

Kidney and Liver Transplantation in HIV-Infected Patients: Case Presentations and Review

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ABSTRACT

Until recently, HIV-infected patients have been excluded from consideration for solid organ transplantation. The relatively high mortality rates among HIV-infected transplant recipients observed in the era prior to the use of highly active antiretroviral therapy (HAART), coupled with long waiting times for cadaveric organs, made it difficult to support organ transplantation in this patient group. However, in response to the marked reductions in morbidity and mortality associated with HIV infection, several transplant centers have developed pilot studies or revised their clinical criteria to allow transplantation in this group of patients. We describe two cases, one kidney and one liver transplant recipient, and review the major clinical and research issues related to this topic. Reports of transplantations in the pre-HAART era highlight two important findings. First, some HIV-infected transplant recipients did very well with long survival periods. However, overall progression to AIDS and death appeared accelerated. We recently reported on our preliminary experience with 45 selected transplant recipients in the HAART era. One-year patient survival rates were similar to unmatched survival data from the United Network for Organ Sharing (UNOS) database. Median CD4⁺ T-cell counts remained stable in the follow-up period compared to pretransplant. HIV-1 RNA nearly uniformly continued to be suppressed below the limits of detection. Preliminary data are promising and support the current efforts to evaluate patient and graft survival among HIV-infected transplant recipients and to explore the mechanisms underlying the many potential complications of transplantation in this population.

INTRODUCTION

UNTIL VERY RECENTLY, HIV-infected patients have been excluded from consideration for solid organ transplantation. Organ allocation policies attempt to balance the individual patient's best interest, while distributing a scarce resource equitably and promoting the best outcomes in aggregate. The relatively high mortality rates among HIV-infected transplant recipients observed in the era prior to the

development of highly active antiretroviral therapy (HAART), coupled with long waiting times for cadaveric organs, made it difficult to support organ transplantation in this patient group. However, with widespread HAART use and advances in the understanding of HIV pathogenesis, there have been marked reductions in morbidity and mortality associated with HIV infection. Immunosuppressive therapy might even reverse some HIV-associated immune dysfunction instead of causing accel-

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eration of HIV-associated CD4⁺ T-cell depletion because immune activation is believed to contribute significantly to CD4⁺ T-cell loss as well as functional defects of the immune system. In response to these developments in the clinical care of HIV-infected patients and the understanding of HIV pathogenesis, several centers in North America and Europe have developed pilot studies or revised their clinical criteria to allow transplantation in this group of patients. A large multisite, National Institutes of Health (NIH)-sponsored study to evaluate the safety and effectiveness of solid organ transplantation is in the final planning stages. We report here on two cases, one kidney and one liver transplant recipient, and review the major clinical and research issues related to this topic.

CASE 1

A 38-year-old man with a history of type 1 diabetes mellitus, hypertension, and renal failure was referred for kidney transplantation. The etiology of his renal failure was presumed to be multifactorial because he did not have a renal biopsy, and he had been managed with maintenance dialysis for eleven years prior to transplant. He received a "high-risk" cadaveric renal allograft as part of a pilot study at the University of California, San Francisco (UCSF). A high-risk organ comes from a donor who is serologically negative for HIV and hepatitis B and C, but has engaged in behaviors that place him or her at risk for being in the "window period" for one or more of these infections. The cadaveric renal transplant was uneventful and the patient was discharged from the hospital 3 days posttransplant with a serum creatinine of 1.8 mg/dL. His maintenance immunosuppressive medications included prednisone, cyclosporine and mycophenolate mofetil (Cellcept[®], Hoffman-LaRoche Inc., Nutley, NJ). Two weeks posttransplant he developed a wound infection that resolved after a series of three courses of oral antibiotics. Three-and-a-half months posttransplant the patient developed large, diffuse, and persistent warts on his hands. At 9 months posttransplant he was diagnosed with a squamous cell carcinoma of the

skin on his head and the mycophenolate mofetil dose was reduced. There was no recurrence of the skin cancer and the warts resolved. Additional complications occurring after the first year posttransplantation included worsening glucose intolerance requiring increased insulin use, hypertension, and an episode of bacterial sinusitis responsive to antibiotics. At two-and-a-half years posttransplant the patient developed acute type 1 rejection that was treated with intravenous corticosteroids and substitution of tacrolimus (Prograf[®], Fujisawa Healthcare, Inc., Deerfield, IL) for cyclosporine. Finally, on anal colposcopic examination at 2½ years posttransplantation he was noted to have developed a new discrete lesion with histopathology consistent with a high-grade squamous intraepithelial neoplasia.

