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Update on Kidney Transplantation in HIV-Infected Recipients

Silas P. Norman, Mallika Kommareddi and Daniel R. Kaul
University of Michigan Medical Center, Ann Arbor, MI, USA

Abstract

HIV infection has historically been a contraindication to kidney transplantation. Prior to the era of potent antiretroviral therapy, the survival of HIV-infected patients was too poor to justify transplantation. In the last 15 years there has been substantial improvement in antiretroviral medications, such that HIV-positive patients are living longer and developing chronic diseases such as end-stage renal disease. The improvement in survival of HIV-positive patients has resulted in transplant centers increasingly considering infected patients appropriate for kidney transplantation. Recently, the results of the first prospective multicenter trial of kidney transplantation into HIV-positive candidates were released, showing the success and challenges of transplantation into this population. In light of the multicenter findings as well as national registry data, kidney transplantation should be considered the standard-of-care renal replacement therapy for HIV-positive end-stage renal disease patients and they should be referred and evaluated for kidney transplantation accordingly. **(AIDS Rev. 2012;14:195-207)**

Corresponding author: Silas P. Norman, spnorman@umich.edu

Key words

HIV. Kidney transplant. Immunosuppression. End-stage renal disease.

Introduction

HIV infection has historically been an absolute contraindication to kidney transplantation. In the last 15 years, however, survival among HIV-infected patients has improved dramatically, prompting a reconsideration of the appropriateness of HIV-positive patients as transplant candidates. In fact, an increasing number of transplant centers in the USA and Europe have been transplanting HIV-positive individuals successfully. Recently, Stock, et al. released the preliminary results of the first prospective, multicenter trial systematically examining patient and graft outcomes in HIV-positive kidney transplant recipients[1]. The study results reinforced the success of transplantation into HIV-positive recipients, finding overall good patient and graft survivals. However, the study also highlighted several challenges to transplantation of the HIV-positive candidate, including drug interactions, infection risk, and the need for coordination of transplant and infectious disease care.

The improvement in HIV-positive patient survival is largely attributable to patient treatment with potent combination antiretroviral therapy (ART), usually involving two nucleoside reverse transcriptase inhibitors (NRTI) along with a protease inhibitor (PI) or nonnucleoside reverse transcriptase inhibitors (NNRTI)[2]. Such combination therapy, most commonly known as HAART (or ART), has significantly extended the lives of HIV-positive patients. One consequence of improved survival is that the major causes of death in the HIV-positive population have transitioned from opportunistic infections to malignancies[3] and chronic diseases[4], including end-stage renal disease (ESRD). As a result of improved HIV-positive patient outcomes, there has been an increasing desire to offer kidney transplantation as a renal replacement therapy to these patients.

Correspondence to:
Silas P. Norman
University of Michigan Medical Center
3914 Taubman Center
Ann Arbor, MI 48109, USA
E-mail: spnorman@umich.edu

Epidemiology of HIV-positive end-stage renal disease population

In the USA, there are approximately one million HIV-positive individuals, of which almost one-half identify as

black/African American[5]. In addition, there are approximately 56,000 new HIV-1 infections annually[5]. A significant number of HIV-positive individuals are at risk for the development of chronic kidney disease (CKD) and ESRD. There are several causes of ESRD in the HIV-positive population, and the specific cause is often difficult to determine due to inconsistencies in disease reporting[6]. Nevertheless, the major cause of ESRD in this population appears to be HIV-associated nephropathy (HIVAN), a disease almost exclusively of African American males[7,8] and associated with a rapid progression to ESRD. In African Americans, HIVAN is the third leading cause of ESRD after diabetes mellitus (DM) and hypertension[9].

The HIV-positive population experiences ESRD from many additional causes besides HIVAN, including glomerulonephritis[10,11] and IgA nephropathy, which may be a direct result of HIV infection[11,12]. Many HIV-positive patients are coinfected with hepatitis C virus (HCV) that can independently cause kidney disease. The incidence of HCV/HIV coinfection can range up to as high as 90% among intravenous drug users[13]. Hepatitis B-associated membranous nephropathy has been documented in HIV-positive patients along with traditional causes such as DM and hypertension[14,15].

In addition to the HIV-associated causes of CKD, some antiretroviral (ARV) agents may result in kidney dysfunction. Indinavir, while rarely used currently, crystallizes in the urine, leading to obstructive uropathy[16]. Proximal tubular disease (Fanconi syndrome) with glycosuria, proteinuria, hypokalemia, and hypophosphatemia has been well described with the use of tenofovir, and if the drug is not discontinued, renal failure may result[17]. In a recent large cohort study, tenofovir was associated with increased risk for proteinuria, rapid decline in kidney function, and CKD. Tenofovir's effects on kidney function were not always reversible with discontinuation of the medication[18]. A recent meta-analysis and systematic review demonstrated a modest decline in kidney function in patients treated with tenofovir versus non-tenofovir-containing regimens but not increased risk of ESRD[19].

Approximately 800 individuals with HIV annually progress to ESRD and as of 2007 there were just over 3,000 prevalent HIV-positive ESRD patients, accounting for 0.6% of all patients with ESRD[9]. Incident HIV-positive ESRD patients tend to be younger (43 vs. 64 years) and more frequently African American (88 vs. 28%) than the overall incident ESRD population[9]. Additionally, HIV-positive patients tend to be more commonly HCV-positive and less likely to have DM[20]. As the survival of the HIV-positive population continues to improve, the HIV-positive ESRD population is expected to grow and a number of these patients will be appropriate for transplantation.

