

Evolving Clinical Strategies for Transplantation in the HIV-Positive Recipient

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The transplant community has been slow to recognize the efficacy of highly active antiretroviral therapy in changing the course of human immunodeficiency virus (HIV) infection to a chronic condition. People infected with HIV are dying less often from progression of HIV to acquired immune deficiency syndrome. Unfortunately, there is an increasing rate of morbidity and mortality from comorbidities resulting in end-stage liver and kidney disease, prompting some transplant centers to eliminate HIV infection as a contraindication to transplantation. This overview will describe the evolving clinical strategies that have resulted in good outcomes after solid organ transplantation in the HIV-positive recipient.

Keywords: Human immunodeficiency virus, Liver transplant, Kidney transplant.

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The presence of human immunodeficiency virus (HIV) was traditionally viewed as a contraindication to transplantation secondary to logical concerns that immunosuppression would exacerbate an already immunocompromised state. Further concerns related to more demand for a limited pool of donor organs, particularly in a group of patients with a limited expectancy for survival. However, the advent of highly active antiretroviral therapy (HAART) has resulted in a marked decrease in morbidity and mortality in people with HIV. As a result, people infected with HIV are dying less often from progression of HIV to acquired immune deficiency syndrome (AIDS) (1). Unfortunately, there is an increasing rate of morbidity and mortality from end-stage liver and kidney disease (1–3), prompting several transplant centers to eliminate HIV infection as a contraindication to transplantation. The transplant community has been slow to recognize that HIV has evolved to a chronic condition, with the majority of U.S. transplant centers still considering HIV to be a contraindication to transplantation (4). Hesitation in evaluation and timely listing have contributed to high mortality rates on the waiting lists, in part related to confusion revolving around the safety and efficacy of transplantation in the HIV-infected recipient (5). This overview will attempt to describe the current clinical

strategies that have resulted in good outcomes after solid organ transplantation in the HIV-positive recipients.

Rationale for Solid Organ Transplantation in the HAART Era

Significant progress has been achieved on several fronts, which have provided the impetus to reconsider HIV positivity as a contraindication to transplantation. Clearly the ability to control HIV with HAART is of pivotal importance in terms of being able to provide the required immunosuppression after transplantation. Initial HAART regimens typically include a protease inhibitor or nonnucleoside reverse transcriptase inhibitor (NNRTI) in combination with two nucleoside analogues. This combination therapy has been effective in providing virologic, immunologic, and survival benefits for patients with HIV.

The ability to suppress HIV viral replication with HAART therapy provided the initial motivation for reconsidering transplantation in people with HIV. However, further impetus for transplantation in this group of patients with an immunodeficient state has been provided by improved prophylaxis and treatment for opportunistic infections. Perhaps the best example of this is the treatment of tissue invasive cytomegalovirus (CMV) disease, which once was a fatal disease in both the immunosuppressed transplant recipient and people with HIV, but has evolved to outpatient management with an oral antiviral agent.

A final major barrier to transplantation in the HIV-positive recipient has been concerns for exacerbation of a compromised immunologic status by immunosuppression. Interestingly, many of the commonly used immunosuppressive agents have anti-retroviral qualities. Cyclosporine may suppress HIV replication associated with inhibition of interleukin-2-dependent T-cell proliferation (6, 7). Other antiretroviral qualities of cyclosporine are mediated by binding to cyclophi-

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lin A, preventing formation of the HIV gag protein/cyclophilin A complex necessary for nuclear import of the HIV-1 DNA (8, 9). There is one prospective study which suggested more rapid immune reconstitution in HIV-positive patients treated with cyclosporine and HAART versus cyclosporine alone (10). Although early clinical trials examining the efficacy of cyclosporine in controlling the HIV virus did not show an effect on viral loads or CD4+ T-cell counts, there is historic literature to suggest that transplant patients who received cyclosporine had a slower rate of HIV disease progression than those who did not (11, 12). Mycophenolate mofetil (MMF), an efficacious and frequently used immunosuppressive agent, inhibits inosine monophosphate dehydrogenase and diminishes the pool of intracellular nucleotides. MMF therefore acts synergistically with some nucleoside analogues, such as abacavir and didanosine, which are integral components of HAART therapy (13, 14). Of potential concern is the *in vitro* antagonism with D4T and AZT. Sirolimus, a TOR inhibitor and more recent addition to immunosuppressive regimens, downregulates the CCR5 receptor, the T-cell receptor for the HIV virion (15). The surprising antiretroviral qualities of many of the currently effective immunosuppressive agents has increased the enthusiasm for transplanting people with HIV, and the immunosuppressive agents with antiretroviral qualities have been the most frequently used drugs in the initial clinical trials. From the HIV side, the issue of decreasing immune activation and thus both decreasing HIV pathogenesis and the target pool available for new HIV infection are equally as compelling with all immunosuppressive therapy.