The pretransplant CD4⁺ T-cell count was 407 cells per cubic millimeter and the HIV-1 plasma RNA was less than 50 copies per milliliter on lamivudine, abacavir, and nelfinavir. In the posttransplant period, the CD4⁺ T-cell count ranged from a low of 249 cells per cubic millimeter 4 days after the institution of antirejection therapy to 1011 cells per cubic millimeter. He underwent 12-hour pharmacokinetic evaluation of nelfinavir and cyclosporin levels at multiple time points posttransplant as part of a study protocol evaluating drug interactions. At month 12 the nelfinavir C_{min} and AUC levels were significantly lower than levels reported in the literature to be efficacious. On review of these data, the patient's antiretroviral regimen was modified at 15 months posttransplant with replacement of nelfinavir with nevirapine, based on stable nevirapine levels observed in other transplant patients. Cyclosporine dose requirements increased as expected with this change and worsening hypertension was noted after these medication adjustments. The plasma HIV-1 RNA levels remained below the limits of detection throughout the posttransplant period.

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CASE 2

A 49-year-old man with end-stage liver disease secondary to chronic hepatitis B infection

(HBV) underwent living donor liver transplantation. He was transplanted under a pilot study protocol at UCSF and was discharged after an uncomplicated 10-day postoperative course. The patient had received lamivudine as part of his antiretroviral therapy for approximately 5 years prior to transplantation and had evidence of lamivudine-resistant HBV relected by an elevated HBV DNA and elevated aminotransferase levels pretransplantation. He received adefovir dipivoxil initially from a "friend" prior to the drug by the Food and Drug Administration (FDA) approval, and subsequently as part of a HBV clinical trial. He received adefovir for 7 months prior to liver transplantation; pretransplant HBV DNA levels were undetectable at the time of the operation. Posttransplant anti-HBV therapy included adefovir, lamivudine, and monthly infusions of high-dose hepatitis B immune globulin (HBIG). HBV DNA remained undetectable throughout the posttransplant period. At 14 months posttransplant he underwent repair of an incisional hernia. Low-grade anal intraepithelial neoplasia was noted on anal colposcopic examination pretransplant and remained stable without evidence of progression at 1 year posttransplant.

The pretransplant CD4⁺ T-cell count was 439 cells per cubic millimeter. The posttransplant CD4⁺ T-cell counts have ranged from 305 to 700 cells per cubic millimeter and at 20 months posttransplant it was 405 cells per cubic millimeter. At the time of transplant, his antiretroviral regimen included didanosine, stavudine, saquinavir, and delavirdine. At 5 months posttransplant the transaminases were mildly elevated at two times the upper limit of normal. A liver allograft biopsy showed moderate hepatic steatosis with macrovesicular fatty changes and no evidence of rejection. One month later the transaminases increased to three to four times the upper limit of normal and the serum lactic acid level was 4.4. The antiretroviral regimen was modified to replace didanosine and stavudine with azidothymidine. At the same time the protease inhibitor and non-nucleoside reverse transcriptase inhibitors were changed to nelfinavir and nevirapine. With these medication changes, serum aminotransferase and lactic acid levels normalized and have subsequently remained in the normal range.