Table 1. Primary causes of end-stage renal disease in HIV-positive kidney transplant recipients

Disease	Frequency
HIV-associated nephropathy	13.6%
Diabetes mellitus	10.4%
Hypertension	39.4%
Glomerulonephritis	12.3%
Other/unknown	24.0%

Data from the Scientific Registry of Transplant Recipients for the period January 1, 1996 through July 31, 2009.

Recent data suggests that HIV-positive candidates may be less likely than HIV-negative candidates to be waitlisted for kidney transplant[21]. Sawinski, et al. recently examined barriers to wait-listing among HIV-positive candidates and found several factors associated with decreased likelihood of active wait-listing, including lack of documentation of HIV control, $CD4^+ < 200$ cells/ml^3, history of drug use, and African American race[21]. In addition, a previous review of data from the Scientific Registry of Transplant Recipients (SRTR) suggested that among HIV-positive recipients, African Americans accounted for only 33% of living donor and 42% of deceased donor recipients, despite their large representation among HIV-positive patients with ESRD[20]. Finally, the distribution of primary causes of ESRD among HIV-positive transplant recipients is different from the HIV-positive ESRD population, suggesting a selection bias in which patients are referred and accepted for transplantation (Table 1). Each of these findings suggests that the barriers to transplant opportunities seen in the general ESRD population, particularly for African Americans, may also extend to HIV-positive patients[22].

Outcomes

Transplant outcomes in the era of combination antiretroviral therapy

Survival of HIV-positive ESRD patients improved substantially in the mid-to-late 1990s[23,24] such that by 2002, the death rate in HIV-positive ESRD patients compared favorably to that seen in DM ESRD patients of the same

era[25]. Ahuja, et al. performed an evaluation of 22 HIV-positive patients with ESRD treated between 1992 and 1999, and showed substantially improved survival among ART-treated patients, with an 80% survival at 28 months (range 11-45 months)[23]. The Viral Activation Transfusion Study (VATS) enrolled 528 HIV-positive patients with a history of cytomegalovirus seropositivity or disease receiving a first transfusion for anemia. The primary endpoints of the study centered on rates of death, opportunistic infection, and repeat transfusions. However, as the study bridged the pre-ART and ART eras, authors were also able to evaluate the impact of ART therapy on the study subjects. The authors observed that the adjusted rate ratio for death was significantly lower (0.38; $p < 0.001$) among ART-treated patients compared to untreated patients[26].

The majority of studies of kidney transplantation into HIV-positive patients in the ART era have focused on well-controlled patients with $CD4^+$ counts > 200 cells/mm^3, undetectable viral loads, and no history of opportunistic infections[27]. Roland, et al. provided one of the first ART era experiences with transplantation in HIV-positive recipients. Ten kidney transplant recipients followed for a mean of 480 days achieved 100% patient and graft survival at one year[27]. As important as the transplant-specific outcomes was the demonstration of effective viral suppression following transplantation. Subsequently, a number of recent studies have reported outcomes very consistent with those seen in HIV-negative recipients[28,29].

More recently, Locke, et al. performed a retrospective analysis of UNOS data from 2004-2007[30]. Compared to HIV-negative recipients, HIV-positive recipients were more likely to be African American (51 vs. 24%), less likely to have DM (22.9 vs. 30.4%), and more likely to be coinfected with HCV (28 vs. 4.1%). Although patient survival in HIV-positive and -negative candidates was equivalent at one year, the one-year graft survival in HIV-positive patients was inferior (85.2 vs. 94.1%; $p = 0.05$). However, the same study noted that in the absence of increased donor age (≥ 50 years), prolonged cold ischemia times, and delayed graft function, HIV-positive patients enjoyed equivalent graft survival as HIV-negative recipients. An additional report by Gruber, et al. reported on outcomes from eight predominantly African American HIV-positive transplants with a median of 15 months follow-up[31]. Recipients were transplanted with interleukin-2 (IL-2) receptor blockade, cyclosporine A (CsA), mycophenolate mofetil (MMF), and prednisone. The authors noted excellent patient (100%) and graft (88%) survivals as well as relatively low rejection rates (13%) at one year following transplantation.

Stock, et al. recently published the results of a five-year prospective study of the outcomes of 150 HIV-positive kidney transplant recipients[1]. The study enrolled from November, 2003 through June, 2009 and included a median posttransplant follow-up period of 1.7 years. The authors reported mean patient survivals at one and three years of 94.6 and 88.2%, respectively. Graft survivals during the same one- and three-year periods were shown to be 90.4 and 73.7%, respectively. Importantly, the study revealed high cumulative rejection rates in HIV-positive kidney transplant recipients at one year (31%) and three years (41%), highlighting some of the ongoing challenges to long-term success in the HIV-positive population. Although the follow-up time was short in this study and the induction criteria varied by center, the study nonetheless is the largest and one of the most informative to date showing outcomes in HIV-positive kidney transplant recipients.