Increasing Demand for Solid Organ Transplantation in the HIV-Positive Patient

Better control of HIV viral replication has changed HIV infection from a rapidly progressive disease to a chronic condition, and has had a dramatic impact on the morbidity associated with chronic infection. Although people are dying less often from progression of HIV disease to AIDS, people with HIV infection are representing a rapidly increasing population on both kidney and liver transplant waiting lists as a result of comorbidities associated with HIV (16).

Demand for Kidney Transplantation

HIV-associated nephropathy (HIVAN) is a collapsing variant of focal sclerosing glomerulonephritis, and about 800 patients/year with this diagnosis have started dialysis as reported to the United States Renal Data System (USRDS) (17). The etiology of HIV nephropathy is unclear, but there is evidence that direct infection of renal tubular and/or mesangial cells by HIV-1 may be a significant factor (18). It is also unclear why this disease afflicts principally African American men, but it is now the third most common etiology of end-stage renal disease among African Americans aged 20–64 years after diabetes and hypertension (17, 19).

In addition to HIVAN, the HIV-infected patient is also at risk for the development of glomerulonephritis associated with hepatitis B virus (HBV) and hepatitis C virus (HCV). Membranous nephropathy has been observed in the HIV/HBV coinfecting patient. Immunoglobulin (Ig) A nephropathy has also been observed in people with HIV, and is likely a direct result of the HIV infection. Finally, kidney disease may

be exacerbated by nephrotoxicity related to the multiple medications associated with HAART and infection prophylaxis (i.e., tenofovir, indinavir, ritonavir, and bactrim), in addition to the well characterized toxicities of the calcineurin inhibitors used for immunosuppressive therapy. Potentially nephrotoxic agents associated with hepatitis B therapy are tenofovir and adefovir, important agents in the management of lamivudine-resistant hepatitis B before and after liver transplantation.

Demand for Liver Transplantation in People With HIV

Coinfection with HCV and HBV in people with HIV infection are frequent as a result of shared transmission modalities. The prevalence of end-stage liver disease in HIV infected patients continues to increase as a result of HCV and HBV coinfection, reported at 22–33% and 9%, respectively (20, 21). Liver disease is now a major cause of death for HIV-positive patients coinfecting with HCV and HBV. There are also data to support that progression of liver disease mediated by viral hepatitis is exacerbated in people with HIV as compared to people who are HIV negative and monoinfected with HBV or HCV (22, 23). Adding to the difficulties, the administration of interferon therapy can be challenging in the coinfecting patients as a result of associated thrombocytopenia, anemia, and leukopenia.

Unfortunately, the HAART regimens that have been so effective in controlling HIV infection can have direct hepatotoxicity, compounding the damage mediated by viral hepatitis. Direct drug toxicity has been associated with the NNRTIs and protease inhibitors that are common components of HAART therapy. Severe hepatotoxicity and even death have been associated with an immune-mediated response to the nonnucleoside analogue nevirapine. The risk of immune-mediated hepatotoxicity to nevirapine is higher in women, during pregnancy, and in persons with relatively high CD4+ counts (24). Fulminant liver failure with mitochondrial injury, lactic acidosis, and massive hepatic steatosis are rare but significant complications associated with the nucleoside analogues (25–27).

Finally, antiretroviral therapy may also indirectly exacerbate liver insufficiency from immune restoration hepatitis or the development of lamivudine-resistant HBV (28–32). For all these reasons, the demand for liver transplantation in the coinfecting patients will continue to increase, further increasing already stressed waiting lists.

Early Outcomes in the HAART Era

Interpretation of the historical data related to patient and allograft survival in HIV-positive people after solid organ transplantation is complicated by the unavailability of HIV RNA viral load or CD4+ T-cell counts in many of these retrospective studies. However, more recent reports of solid organ transplants performed in HIV-positive recipients during the HAART era have demonstrated comparable results to HIV-negative recipients in selected patients and are summarized below.

Results of Liver Transplantation in the HAART Era

There have been numerous reports of successful liver transplantation in people with HIV during the HAART era, which were summarized in a report from the Scientific Reg-

istry of Transplant Recipients (SRTR) (33), with 1-year survival rates ranging between 60–100% (34–38). In the largest report which pooled data from the University of Pittsburgh, University of Miami, University of California San Francisco, King's College (London), and the University of Minnesota, survival data was compared to a United Network for Organ Sharing (UNOS) database cohort of matched HIV-negative controls. Cumulative survival at years 1, 2, and 3 (87%, 73%, and 73%) was similar to age- and race-matched HIV-negative recipients from the UNOS database (87%, 82%, and 78%). However, poorer survival rates within the HIV-positive recipients were associated with HCV infection, intolerance of HIV medication posttransplant, and posttransplant CD4 counts less than 200. Although the HCV cohort had significantly poorer survival in the HIV-positive recipients, the difference in survival between HCV monoinfected (UNOS database) versus coinfecting recipients did not reach statistical significance at the $P < 0.05$ level (36).

