate of 85% and a 1-year allograft survival rate of 75%.<sup>19</sup> Patients were given basiliximab induction and maintained on triple immunosuppression with cyclosporine and sirolimus. Protocol surveillance biopsies were performed, with acute rejection diagnosed in 22% of patients and subclinical acute rejection in 29%. In contrast to other studies, some patients did experience temporary increases in their viral loads, but with alterations in ART regimens all patients were able to achieve viral suppression. Of the 7 patients who died during the study period, 3 died from infection, but none were directly attributable to HIV disease.<sup>19</sup>

The survival rates observed in these pilot studies are comparable with other high-risk patient groups<sup>18,20</sup> and appear to be superior to those of HIV-infected patients maintained on dialysis.<sup>15,19</sup> A review of the US Renal Database System also has suggested similar patient survival for HIV-positive transplant recipients compared with the general transplant population.<sup>21</sup> Caution should be used when interpreting these data because as a result of stringent screening criteria, HIV-positive transplant recipients represent a small, highly selected proportion of the HIV-positive ESRD population. Larger studies are required to show unequivocal survival benefit, and are underway.

## IMMUNOSUPPRESSION

Immunosuppression dosing in HIV-infected renal transplant recipients is understandably complicated, and requires close cooperation between HIV providers and the transplant team. Protease inhibitors and nonnucleoside reverse transcriptase inhibitors affect the pharmacokinetics of calcineurin inhibitors (CNIs) through their activity on the shared cytochrome CYP3A4. In general, protease inhibitors inhibit CYP3A4 activity and may increase CNI levels, whereas nonnucleoside reverse transcriptase inhibitors induce cytochrome activity and lead to lower CNI levels.<sup>22</sup> Calcineurin inhibitors, mycophenolate mofetil, and sirolimus also show some antiviral activity *in vitro*,<sup>23-25</sup> although data on the clinical relevance of these effects are limited to small studies.<sup>26</sup>

There has been interest and concern regarding the use of induction agents in HIV-positive renal transplant recipients. Rejection episodes have been treated successfully with corticosteroids and CNI switching in some patients, but more severe rejections have required the use of thymoglobulin or other lymphocyte-depleting agents. Case reports of thymoglobulin use in these patients are notable for swift, profound, and prolonged CD4+ T-cell depletion. Thymoglobulin was effective at reversing rejection, but patients who receive it are at increased risk for infections, mostly nonopportunistic.<sup>27</sup>

## CONCLUSIONS

HIV infection is associated with an increased risk for ESRD, particularly among African American patients. Renal transplant in HIV-infected ESRD patients is feasible, and may confer a survival benefit for patients. Special care must be given to the management of immunosuppression and ART posttransplant. These patients may be at increased risk as compared with the general transplant population for acute rejection, and lymphocyte-depleting therapies must be used with great care. HIV-positive renal transplant patients remain a challenging population that is best cared for in an academic institutional setting equipped to provide the multidisciplinary treatment approach they require.

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