Interestingly, registry data has been of limited utility in examining the national experience with transplants into HIV-positive recipients. The major drawback has been inconsistent reporting of HIV status. A review of first-time kidney transplant recipients from January 1, 1996 through July 31, 2009 using SRTR data suggests that HIV-positive graft and patient survival is inferior to that experienced in HIV-negative recipients (Fig. 1). However, of the 169,000 recipients available for analysis, more than 80,000 had missing HIV serology status and only 314 recipients were noted to be HIV positive. In addition, there are no HIV-positive recipients reported between 1996 and 1999, despite the fact that these transplants are documented in the literature. Despite the limitations of the data, it is worth noting that the one-year and five-year unadjusted posttransplant survivals (91 and 64% graft, 94 and 72% patient, respectively) among HIV-positive recipients are consistent with the survivals (89 and 62% graft, 96 and 82% patient, respectively) among HIV-negative African American recipients[32], and better than expected on dialysis[9], reinforcing kidney transplant as the standard-of-care therapy for HIV-positive patients with ESRD.

HIV replication and the impact of transplant immunosuppression

There are two phases of HIV infection that set the stage for both the immune dysfunction seen in HIV-positive patients and for potential benefits of transplant immunosuppression (Fig. 2). Phase one is the acute phase of HIV infection, primarily involving innate immunity. The virus initially infects $CD4^+$ memory T-cells

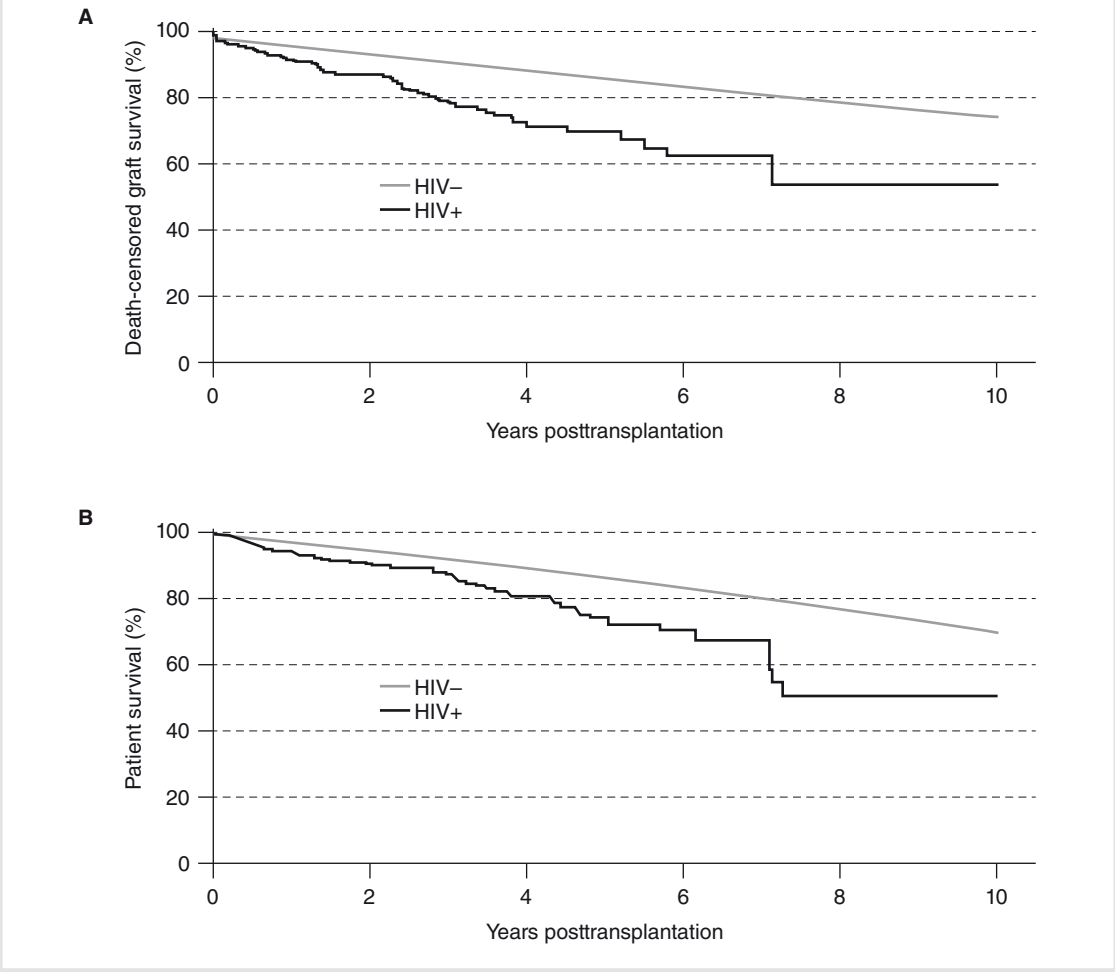

Figure 1. *Posttransplant survival by HIV status.* ***A:*** *Death-censored posttransplant graft survival by HIV status. The analysis includes 80,366 first-time, kidney only recipients transplanted January 1, 1996 to July 31, 2009, with follow-up through December 1, 2010. HIV-negative: 80,052; HIV-positive: 314. Median follow-up of four years for death-censored graft survival.* ***B:*** *Posttransplant patient survival by HIV status. The analysis included 80,366 first-time, kidney only recipients transplanted January 1, 1996 to July 31, 2009, with follow-up through December 1, 2010. HIV-negative: 80,052; HIV-positive: 314. Median follow-up of five years for patient survival.*

that also express CCR5 and are present in the mucosa. The initial infection involves recruitment of inflammatory cells and increased expression of proinflammatory cytokines including interleukins 1β, IL-6 and IL-18, along with tumor necrosis factor[33]. There is further spread of HIV, resulting in depletion of $CD4^+/CCR5^+$ lymphocytes, particularly in the gut-associated lymphatic tissue (GALT)[34]. During this time, patients experience peak viremia followed by modest T-cell rebound, although the GALT lymphocyte concentrations remain low. There is an attempt to suppress the inflammatory response through the production of anti-inflammatory molecules such as IL-10 and transforming growth factor-β (TGF-β), but the suppression is usually inadequate[35]. The extent of this initial infection and reservoir of infected $CD4^+$ cells helps determine the overall trajectory of HIV infection.