Progression of HIV after liver transplantation and initiation of immunosuppression has not been an issue in the vast majority of cases that have been reported during the HAART era. Similarly, results from clinical trials suggest that recurrence of hepatitis B can be prevented after transplantation in the coinfecting patients, similar to the excellent results seen in the HIV-negative population. Although there was some concern with the control of hepatitis B in the high percentage of coinfecting patients with lamivudine resistance, the development of further resistance to adefovir or tenofovir has not been observed (39). Further increases in the number of agents available to treat breakthrough hepatitis B suggest that long-term control of hepatitis B will be feasible.

Unfortunately, hepatitis C recurrence remains a significant concern in the coinfecting patients. Despite earlier reports demonstrating fulminant recurrence of hepatitis C after transplantation in the coinfecting patients (37, 38), other reports have suggested that the recurrence is not significantly different than the experience seen in the hepatitis C recipients who are HIV negative (36). Most centers are treating with interferon and ribavirin when there is histologic evidence of hepatitis C progression, and there have been some cases of viral clearance in the coinfecting recipients (see current management strategies, below).

Results of Kidney Transplantation in the HAART Era

Excellent early results from prospective pilot trials of kidney transplants in the HIV-positive patients during the HAART era suggest that this is a safe and efficacious procedure. One-year graft survival has been comparable to HIV-negative patients, and in one series was 100% at a mean follow-up of 480 days (38). Progression of HIV disease was not an issue, and all patients have had controllable HIV viremia posttransplant. Surprisingly, acute rejection was seen in more than half of the patients, a rate that was double that seen in HIV-negative patients. In fact, the rejection was classified as moderate to severe in more than half of the cases, requiring aggressive therapy with thymoglobulin (40). This may be a result of immune dysregulation, although it could also represent insufficient immunosuppression due to changes in overall drug exposure. Fortunately, there have been few graft losses and renal function has been preserved after treatment, although the long-term impact from the rejection episodes

may only become evident in the long-term data. Another prospective trial using more aggressive induction therapy with an anti-CD25 antibody and maintenance with sirolimus therapy has had lower rejection rates, but a 1-year patient and graft survival of 85% and 75%, respectively (41). In any case, progression of HIV has not been seen in any of the kidney transplant recipients, and supports the role of kidney transplantation in the HIV-positive patient.

Other larger retrospective reports on kidney transplants performed during the HAART era are consistent with the early graft and patient survival results seen in the prospective pilot trials, and include: 1) a retrospective review of 47 HIV-infected patients in the United States Kidney Data System (42); 2) a review of 18 patients transplanted at four U.S. transplant centers through 2003 (43); and a report of 63 deceased donor kidney transplants and 37 living donor kidney transplants from the SRTR (33).

Evolution of Clinical Strategies

Selection Criteria

The criteria for proceeding with transplantation in the HIV-positive patient continue to evolve and are slowly being liberalized. In the initial clinical trials, transplantation has been limited to the HIV-positive recipients with an intact immune system and controllable HIV viremia on HAART therapy. Although patients with a history of opportunistic infections were originally excluded from the clinical trials, this has been changed as a result of good initial outcomes and experience with HIV-infected transplant recipients with a history of opportunistic infections who did not experience recurrence of disease. After initiation of HAART therapy and reconstitution of the immune system, the opportunistic infections were controlled. For this reason, most centers are now including patients with a history of opportunistic infections which were controlled after initiation of HAART therapy, reconstitution of the immune system, and appropriate antibiotic therapy. However, opportunistic infections for which there is no reliable therapy in the immunosuppressed posttransplant setting remain a contraindication to transplantation in the HIV-infected recipient. These include progressive multifocal leukoencephalopathy, chronic cryptocryptidiosis, and drug-resistant fungal infections.