ETIOLOGY, PREVENTION, AND MANAGEMENT OF END-ORGAN DISEASE IN HIV-INFECTED PATIENTS

End-stage renal disease

HIV-infected patients experience renal failure for the same reasons that uninfected patients do (i.e. as a result of diabetes, hypertension and other systemic and primary renal diseases).¹ In addition, medications commonly used in the management of HIV infection can cause direct (e.g., indinavir) or allergic interstitial disease (e.g., sulfa-containing agents such as trimethoprim-sulphamethoxazole) that may affect the kidneys. HIV-associated nephropathy, or HIVAN, is a common and potentially reversible cause of renal failure seen predominantly in African American men with HIV infection.² Hepatitis C virus (HCV)-associated membranoproliferative glomerulonephritis and cryoglobulinemia, hepatitis B virus (HBV) associated membranous glomerulonephritis, as well as a number of less common processes, can also cause renal failure.¹

It is very important to identify early changes in creatinine, to evaluate the urine for protein and hematuria, to attempt to modify potentially reversible causes of renal insufficiency, and to obtain a renal biopsy to assist in diagnosis if conservative measures fail to reverse early renal insufficiency. HIVAN is an area of active investigation in the context of transplantation because of the concern that it might recur in the posttransplant setting, with the hypothesis that genetic factors in the recipient and/or donor may play a role in recurrent disease. Unfortunately, many patients referred for renal transplantation evaluation are on dialysis and have not undergone a kidney biopsy. Kidney biopsy is potentially dangerous in the uremic patient and, consequently, is not often performed at this disease stage. In addition, histologic evaluation of end-stage kidney is rarely of diagnostic benefit, making the question about HIVAN recurrence challenging to address.

End-stage liver disease

HIV-infected patients have a high prevalence of HBV and HCV coinfection because of their

shared routes of infection.³ All HIV-infected patients should be screened for evidence of prior exposure to HBV (hepatitis B surface antibody and/or antibody to core antigen) or chronic infection (hepatitis B surface antigen and/or antibody to core antigen). Patients lacking evidence of prior exposure to HBV (i.e. hepatitis B surface and core antibody and hepatitis B surface antigen all negative) should be vaccinated against hepatitis B virus. All HCV-infected patients who are not immune to hepatitis A, whether they receive a transplant or not, should be vaccinated against hepatitis A.

Early detection of chronic hepatitis B infection provides the opportunity for treatment and may potentially prevent liver disease progression and the need for liver transplantation. The main challenge in the treatment of patients with HBV and HIV coinfections is minimizing the development of hepatitis B drug resistance. Lamivudine is very active against HBV, however, resistance to lamivudine starts to develop after 6 months of therapy and increases with longer treatment duration.⁴ Adefovir and tenofovir are active against both lamivudine sensitive and resistant HBV, however, long-term data on the efficacy of tenofovir are lacking.^{5,6} No studies have evaluated the relative efficacy of initial mono-agent versus dual-agent therapy. However, if the lessons learned in the management of HIV infection apply to HBV, use of multiple agents in initial therapy may result in reduced development of drug resistance. The use of lamivudine as HIV therapy in a patient with unrecognized HBV infection could limit future HBV treatment choices because of the development of hepatitis B viral resistance to lamivudine. Likewise, the treatment of HBV infection with lamivudine, adefovir or tenofovir alone in a coinfecting patient will lead to HIV resistance to the agents used, thereby compromising future anti-HIV treatment options. Both hepatologists and HIV treatment providers must be aware of these issues. In our early experience at UCSF, we have been able to control posttransplant HBV replication and prevent recurrent disease in patients with the use of antiviral agents (lamivudine, adefovir and/or tenofovir) combined with high-dose hepatitis B immunoglobulin (unpublished data).

Hepatitis C is a more common coinfection in the HIV-infected populations than HBV and it has been associated with increasing hospitalization and deaths rates as the incidence of life-threatening opportunistic complications decreases and patients live longer.⁷ HCV and HIV coinfection presents a number of challenges in the transplant setting. First, HIV infection is associated with and accelerated progression of HCV disease.⁸ In addition, hepatitis C infection persists posttransplantation in all transplant recipients, with a variable rate of disease progression ranging from the unusual fulminant hepatitis to the more common progressive hepatitis. The treatments available for HCV infection are less often effective and much more difficult to tolerate than anti-HBV therapies. Thus, HIV-HCV coinfecting transplant recipients may be at greater risk of progressive liver disease and recurrent cirrhosis following transplantation. Some patients, however, may do as well as HCV monoinfected transplant recipients. Preliminary data provide conflicting results on the outcome of HCV/HIV coinfecting patients; studies to date are limited by small sample size.^{9,10}