Persistent viremia, disruption of the GALT, and T-cell activation set the stage for phase two of HIV infection.

During phase two, chronic HIV infection is characterized by chronic immune activation and involves both the innate and adaptive immune systems. There is immune hyperactivation involving increased T-cell expression of molecules, such as CD38, HLA-DR, and Fas, among other factors[36]. In addition, there appears to be translocation of microbial products through the

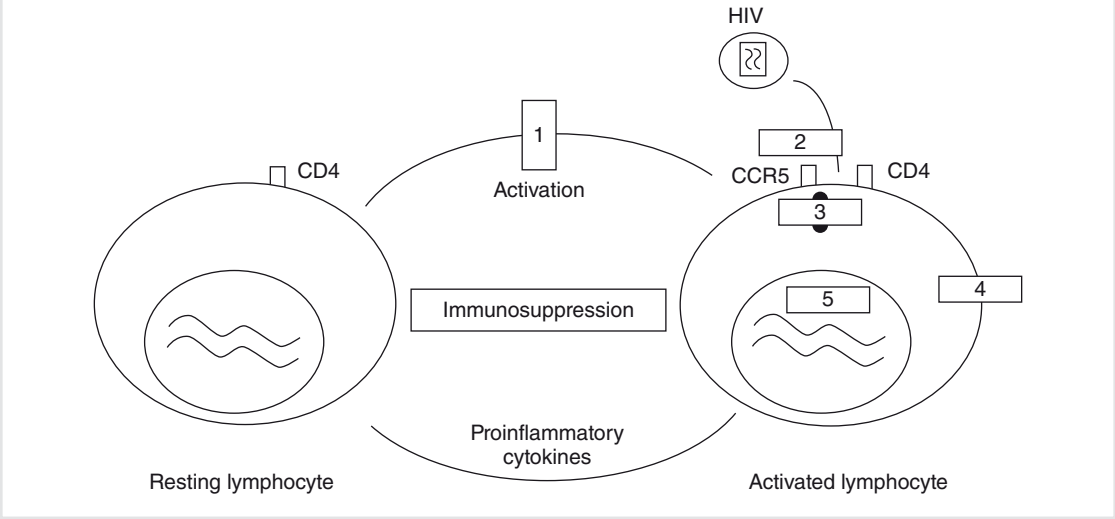

Figure 2. *Immunosuppression impact on HIV replication.* ***1:*** *Suppression of lymphocyte activation.* ***2:*** *Competitive inhibition of the CCR5 receptor (sirolimus).* ***3:*** *Interference with HIV un-enveloping (cyclosporine).* ***4:*** *Interference with normal lymphocyte growth and replication (cyclosporine and tacrolimus).* ***5:*** *Disruption of interleukin-2/proinflammatory cytokine production via nuclear factor kappa B (steroids).*

disrupted gut epithelium, exposing the patient to inflammatory mediators such as bacterial lipopolysaccharide, which stimulates ongoing immune activation[37]. An antibody response can further impact the outcome of infection with damage generated through antibody binding to infected cells, complement activation, and immune complex deposition[38]. Finally, memory $CD4^+$ central T-cells are stimulated. In the initial infection, naive and resting central T-cells are relatively protected from HIV infection as they do not express CCR5. However, as the memory $CD4^+$ cells attempt to reconstitute the $CD4^+$ population, they express CCR5 and become activated. The activated T-cells then provide additional targets for HIV infection[39]. Even in ART-treated patients who are apparent responders, a chronic inflammatory response appears to persist. The chronic immune activation in HIV-positive patients is important as it appears to be the mechanism of tissue damage in these patients. As such, medications that can disrupt cell infection by the HIV virions or suppress T-cell activation may be beneficial to HIV-positive patients. Transplant immunosuppression may meet some of these challenges.

Growth of HIV within host cells and infection of naive cells requires components of the host cell machinery, most notably cyclophilin A (CpA). During the replication process, the p24 region of the HIV Gag polyprotein binds and incorporates CpA into new immature virions[40]. Wiegers and Krausslicht showed that the infectivity of naive cells is dependent on availability of CpA[41] and Streblow, et al. reported that the process of incorporation of CpA is essential to the production of infectious HIV particles[42]. Available data suggests that CpA may act as an un-coating factor in a newly infected cell by destabilizing the mature capsid in a step between virion entry and reverse transcription[43]. Following production of mature virion particles, the new virions bud from the host cell and go on to infect additional lymphocytes, attaching to naive $CD4^+$ cells using the chemokine receptor CCR5 as a coreceptor to gain initial entry into new cells[44].

Both CsA and tacrolimus (Tac), the primary anti-rejection medications used, have been demonstrated to impact HIV replication. Pretreatment of cells in culture with CsA (which binds CpA to suppress IL-2-mediated lymphocyte activation) has been demonstrated to decrease infectivity of HIV-naive cells and to inhibit viral production in chronically infected cells[45]. Tacrolimus has also been suggested to be beneficial in the treatment of HIV infection[46]. Although Tac has no effect on Gag processing and does not interfere with initial HIV infection, Tac does interfere with growth of chronically HIV-infected cells[47]. In addition, there are reports that sirolimus use may be associated with downregulation of the CCR5 receptor, which may decrease HIV infectivity[48].