The absolute CD4+ T-cell count continues to be used as a reflection of the intact immune system. CD4+ T-cell counts greater than 200 cells/mL are currently required for most centers performing kidney transplants in the HIV-positive recipient. For patients with end-stage liver disease and portal hypertension, the T-cell requirement has been dropped to 100 cells/mL as a result of lower T-cell counts noted in potential liver transplant recipients with splenomegaly and presumed splenic sequestration of T lymphocytes. A demise in CD4+ T-cell counts associated with rapid decompensation of liver disease has been noted in several coinfecting potential liver recipients, which occurs at the same time point at which the Model for End-Stage Liver Disease score escalates to a number required for donor liver allocation. For this reason, the CD4+ T-cell count requirement of 100 cells/mL has been extended to a period of three months prior to the time of the liver transplant in the current multisite National Institutes of Health

protocol addressing the safety and efficacy of solid organ transplantation in the HIV-positive recipient (www.HIVtransplant.com). For children, the absolute T-cell counts are not relevant, but rather the percentage of CD4+ cells. For children 1–2 years of age, the CD4+ percentage should be greater than 30. For children between 2–10 years of age, the percentage should be greater than 20.

Most transplant centers require an undetectable HIV RNA to reflect sufficient control of the virus on HAART therapy as a requirement for proceeding with kidney transplantation in the HIV-positive recipient. However, for liver transplant recipients who are unable to tolerate HAART therapy as a consequence of drug-related hepatotoxicity, the requirement for an undetectable viral load is waved if an experienced HIV clinician can confidently predict full suppression with HAART therapy after liver transplantation. This determination is based on a review of the HAART history, HIV RNA history, and resistance testing. It remains controversial whether patients with high CD4+ counts, but detectable HIV RNA and multidrug resistance, should be excluded from transplantation. Most centers continue to regard this scenario as an exclusion criteria, although evolution of these principles will occur with further experience demonstrating the safety of immunosuppression in this category of potential recipients.

The issue of proceeding with transplantation in the HIV-positive recipient with a history of Kaposi's sarcoma (KS) is also unresolved, although most current clinical trials include patients with resolved cutaneous KS. Some transplants in HIV-positive recipients with a history of pulmonary KS have also been performed if the development of KS occurred prior to the initiation of HAART therapy, and resolved after reconstitution of the immune system with antiviral agents (44). The hesitation to proceed with transplantation in this scenario is based on the experience in the HIV-negative patients who have developed KS and required cessation in immunosuppression to control the KS. However, the situation in the HIV-positive patient with a reconstituted immune system may be a different situation, and the issue of proceeding with transplantation in the HIV-positive recipient with a history of KS will depend on the initial experiences in the pilot trials.

Immunosuppression, HAART, and Drug Interactions

Despite the initial hypothesis that less immunosuppression would be required in the immunocompromised HIV-positive transplant recipient, the early experience has clearly demonstrated that the HIV-positive recipient is capable of mounting an alloimmune response. In fact, the early results for kidney transplantation in the HIV-positive recipient suggest that immune dysregulation in these recipients may contribute to higher rejection rates than in the HIV-negative recipient (38, 40). These higher rejection rates have not been noted in most of the early liver transplant experience, although these patients have acute rejection rates comparable to the HIV-negative transplant recipients (36, 38). The fact that the kidney transplant recipients appear to be vulnerable to aggressive early rejection has resulted in an evolution in the immunosuppressive strategies.

Based on the historic data on HIV-positive transplant recipients that reported that immunosuppression with lym-

pho-depleting regimens was responsible for rapid progression from HIV positivity to AIDS, most centers currently transplanting HIV-positive recipients have avoided OKT3 and thymoglobulin as induction agents. However, based on the higher than expected incidence of aggressive rejection episodes in the kidney transplant recipients, many centers have used the interleukin-2 receptor inhibitors for induction therapy, although the efficacy in decreasing the higher rejection rates remains unresolved. Immunosuppressive regimens in the liver transplant recipients have avoided induction therapy, as rejection in the liver recipients has been successfully managed with steroid therapy and adjustments in maintenance therapy.

Maintenance therapy for kidney and liver transplant recipients at most centers performing transplants in people with HIV consists of steroids, a calcineurin inhibitor (tacrolimus or cyclosporine A), and the antiproliferative agent MMF. As described above, both cyclosporine A and MMF have well-described antiretroviral qualities, and they are the preferred agent at our institution based on these qualities. Many transplant centers utilize tacrolimus as the preferred calcineurin inhibitor, but our decision to use cyclosporine A as the first-line calcineurin inhibitor is based on both the anti-retroviral qualities as well as decreased propensity for inducing glucose intolerance as compared to tacrolimus. Since the protease inhibitors commonly used in antiretroviral regimens can also be diabetogenic, the judicious use of the calcineurin inhibitors is justified. Since some degree of renal insufficiency is unfortunately present in many HIV recipients, the TOR inhibitor sirolimus may be a useful alternative to the calcineurin-based regimens. This potent immunosuppressive agent is less nephrotoxic and beta cell toxic than the calcineurin inhibitors, and has provided effective maintenance therapy in several HIV-positive recipients who have been intolerant of the calcineurin inhibitors. Sirolimus has recently been found to be a very effective antiproliferative agent for the treatment of KS (45), and its potential use as both an effective agent against KS and the alloimmune response makes this an attractive immunosuppressive agent. As described above, sirolimus downregulates the CCR5 receptor for the HIV virion, further increasing the potential importance of this agent in the immunosuppressive regimens in the HIV-positive recipient (15). Although downregulation of the CCR5 receptor by sirolimus could favor the emergence of an HIV strain utilizing the CXCR4 receptor (associated with poorer outcomes), this has not been reported in any of the HIV-positive recipients on sirolimus therapy.