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SOLID ORGAN TRANSPLANTATION IN HIV-INFECTED PATIENTS: OUTCOMES DATA

Pre-HAART era

Prior to widespread screening of potential transplant recipients, donors, and the blood supply, a few patients received solid organ transplants without identification of their positive HIV status. Others acquired HIV infection in the peritransplant period as a result of HIV transmission from either the allograft or from blood products. Many case reports and several case series describe such experiences in the pre-HAART era. These data are impossible to generalize to the current treatment era due to improvement in the management of HIV, the prevention and treatment of opportunistic complications, and improvement in immunosuppressive medications. In addition, CD4⁺ T-cell counts, HIV-1 plasma RNA levels and antiretroviral treatment regimens are often unreported in the pretransplant and/or post-

transplant period. Despite these limitations, these reports highlight two important findings. First, some HIV-infected transplant recipients did very well with excellent functional status and long survival periods.^{11,12} However, overall progression to AIDS and death appeared accelerated compared to nontransplant recipient.^{13,14}

HAART era

There are only four published case reports or case series reporting outcomes of HAART-treated transplant recipients in the United States and Europe.^{9,15-17} We recently reported on our preliminary experience with 45 selected transplant recipients in a review article in *Transplantation*.¹⁸ Both prospective and retrospective patients were included; the inclusion criteria were similar in both groups. Twenty-six patients received kidney transplants and 19 received liver transplants. The median follow-up period was 314 days. One-year patient survival rates were similar to unmatched survival data from the United Network for Organ Sharing (UNOS) database. Two kidney recipients died, both from bacterial infections. A death from *Staphylococcal* sepsis occurred 6 months after organ failure, return to dialysis and cessation of immunosuppressive therapy. The second death results from ischemic bowel and *Enterococcal* sepsis. Four liver recipients died. One died of postoperative pancreatitis. Another died of recurrent HCV infection and cirrhosis at 15 months posttransplantation. One patient experienced a severe rejection episode after his HIV provider stopped his protease inhibitor (PI)-containing HAART regimen for a "drug holiday." With the dramatic reduction in PI-induced p450 enzyme inhibition, his calcineurin inhibitor drug level decreased dramatically leaving him vulnerable to rejection. The last patient died of an unusual fungal infection, *Rhizopus cavernous* sinusitis, at 4½ years posttransplant. There were only two opportunistic complications in this cohort. One was a case of cytomegalovirus (CMV) esophagitis in a patient with a CD4⁺ T-cell count of 200, suggesting this was a transplant complication rather than an HIV-related complication. The second was a very mild case of *Candida esophagitis* in a

diabetic kidney transplant recipient. Median CD4⁺ T-cell counts remained stable in the follow-up period compared to pretransplant. HIV-1 RNA nearly uniformly continued to be suppressed below the limits of detection. These promising data are limited by the combined prospective and retrospective nature of the data collection, the relatively small number of subjects evaluated, and the short duration of follow-up. Longitudinal studies with longer follow-up periods are clearly needed.

COMPLICATIONS: INFECTIONS, METABOLIC DISTURBANCES, AND ORGAN REJECTION

Although the primary focus of most studies has been on patient and graft survival, CD4⁺ T-cell count and HIV-1 RNA changes and the incidence of opportunistic complications, the cases we presented here illustrate the many complications that can occur in transplant recipients, some of which may be further complicated by HIV infection, common coinfections, and drug toxicities. HIV-infected patients are at increased risk for bacterial infections including community acquired pneumonia, sinusitis, and bronchitis, and thus may be more susceptible to posttransplant bacterial soft-tissue infections. Solid organ transplantation is complicated by systemic illnesses caused by a number of viral infections, including the human herpesviruses CMV and human herpesvirus 8¹⁹ and human papilloma virus (HPV). Future studies will need to evaluate the incidence of these diseases in HIV-infected transplant recipients compared to HIV-negative transplant recipients, and will explore markers of viral evolution and host immune response to try to elucidate the mechanisms underlying any observed clinical manifestations of disease.