Clinically, there has been concern that transplant immunosuppression may worsen the progression of HIV disease, but data have been mixed. Andrieu, et al.

Table 2. Typical posttransplant immunosuppressive regimen

Induction Agent	IL-2 receptor blocker (basiliximab, daclizumab)*
Calcineurin inhibitor	Tacrolimus (Prograf®) or cyclosporine A (Neoral®, Gengraf®)
Anti-metabolite	Mycophenolate mofetil or sodium (Cellcept®, Myfortic®)
Glucocorticoid	Prednisone
CMV prophylaxis	Valganciclovir (Valcyte®)
PCP prophylaxis	Trimethoprim/ sulfamethoxazole
Fungal prophylaxis	Nystatin oral solution

*Avoid thymoglobulin and alemtuzumab.
CMV: cytomegalovirus; PCP: *Pneumocystis carinii pneumonia.*

documented increased plasma viral RNA in CsA-exposed HIV-positive patients[49]. Erice, et al. performed a retrospective study of 88 solid organ transplant recipients, 66 of whom acquired HIV during or following transplantation. The authors observed that recipients with HIV pretransplantation showed a faster rate of progression to AIDS than those with newly acquired infections[50]. Overall, however, there had been no consistently negative clinical impact of transplant immunosuppression on HIV progression among kidney transplant recipients in the current era. In fact, transplant medications may be helpful to HIV-positive patients by suppressing lymphocyte activation. Rizzardi, et al. in a 2002 study demonstrated the clinical effectiveness of treating ART-naive subjects with ART alone or ART plus CsA for the first six months[51]. The CsA-treated subjects achieved equivalent viral suppression and improved $CD4^+$ counts compared to non-treated subjects.

Challenges

Immunosuppression

Choice of immunosuppression for HIV-positive transplant recipients has sought to balance the need to suppress rejection with the need to minimize infections and drug interactions. In the USA, most kidney transplant recipients are on a triple-drug immunosuppressive regimen, typically consisting of a calcineurin inhibitor (CNI, tacrolimus or cyclosporine), an antimetabolite in the form of MMF or mycophenolate sodium, and corticosteroids (Table 2). These drugs work together to suppress the elaboration of IL-2, activation and proliferation of lymphocytes, and generation of anti-HLA antibody. Such regimens have been demonstrated to be well tolerated and result in low rejection and complication rates.

At the time of transplantation, high immunologic risk candidates (African Americans, HLA-sensitized, repeat transplants) are typically given additional induction therapy. In the USA, induction consists of either antithymocyte globulin (thymoglobulin) or the IL-2 receptor antibodies (daclizumab and basiliximab)[52]. In HIV-positive recipients, the IL-2 receptor antibodies have typically been used to avoid prolonged and profound T-cell suppression associated with thymoglobulin use[53,54]. Consistent with profound immune suppression, an increased frequency of infections in thymoglobulin-treated patients has also been documented by several authors[55]. While less information is available regarding alemtuzumab, for similar reasons this drug should be avoided in HIV-positive patients.

Early experience with Tac was associated with a significant increase in new-onset DM after transplantation in recipients also taking PI[55]. More recently, centers are again starting to utilize lower doses of Tac in HIV-positive regimens[56]. In addition, there are centers reporting use of sirolimus instead of the CNI with good results[57]. Historically, the regimens for HIV-positive patients involved the use of steroids, in part because of the beneficial effect steroids may have on the lymphocyte count. Most recently, similar to the general transplant population, steroid-avoidance protocols have been offered to the HIV-positive transplant population[58].

Infection

The majority of infections reported in HIV-positive recipients following transplantation have not been opportunistic in nature, but some have been severe[55]. A number of posttransplant infections appeared to follow treatment with thymoglobulin for rejection episodes. The frequency of infections has not proved prohibitive to transplantation, and overall infections have decreased as experience in transplantation of HIV-positive candidates has improved. In a recent publication, Roland et al.[59] reported good patient and graft outcomes and noted that with appropriate, aggressive opportunistic infection prophylaxis, excess infection was an infrequent issue.

Rejection

Although HIV-positive transplant outcomes have steadily improved in the ART era, frequent rejection

episodes were reported in the early ART era experience and in the recent multicenter trial[1,55,59]. High rejection rates have likely resulted from a cautious approach to potent immunosuppression combined with multiple drug interactions. For example, in the Stock multicenter trial, the median one-month CsA and Tac levels were relatively low, possibly contributing to rejection episodes. Alternatively, HIV-positive patients with graft dysfunction may have been more likely to be referred for kidney biopsy, increasing the frequency of diagnosis. Recent single-center studies have reported rejection rates more in line with the general kidney transplant population[31,56], perhaps a sign of the maturing experience with transplantation in this patient group. How to most safely and effectively treat transplant rejection continues to be unclear. Patients have been effectively treated for mild rejections with steroid therapy with minimal side effects. However, for more aggressive rejections, thymoglobulin has been used with reasonable trepidation, given the length of time bone marrow suppression may persist.