The pharmacokinetic interactions between immunosuppressive and HAART agents can be profound, and continue to be defined. The inhibition of the cytochrome p4503A system by the commonly used protease inhibitors results in a dramatic impact on the levels of the calcineurin inhibitors (tacrolimus and cyclosporine A) and TOR inhibitors (sirolimus), resulting in the necessity for close monitoring and significant dose reduction in the immunosuppressive agents (46, 47). The initial dosages of the immunosuppressive agents require reduction by well over 50% of expected doses, and require further adjustments over time. The reciprocal reduction of the dosing for the protease inhibitors based on the inhibition of the cytochrome p4503A metabolic pathway is not necessary. The NNRTI efavirenz is an inducer of the

p4503A system, having the opposite effect on the dosing of tacrolimus, cyclosporine A, and sirolimus (48). The induction of the P4503A system by efavirenz is less profound than the inhibitory effects of the protease inhibitors. For this reason, when these agents are used together, the dosing of the immunosuppressive agents effected by the p4503A system should be similar to those used when protease inhibitors are used in the absence of NNRTIs. Several antibiotics and antifungal agents commonly used for prophylaxis and treatment in the immunosuppressed patients also can have dramatic effects on inhibiting the cytochrome p4503A system. Fluconazole is the one of the more commonly used antifungal agents for both prophylaxis and treatment in the immunosuppressed transplant recipient, and further dose reduction of the calcineurin inhibitors and sirolimus is required when this agent is used in the HIV-positive recipients taking protease inhibitors.

In the initial trials, there was no progression of HIV to AIDS in the transplant recipients regardless of the HAART regimen. Although the NNRTI-based regimens used in the absence of protease inhibitors may facilitate the dosing of the immunosuppressive regimens, most centers currently maintain the HAART regimen that controlled the HIV infection prior to transplant. The fact that HIV has been well controlled in all the initial trials regardless of the components of HAART regimens suggests that antiretroviral dosing has been adequate. If any of the HAART drugs are resulting in toxicity (i.e., hepatotoxicity, neuropathy) requiring temporary cessation of these agents, it is important to discontinue all components of the HAART therapy to avoid the development of HIV resistance. The initial experience has suggested that the HIV-positive transplant recipient can tolerate being without HAART for several weeks without losing viral control and/or subsequent CD4+ T-cell loss. There are a few other issues related to HAART choices in patients receiving immunosuppression. Atazanavir should be avoided in patients on proton pump inhibitors, which are commonly used in patients on MMF and steroids. In patients receiving MMF, the theoretic avoidance of zidovudine and stavudine is based on their *in vitro* antagonism of these agents (13, 14, 49, 50). Finally, zidovudine is the only myelotoxic HAART agent, which is a significant consideration when considering the additive myelosuppressive effects of immunosuppression and prophylactic antibiotics.

HBV Management

Lamivudine and emtricitabine are commonly used nucleoside analogues in HAART regimens, which also have activity against HBV. It is important to note that lamivudine resistance develops in more than 50% of patients after 3 years of therapy. In fact, liver decompensation related to lamivudine resistance has resulted in the referral of numerous HBV/HIV coinfecting patients for liver transplantation. Appropriate management with adefovir dipivoxil and/or tenofovir has provided effective rescue and eliminated the necessity for liver transplantation (51, 52).