Metabolic side effects are associated with specific antiretroviral classes (e.g., diabetes and lipid abnormalities) and possibly with HIV infection itself (e.g., abnormal bone metabolism with avascular necrosis, osteoporosis and osteopenia). Immunosuppressive drugs share some of these side effects. The cumulative effect of HIV, its treatments, and immunosuppression

on the incidence and severity of these metabolic events is unknown. Determining the causative agent of the observed metabolic disturbance, and deciding how to balance the risks and benefits of each medication, is a significant challenge in the management of patients on both immunosuppressive and antiretroviral agents.

It was initially hypothesized that rejection would be uncommon in HIV-infected transplant recipients and that they would require significantly less intense anti-rejection therapy since they already had HIV-associated T-cell associated immune deficits. The opposite may, in fact, be the case. In the multisite data set discussed above, 38% of kidney recipients experienced a rejection episode.¹⁸ There does not appear to be a specific pattern to the timing of rejection occurrence nor to the type (tubular, vascular or humeral) of rejection seen.

MEDICATION INTERACTIONS AND DRUG SIDE EFFECTS

As anticipated based upon the relative potency of p450 enzyme inhibition associated with the PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes, these antiretroviral (ARV) classes require calcineurin inhibitor dose adjustments to achieve therapeutic and nontoxic drug levels.²⁰ While the NNRTIs require minimal to no adjustments in the dose of calcineurin inhibitors, PI coadministration requires significant but fairly predictable adjustments in the dose of calcineurin inhibitors. Changes in hepatic metabolism of the ARVs are anticipated after transplant in the liver recipient. Medication side effects can be challenging to manage, and the use of HCV therapy post-transplant adds an additional layer of complexity and may increase the risk of potentially life-threatening side effects.

ORGAN DONOR OPTIONS

The wait for cadaveric donor organs can be long, commonly several years for a kidney. Cadaveric livers are allocated based on need using a system called MELD (Model of End-Stage Liver Disease) that includes bilirubin, INR, and creatinine. The use of donor organs for HIV-

infected patients with liver, kidney, or other organ failure is controversial. Some have argued that it is unethical to remove cadaveric organs from the donor pool for use in an experimental setting, or for use in a group of patients who have traditionally been excluded from transplant because of concerns about poor outcome. Transplant surgeons and physicians have an obligation to utilize organs in manner that results in optimal outcomes. There is concern about using organs for indications for which there is limited information on long-term outcome because this use results in the loss of that organ for a patient who might have had a better outcome. Previous expansion of eligibility criteria for transplantation has been experimental by definition and medical progress dictates that this experimentation continues. Not long ago, HBV infection was considered an absolute contraindication for liver transplantation in many programs because of the severity of reinfection of the allografts and poor graft and patient survival. Likewise, hepatocellular carcinoma is a relatively new indication for liver transplantation. Thus, it can be argued that as long as HIV-infected patients are experiencing reductions in mortality it would be unethical to withhold this option in the absence of evidence that it is either unsafe or ineffective.²¹ Similar concerns are expressed regarding living organ donation to this patient population. In this case, the question is: Is it ethical to subject a donor to risk when the outcome in the recipient is unknown? For this reason, disclosure of HIV status of the potential recipient and the unknown outcome of transplantation in the context of HIV infection to the potential living donor is required so that donors can make informed choices about organ donation.

CONCLUSION

Preliminary data are very promising and support the current efforts to evaluate patient and graft survival among HIV-infected transplant recipients and to explore the mechanisms underlying the many potential complications of transplantation in this population. Information regarding the NIH-sponsored multisite U.S. study of organ transplantation in HIV-infected patients is available at www.emmes.com

(click on Project Directory to find details about participating sites, patients referral, and current studies).

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Is “than” wanted?