Drug interactions

Drug interactions remain a significant challenge in the management of HIV-positive patients (Table 3). The interactions between ART and transplant immunosuppression are diverse and can vary even within classes of ART. The main interactions that tend to be considered are the interactions between CNI and the PI. The majority of the PI are potent inhibitors of the cytochrome p-450(3A4) system of the liver responsible for metabolizing both immunosuppressants and many of the ART medications. When used in combination with PI, dramatic increases in the bioavailability of the CNI may occur[60]. The use of CsA or Tac and PI requires significant reduction of CNI doses, extension of dosing frequencies, or both[61,62]. Also important for practitioners to appreciate is that stopping a PI without upward adjustment of calcineurin doses can precipitate rejection[63].

The PI are also substrates and inhibitors of the p-glycoprotein (multidrug resistant protein) efflux pumps present on the apical surfaces of several epithelial cells[64], which may further contribute to increased CNI exposure in PI-treated patients. Although the data on the use of sirolimus and everolimus in HIV-positive recipients is limited, given that they are metabolized by the p-450 system and are a substrate for P-glycoprotein, similar drug-drug interactions with PI are to be expected[65].

The NNRTI are p-450 substrates and inducers of the p-450 system, leading to the sub-therapeutic levels of CNI or sirolimus[66]. The NRTI are not substrates for p-450, so overall less drug interactions with transplant immunosuppression are expected. However, the NRTI can potentially contribute to both anemia and neutropenia[60]. As such, use with common transplant medications such as valganciclovir, azathioprine, MMF, and mycophenolate sodium can lead to significant leukopenia and inadvertent suppression of the $CD4^+$ cell count. Maraviroc, the only currently licensed CCR5 antagonist, is a p-450(3A4) substrate, but does not inhibit or induce the enzyme and would not be expected to interact with CNI. The integrase inhibitor raltegravir is metabolized by glucuronidation and interactions with CNI should also be minimal[67].

Both MMF and mycophenolate sodium are hydrolyzed to the active metabolite mycophenolic acid. Mycophenolic acid is an inosine monophosphate dehydrogenase inhibitor and interferes with the conversion of inosine monophosphate to guanosine monophosphate. There is suggestion in vitro of synergistic antiviral effects when MMF is used with several ARV, including abacavir, didanosine, and tenofovir[68]. At the same time, MMF may interfere with the effects of zidovudine and stavudine, decreasing treatment effectiveness[69].

Prednisone and other glucocorticoids may increase the $CD4^+$ count in HIV-positive patients[70]. In addition, the patient steroid exposure tends to rise when used in combination with CNI. Glucocorticoids are inducers of the p-450 system[71]. The tapering down of steroids that usually occurs following transplantation may be accompanied both by decreases in $CD4^+$ counts as well as increases in calcineurin levels[72]. These effects may be associated with an increased risk of infection and potential nephrotoxicity. As such, patients should be followed closely as steroid doses are decreased.

Antiretroviral medication dosing in patients with renal dysfunction

Effective dosing of ARV in patients with ESRD can be challenging. Additionally, a number of successful kidney transplant recipients over time may have a decline in their kidney function. Providers caring for the HIV-positive kidney transplant recipient need to be aware of the special considerations for ARV dosing in patients with impaired kidney function. The Department of Health and Human Services (DHHS) Guidelines for HIV treatment provide a periodically updated table of appropriate renal dosing of ARV[67]. In general, PI and NNRTI are hepatically metabolized and do not require dose adjustment based on changes in renal function.

Table 3. Expected antiretroviral and immunosuppressive interactions

Antiretroviral	Effect of immunosuppression on antiretroviral levels	Effect of antiretroviral on immunosuppression	Expected clinical effects	Mechanism of interaction	Suggested management
Nucleoside analogues					
– Abacavir (Ziagen®)	No significant change	Not studied	Synergistic with mycophenolate *in vitro*	Both purine synthesis inhibitors	No dose adjustment necessary
– Didanosine (Videx®)	Not studied	Not studied	None expected	None expected	No dose adjustment necessary
– Emtricitabine (Emtriva®)	Not studied	Not studied	None expected	None expected	No dose adjustment necessary
– Lamivudine (Epivir®)	Not studied	Not studied	None expected	None expected	No dose adjustment necessary
– Stavudine (Zerit®)	Activity antagonized by mycophenolate	Not studied	Decreased stavudine activity	Antagonism noted *in vitro*	Avoid stavudine if possible
– Tenofovir (Vired®)	With mycophenolate increased C_{max}, no change in AUC	None expected	None expected	Unclear	No dose adjustment necessary
– Zidovudine (Retrovir®)	Activity antagonized by mycophenolate	Not studied	Decreased zidovudine activity	Antagonism noted *in vitro*	Avoid zidovudine if possible
Nonnucleoside reverse transcriptase inhibitors					
– Delavirdine (Rescriptor®)	Not studied	May increase CNI/SR* levels	Increased risk for CNI/SR toxicity	Delavirdine inhibition of CYP3A4	Monitor CNI/SR levels and adjust as necessary
– Efavirenz (Sustiva®)	Not studied	May decrease CNI/SR levels	Increased risk for acute rejection	Efavirenz induction of CYP450 3A4	Monitor CNI/SR levels and adjust as necessary
– Etravirine (Intelence®)	Not studied	May alter CNI/SR levels,	Significant interaction unlikely	Substrate for CYP450 3A4 and P-glycoprotein	Monitor CNI/SR levels and adjust as necessary
– Nevirapine (Viramune®)	Not studied	May decrease CNI/SR levels	Increased risk for acute rejection	Nevirapine induction of CYP450 3A4	Monitor CNI/SR levels and adjust as necessary
– Rilpivirine (Edurant®)	Not studied	May alter CNI/SR levels	Significant interaction unlikely	Rilpivirine is a substrate for CYP450 3A4	Monitor CNI/SR levels and adjust as necessary
Protease inhibitors					
– Atazanavir (Reyataz®)	Not studied	May increase CNI/SR levels	Increased risk of CNI/SR toxicity, excess immune suppression	Atazanavir inhibition of CYP450 3A4	Decrease CNI/SR dose and/or frequency as indicated by levels
– Darunavir (Prezista®)	No significant change	May increase CNI/SR levels	Increased risk of CNI/SR toxicity	Darunavir inhibition of CYP450 3A4	Decrease CNI/SR dose and/or frequency as indicated by levels