The current success of liver transplantation for HBV-mediated liver disease is related to significant advances in the ability to control reinfection posttransplant. Because the HIV/HBV-coinfecting patients are often resistant to lamivudine as a result of the use of this agent in many HAART reg-

imens, there were appropriate concerns that the HIV-positive patient with lamivudine resistance would be at an increased risk for recurrent HBV posttransplant (53–55). In the early experience, recurrent HBV has been controlled with long-term management with hepatitis B immune globulin, lamivudine, adefovir, and/or tenofovir (39). The initial algorithm for HBV treatment during the perioperative transplant course is as follows: 1) 10,000 IU during the anhepatic phase; 2) 5000 IU every 6 hr on postoperative days 1 and 2; 3) 10,000 IU every day on postoperative days 3–7; 4) 10,000 IU every month for the first 3 months; 5) 5000 IU every month for the next 3 months; and 6) 2500 IU monthly, indefinitely. In many liver transplant recipients, HAART therapy cannot be reinitiated in the early posttransplant period, and in these cases, it should be emphasized that lamivudine and tenofovir should also be held. Both of these agents have antiretroviral effects, and the use of these agents for the treatment of HBV in the absence of the other HAART components can lead to HIV resistance. For this reason, lamivudine and tenofovir should only be reinitiated at the time these recipients can tolerate the complete HAART regimen. However, during this early period, it is imperative that HBV be controlled to prevent reinfection. In this scenario, adefovir can be used to control recurrence of HBV. Adefovir at HBV treatment doses has no anti-HIV effects, and thus no risk of HIV resistance. Entecavir was initially thought to have no effect on the HIV virus, but recently has been identified as having significant anti-HIV properties. For this reason, entecavir should not be utilized until the entire HAART regimen can be restarted, similar to the restrictions for lamivudine and tenofovir. Once HAART is re-established, long-term management should consist of hepatitis B immune globulin maintenance therapy as described, and a combination of lamivudine, adefovir, and/or tenofovir should be taken as before the transplant. It is also necessary to make the appropriate dose adjustments for renal insufficiency, which is frequently present after liver transplantation. Using this strategy, the HIV/HBV-coinfecting patients have had excellent results after liver transplantation, similar to those observed in the HIV-negative recipients.

HCV Management

The ability to control HCV recurrence after liver transplantation has not paralleled the remarkable progress seen with the ability to control HBV after liver transplantation. Furthermore, the rapid recurrence of HCV after liver transplantation in the HCV/HIV-coinfecting recipient has been seen on several occasions in the early experience, and there are significant concerns that the HIV/HCV-coinfecting patients are at risk for poorer outcomes than the rest of the HIV-positive recipients. For the HCV-positive and HIV-negative transplant recipient, there is nothing in the literature to suggest the rates of HCV clearance are better when the recipients receive preemptive therapy with interferon and ribavirin after transplantation. Furthermore, the complexity of the drug interactions and toxicities which are invariably present in patients on HAART and immunosuppression would make preemptive therapy extremely challenging if not impossible in the early posttransplant period. For all these reasons, the current recommendations for the HIV/HCV-coinfecting recipient are no different from those observed for the HIV-

negative recipients. HCV treatment should be initiated when there is histologic evidence for progressive or severe recurrence, with an HAI score greater than 8 or fibrosis stage higher than 2. Treatment with interferon and ribavirin can be extremely challenging in this group of patients who are at an increased risk for lymphopenia and thrombocytopenia. Adjunctive therapy with growth factor and antidepressants is almost always necessary. Although dual therapy with interferon and ribavirin has proven more efficacious, caution and dose adjustment of the ribavirin is extremely important in the patients with renal insufficiency.

Our current strategy for immunosuppression in the HCV/HIV-coinfected group has been to utilize cyclosporine for maintenance therapy. Cyclosporine A has recently been shown to have anti-HCV qualities (56), in addition to the anti-HIV qualities already discussed. In addition, it is important to use cautious administration of steroids in the HCV/HIV-coinfected group, as several transplant physicians and surgeons have associated the use of bolus steroids with exacerbation of HCV (57). Interestingly, the spontaneous clearance of HCV has been observed in a few of the coinfecting patients (unpublished data), and the combination of cyclo-

sporine A and HAART may have synergy in facilitating the control of HCV. It is clear that the management of recurrent HCV will have a pivotal role in determining the safety and efficacy of transplantation in the coinfecting patients. The identification of subgroups within the HIV/HCV cohort who will benefit from transplantation remains to be determined, and will require a rigorous analysis of larger numbers of transplants currently being performed as part of the large multicenter trials.

HIV-Specific Health Care Issues and Prophylaxis for Opportunistic Infections

Transplant physicians and surgeons routinely provide prophylaxis for CMV, fungal infections, and *Pneumocystis carinii* pneumonia (PCP) during the early postoperative period. Clearly, these regimens for prophylaxis should be applied in the management of the HIV-positive recipient. In addition to the routine prophylaxis provided to the HIV-negative transplant recipient, Table 1 outlines the HIV-specific strategies for primary (no history of opportunistic infection) and secondary (prior history of opportunistic infection) prophylaxis.