(Continue)

Table 3. Expected antiretroviral and immunosuppressive interactions *(continued)*

Antiretroviral	Effect of immunosuppression on antiretroviral levels	Effect of antiretroviral on immunosuppression	Expected clinical effects	Mechanism of interaction	Suggested management
Nonnucleoside reverse transcriptase inhibitors					
– Fosamprenavir (Lexiva®, Telzir®)	Not studied	May increase CNI/SR levels	Increased risk of CNI/SR toxicity	Substrate for CYP450 3A4 and P-glycoprotein	Decrease CNI/SR dose and/or frequency as indicated by levels
– Indinavir (Crixivan®)	No significant change	May increase CNI/SR levels	Increased risk of CNI/SR toxicity	Indinavir inhibition of CYP450 3A4	Decrease CNI/SR dose and/or frequency as indicated by levels
– Lopinavir/ritonavir (Kaletra®)	No significant change	May increase CNI/SR levels	Increased risk of CNI/SR toxicity	Lopinavir/ritonavir inhibition of CYP450 3A4	Decrease CNI/SR dose and/or frequency as indicated by levels
– Nelfinavir (Viracept®)	Initial increase, then returns to baseline	May increase CNI/SR levels	Increased risk of CNI/SR toxicity	Nelfinavir inhibition of CYP450 3A4	Decrease CNI/SR dose and/or frequency as indicated by levels
– Ritonavir (Norvir®)	No significant change	May increase CNI/SR levels	Increased risk of CNI/SR toxicity	Ritonavir inhibition of CYP450 3A4	Decrease CNI/SR dose and/or frequency as indicated by levels
– Saquinavir (Invirase®, Fortovase®)	No significant change	May increase CNI/SR levels	Increased risk of CNI/SR toxicity	Saquinavir inhibition of CYP450 3A4; competitive binding of P-glycoprotein	Decrease CNI/SR dose and/or frequency as indicated by levels
– Tipranavir (Aptivus®)	No significant change	May increase CNI/SR levels	Increased risk of CNI/SR toxicity	Tipranavir inhibition of CYP450 3A4; competitive binding of P-glycoprotein	Decrease CNI/SR dose and/or frequency as indicated by levels
–Fusion inhibitors					
– Enfuvirtide (Fuzeon®)	No significant change	No expected change	No expected impact	Enfuvirtide not a CYP450 3A4 substrate	No interaction expected
Chemokine Coreceptor Antagonists					
– Maraviroc (Selzentry®, Celsentri®)	Not studied	May alter CNI/SR levels	Significant interaction unlikely	Substrate for CYP450 3A4 and P-glycoprotein	Monitor CNI/SR levels and adjust as necessary
Integrase inhibitors					
– Raltegravir (Isentress®)	No significant change	No expected change	No expected impact	None expected	No dose adjustment necessary

CNI/SR: tacrolimus, cyclosporine/sirolimus. Although not studied, everolimus would be expected to have similar interactions.

Nucleosides and nucleotides, however, are primarily renally cleared and must be dose adjusted based on renal function[17]. The fusion inhibitor enfuvirtide and the integrase inhibitor raltegravir do not require adjustment for renal dysfunction or dialysis; however, maraviroc, a CCR5 inhibitor, does require reduced dosing when the creatinine clearance falls below 30 ml/min[67]. Tenofovir is associated with both acute and chronic declines in renal function and should be used with caution in transplant recipients. Provider awareness and monitoring (at least semiannually) of kidney function in tenofovir-treated patients is critical to avoid tenofovir-induced CKD.

Evaluation of candidates

In kidney transplantation, the ideal is to perform a preemptive (prior to dialysis) kidney transplant to afford the best graft and patient outcomes[73]. As such, early referral for evaluation, both from general nephrologists and from infectious disease primary care providers is essential. The effective evaluation of the HIV-positive candidate requires ongoing engagement from both the transplant center and the infectious disease care provider. Most evaluations generally follow the guidelines of the NIH-sponsored multicenter trial[74]. The HIV-positive candidate requires all of the same workup prescribed for the HIV-negative transplant candidate. The primary goal of kidney transplantation is to provide a survival benefit to the patient compared to dialysis therapy. Acceptable medical candidates for kidney transplantation should generally be in good health, have good functional status, and minimal cardiovascular comorbidities. In addition, candidates must be free of all opportunistic infections, with appropriate documentation prior to transplantation. Patients with HIV should be medically adherent and controlled on a combination ART regimen. Control of HIV is demonstrated by undetectable viral loads and $CD4^+$ counts > 200 cells/mm^3 for at least six months prior to transplantation. Patients coinfected with hepatitis B or C virus need additional evaluation by hepatology to ensure good liver synthetic function prior to kidney transplantation. Finally, patients with a history of progressive multifocal leukoencephalopathy, lymphoma, pulmonary aspergillosis, significant (e.g., visceral) Kaposi's sarcoma, or coccidiomycosis are typically not considered candidates due to the potential worsening or recurrence of disease once on transplant immunosuppression. In selected circumstances (e.g., distant aspergillosis with radiological and clinical resolution) patients may be considered candidates for kidney transplantation.

Following successful transplantation, tight coordination of medical care remains an essential component of optimal patient management. Clear, consistent communication between transplant and HIV providers is critical as adjustments to either immunosuppressive medications or ARV may require changes in dosing of the other. Many centers appear to benefit from having dedicated transplant and infectious disease providers for the care of the HIV-positive candidates and recipients who can serve as consistent contacts for management of these complicated patients.

Antiretroviral drug selection in the HIV-positive kidney transplant recipient

The optimal ARV regimen in patients being considered for kidney transplantation differs from regimens in non-transplant candidates. The primary considerations include posttransplant drug interactions, nephrotoxicity, and avoiding drugs that require frequent dose adjustment with fluctuating kidney function posttransplantation. Since these patients are generally on dialysis or have advanced CKD, combination pills (e.g., Complera®, Atripla®, Combivir®, Epzicom®) cannot be used as dose reductions of some components are necessary.

The use of tenofovir in pretransplant patients merits discussion. While weekly administration in dialysis patients (where further kidney toxicity is of limited concern) is an attractive option, the potential nephrotoxicity posttransplantation can be challenging to manage. Optimal management requires a stable, tolerated, effective ARV regimen that is unlikely to require a change of agents posttransplantation. Patients already face the challenge of complying with a complex immunosuppression regimen, and introducing a new ARV and then attempting to differentiate adverse events is difficult. As discussed above, with some exceptions (e.g., maraviroc), only NRTI require adjustment for renal function. As abacavir is an exception to this rule, many experts prefer abacavir pretransplantation.

Drug interactions are the other major driver of ARV selection pre- and posttransplantation. If other alternatives exist, PI (particularly those requiring ritonavir boosting) should be avoided due to the difficulty of managing CNI dosing after transplantation. The NNRTI efavirenz, nevirapine, and etravirine are net p-450(3A4) inducers and achieving therapeutic CNI levels may be more difficult. Rilpivirine and maraviroc are substrates but not inducers of the p-450(3A4) enzyme and would be expected to have less significant CNI interactions.

Among the NRTI, an interaction between MMF and the thymidine analogues (zidovudine and stavudine) may decrease treatment effectiveness of these ARV.

Taking into consideration all of these factors, recommended regimens include abacavir and lamivudine combined with raltegravir or an NNRTI (efavirenz, rilpivirine). These combinations limit drug interactions, potential nephrotoxicity, and the need to modify dosing (only lamivudine requires modification) after transplantation. These regimens are all listed as "alternative regimens" in the DHHS guidelines. Currently, all DHHS preferred regimens include tenofovir, which is not a first-line choice in kidney transplant recipients for reasons stated above. Of course, an individual patient intolerance or viral resistance may require the selection of alternative ARV.

Conclusion

End-stage renal disease in the setting of HIV has progressed from an absolute contraindication to transplantation to an increasingly routine procedure in a relatively short time. With careful patient selection and coordinated transplant and infectious disease care, HIV-positive recipients are achieving patient and graft outcomes comparable to the general transplant population. Based on the successful outcomes of the recent multicenter trial, we can expect further expansion of transplant opportunities and possibly a reduction in infectious complications in this patient group. Kidney transplantation should be considered the standard-of-care therapy to treat ESRD in the HIV-positive population and should be offered to all well-controlled, medically adherent HIV-positive patients affected with ESRD.

Executive summary

Epidemiology of HIV-positive end-stage renal disease population

Approximately 800 HIV-positive individuals develop end-stage kidney disease annually in the USA. The major causes of ESRD include HIV-associated nephropathy, glomerulonephritis and hepatitis B and C. Given the improved survival in HIV-positive patients, the prevalence of HIV-positive ESRD patients is expected to grow.

Outcomes

In the current era of potent antiretroviral therapy, the survival of HIV-positive patients with ESRD is not significantly different than the general ESRD population. As such, kidney transplantation is an appropriate option for well-controlled HIV-positive patients. The most recent kidney graft and patient survivals post-transplantation have improved and approach those seen in the general population.

HIV replication and the impact of transplant immunosuppression

An examination of the normal pathway of HIV infection and replication highlights a number of opportunities for improved control with transplant immunosuppression. Current immunosuppression may limit the extent of initial HIV infection, decrease availability of naive active lymphocytes, and suppress the chronic inflammatory state that is characteristic of HIV infection.

Challenges

There are multiple challenges in the care of the HIV-positive kidney transplant recipient, including choice of immunosuppression, infection risk, and how to best treat rejection episodes without worsening HIV control. Perhaps the greatest challenge in management is recognizing the multiple potential drug interactions between antiretroviral therapy, particularly the protease inhibitors, and transplant immunosuppression. In addition, recognition of a patient's current level of kidney function is critical to medication selection and dosing. Further, medications such as the commonly used antiretroviral agent tenofovir may cause direct kidney toxicity. Best management requires knowledge of interactions and constant communication between the HIV and transplant providers to limit unintended negative interactions.

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