TABLE 1. Opportunistic infection prophylaxis

Condition	Primary prophylaxis ^a	Secondary prophylaxis ^b
<i>Pneumocystis carinii</i> pneumonia	Indicated for life; initiate immediately posttransplant Preferred: TMP-SMX Alternatives: dapsone if not G6PD deficient, atovaquone	Indicated for life; initiate immediately posttransplant Preferred: TMP-SMX Alternatives: dapsone if not G6PD deficient, atovaquone
Toxoplasmosis	Toxoplasmosis IgG-positive patients with CD4 ⁺ T-cell count \leq 200 Preferred: TMP-SMX Alternatives: atovaquone, sulfadiazine + pyrimethamine + leucovorin	CD4 cell count below 200 cells/mL Discontinue when CD4 ⁺ T-cell count is above 200 cells/mL for 3–6 months ^c Alternative: sulfadiazine + pyrimethamine + leucovorin
<i>Mycobacterium avium</i> complex	Indicated when CD4 ⁺ T-cell count \leq 50. Discontinue when the CD4 count is above 100 cells/mL for 3–6 months Preferred: azithromycin (1200 mg weekly) Alternative: clarithromycin	CD4 cell count below 50 cells/mL Discontinue when CD4 ⁺ T-cell count is above 100 cells/mL for 3–6 months ^c Alternative: clarithromycin + ethambutol
Cytomegalovirus	No HIV-specific indication	CD4 cell count below 75–100 cells/mL Discontinue when CD4 ⁺ T-cell count is above 100–200 cells/mL for 3–6 months ^c Preferred: valganciclovir Alternatives: foscarnet, cidofovir
Cryptococcosis, extrapulmonary	No HIV-specific indication	CD4 cell count below 200 cells/mL Discontinue when CD4 ⁺ T-cell count is above 200 cells/mL for 3–6 months ^c Fluconazole
Histoplasmosis	No HIV-specific indication	Continue regardless of CD4 ⁺ T-cell count (this criterion should be modified if/when the DHHS guidelines are modified), itraconazole

^a No history of the infection. See reference (63) for additional alternatives, drug interactions, dosing in renal insufficiency.

^b Prior history of the infection. See reference (63) for additional alternatives, drug interactions, dosing in renal insufficiency.

^c Secondary prophylaxis should also be reinstated immediately posttransplant for 1 month and during the treatment of acute rejection for 1 month following completion of acute rejection therapy. If the CD4⁺ T-cell count is suppressed, continuation should be guided by the CD4⁺ T-cell count.

Primary prophylaxis for PCP after transplantation in the HIV-negative population is generally administered for one year, although some programs provide indefinite prophylaxis. However, in the HIV-positive transplant recipient, the current recommendations are for lifetime prophylaxis with trimethoprim-sulfamethoxazole regardless of CD4+ T-cell count. For patients allergic to sulfa drugs, dapsone (non-G6PD-deficient recipient) or atovaquone are viable options. Prophylaxis for *Mycobacterium avium* complex (MAC) are not part of standard regimens in the HIV-negative population. However, HIV-infected recipients are at risk for developing disseminated MAC with a CD4 count below 50 cells/mL, and should receive primary prophylaxis with weekly azithromycin. MAC prophylaxis will be guided by the CD4 counts, and will be terminated when CD4 counts escalate above 50 cell/mL. In addition to MAC prophylaxis, patients with CD4+ counts less than 50 cells/mL are at risk for CMV retinitis, and should have biannual ophthalmologic examinations as well as urgent fundoscopic examination with any visual changes.

The current protocol for patients with HIV infection is to undergo treatment for tuberculosis for purified protein derivative positivity on routine screening, as the annual risk of developing active tuberculosis is about 10% in these patients. As with HIV-negative transplant recipients, secondary prophylaxis with a 9-month course of INH should be initiated posttransplant for patients who have been previously treated for active tuberculosis.

Secondary prophylaxis for patients with a history of opportunistic infections should be provided for MAC, toxoplasmosis, cryptococcosis, and histoplasmosis as outlined in Table 1. This treatment should be continued for several months after CD4+ counts have increased above the threshold that required the implementation of prophylactic regimens. In addition to providing secondary prophylaxis for drops in CD4+ counts, secondary prophylaxis should be provided for 1 month after transplantation, as well as after aggressive treatment for rejection with lymphocyte-depleting agents. If the CD4+ T-cell count remains suppressed after one month of secondary prophylaxis after transplantation or treatment of rejection, continuation of prophylaxis should be guided by the CD4+ T-cell count as outlined in Table 1.

Patients with HIV infection are at an increased risk for human papillomavirus (HPV) mediated anal and cervical cancers. The impact of immunosuppression on progression of atypical lesions mediated by HPV is unknown and is being monitored in current clinical trials. Routine PAP smears as well as colposcopy should be pursued when available as a result of the atypical anal and cervical lesions which have been identified in HIV-positive patients (58, 59) and the unknown impact of immunosuppression on these lesions.

Immunization strategies for HIV-positive transplant patients are similar to those currently used for HIV-negative recipients. Prior to transplantation and the initiation of immunosuppression, patients should be vaccinated with pneumococcal vaccine, as well as hepatitis A and B vaccines. Adult patients should not be vaccinated against varicella, but should receive immunoglobulin G after exposure. Household contacts should not receive live attenuated vaccines such as oral polio vaccine and smallpox inoculation.

CONCLUSIONS

The transplant community has been slow to recognize the efficacy of HAART therapy in changing the course of HIV infection to a chronic condition. With the aging of the HIV-infected patients, the transplant community will need to address the increasing need for transplantation as a result of the higher rates of kidney and liver failure associated with the co-morbidities of HIV infection. A significant number of the patients transplanted during the pilot trials continue to have well-functioning kidney and liver allografts 3 to 5 years after liver and kidney transplantation. Transplants performed during the HAART era demonstrate that HIV-infected transplant recipients are able to maintain HIV RNA suppression with HAART therapy. CD4+ counts have remained stable, with the exception of the transplant recipients requiring rejection therapy with T-cell depleting agents. Although some patients receiving thymoglobulin had CD4 counts less than 50 cells/mL for more than 1 year, there were no significant opportunistic infections, although this group of patients was vulnerable to serious bacterial infections.

The early University of California San Francisco data has had some unexpected findings. The extremely high incidence of rejection seen in the infected kidney transplant recipients suggests that HIV infection does not result in the absence of an immune system, but rather a highly dysregulated response. The causes of the high incidence of rejection remain to be elucidated, but speculation has included: 1) lack of sufficient immunosuppression as a result of the complicated pharmacokinetic interactions of the HAART and immunosuppressive agents; 2) crossreactivity with major histocompatibility complex like antigens, resulting in accelerated rejections; and 3) a potent innate immune response in the absence of a normal T-cell repertoire.

Hepatitis C reinfection after liver transplantation is problematic in all patients regardless of HIV status. However, the HIV/HCV-coinfected patients may be especially vulnerable to recurrent disease, and are responsible for the poorer outcomes for this group. Although the HIV/HCV-coinfected patients have had significantly poorer results as compared to other HIV-positive liver transplant recipients, there are also a number of HIV/HCV-coinfected patients who have done very well. In fact, a few HIV/HCV-coinfected patients have spontaneously cleared HCV virus in the absence of interferon therapy. This unexpected finding may be related to the antiretroviral agents that have been utilized in the trial, and this extremely interesting observation will receive considerable attention in future studies.

The HIV/HBV-coinfected patients have done extremely well, despite the presence of lamivudine resistance in the majority of these patients who have been on epivir therapy as a component of HAART. The development of further resistant hepatitis B mutations has not been observed with post-transplant immunosuppression. HPV infection has resulted in the development of atypical anal lesions, and progression of the atypical lesions has been observed in a few of the HIV-infected recipients. For this reason, cervical and anal PAP smears are indicated, as this may prove to be a significant problem. One of the patients has had progression of an atypical anal lesion to carcinoma, and has had successful surgical excision as a result of the aggressive monitoring. HHV8, the

etiologic component of KS, has surprisingly not been problematic posttransplant. With the current success of rapamycin in controlling KS, initial safety issues in the HIV/HHV-8-positive recipients are less concerning.

Finally, the pharmacokinetic interactions between HAART and immunosuppressive medications are profound. The protease inhibitors are the most potent inhibitors of the cytochrome P450 system, and major adjustments in the calcineurin and TOR inhibitors are required to prevent the development of toxic drug levels.

Third-party payers are increasingly supporting transplantation in HIV-positive patients with well-controlled disease. There is increasing international acceptance for transplantation in people infected with HIV. UNOS does not list HIV infection as a contraindication for transplantation. The United States Veteran Affairs Administration has revised its inclusion/exclusion criteria to permit solid organ transplantation in people with stable HIV disease (60). Spain and the United Kingdom have provided guidelines for transplantation in HIV-positive recipients (61, 62).

The blanket exclusion of HIV-infected patients can no longer be justified based on the early results demonstrating the safety and efficacy of transplantation in this group of patients. It is imperative the HIV-positive patients, HIV health care providers, and the transplant community are aware that transplant is a viable option for the HIV-infected patient. Unnecessary and unacceptable delays in referral will result in increased rates of morbidity and mortality.

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