Perspective

Solid-Organ Transplantation in HIV-Infected Patients in the Potent Antiretroviral Therapy Era

Improvements in antiretroviral therapy, opportunistic infection prophylaxis, and antirejection treatment have made solid-organ transplantation a potential option for HIV-infected patients. Preliminary experience in a small group of kidney and liver transplant recipients suggests that CD4+ cell counts and plasma HIV RNA level suppression can be maintained. As few opportunistic infections have been seen, a history of some opportunistic infection conditions may not be a contraindication to transplantation; this question is under investigation. Kidney graft rejection rates appear to be higher in HIV-infected patients, but one-year patient-survival and graft-survival rates appear to be similar to those in HIV-uninfected populations. A large multicenter study of the safety and efficacy of kidney and liver transplantation in HIV-infected patients is under way. Findings from this study should help to provide guidance in achieving optimal outcomes in this population. This article summarizes a presentation by Michelle E. Roland, MD, at the February and April 2004 International AIDS Society–USA courses in Atlanta, Los Angeles, and Chicago.

HIV-infected persons traditionally have not been considered to be good candidates for solid-organ transplantation. The poor life expectancy associated with HIV disease prior to the advent of potent antiretroviral therapy motivated the decision to use scarce donor organs in patients with better prognoses. Further, there has been understandable concern over the potentially dangerous effects of posttransplantation immunosuppressive therapy in patients with HIV disease. A survey of US transplantation centers published in 1998 showed that only 9% and 5% of responding centers would consider HIV-infected patients with end-stage renal disease for cadaveric and living-donor transplantations, respectively. However, with the improved survival and clinical status of HIV-infected persons in the current treatment era, solid-organ transplantation is more frequently being considered and performed in such patients.

Recognition of the role of immune activation in HIV disease pathogenesis has also raised the possibility that immunosuppressive therapy may provide benefit rather than necessarily contributing to more rapid HIV disease progression in transplant recipients. Indeed, immunosuppressant drugs may exert antiviral effects, whether by reducing cellular targets for the virus, via direct antiviral effects (eg, cyclosporine, which appears to interfere with HIV gag processing), or through potentiation of antiretroviral drug activity (eg, mycophenolate mofetil interactions with nucleoside reverse transcriptase inhibitors [nRTIs]). All of these factors have contributed to interest in formal study of transplantation outcomes in HIV-infected patients and identification of patient characteristics that may help to achieve optimal outcomes.

Findings in Transplant Recipients in the Potent Antiretroviral Therapy Era

Published information on HIV-infected transplant recipients in the pre-potent antiretroviral therapy era consists of case reports and case series of anecdotal experiences with varied results. In these reports, baseline characteristics and outcomes with regard to such HIV disease factors as CD4+ cell counts, HIV RNA levels, and opportunistic infection frequency and type generally are poorly defined. This early experience also does not reflect improvements in opportunistic infection prophylaxis and antirejection therapy that have occurred in recent years.

At the XIV International AIDS Conference in Barcelona in 2002, Dr Roland and colleagues first reported on the largest group of HIV-infected transplant recipients studied to date (Roland and Stock, *Transplantation,* 2003). The report included analysis of patients prospectively enrolled in an ongoing pilot multicenter transplantation study and retrospective review of patients from study transplant centers that used the same protocol for transplantation as centers in the ongoing study.

For the purposes of this analysis, patients were defined as "eligible" — those who met the study criteria for eligibility — and "ineligible." Eligibility criteria included absence of history of opportunistic infection; CD4+ cell counts greater than 200/μL in kidney transplant recipients and greater than 100/μL in liver transplant recipients; and plasma HIV RNA levels below detection limits using ultrasensitive assays in kidney or liver recipients, or intolerance to antiretroviral therapy but predicted ability to achieve viral suppression posttransplantation in liver recipients.

Among the 45 eligible patients, 26 received kidney transplants and 19 received liver transplants. Eight patients were considered ineligible because of elevated HIV RNA level, low CD4+ cell count, history of opportunistic infection or neoplasm, or incompletely evaluated altered mental status. Among the eligible subjects, 92% of kidney recipients and 95% of liver recipients were men and the median ages of kidney and liver recipients were 45 and 43 years, respectively. Among the kidney recipients, 54% were African American, 42% were white, and 4% were Asian. Among the liver recipients, 79% were white, 11% were Hispanic, 5% were African American, and 5% were Asian. Median baseline CD4+ cell counts were 441/μL (range, 200-1054/μL) in kidney recipients and 280/μL (range, 103-973/μL) in liver recipients. Liver

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recipients had a range of HIV RNA levels of below 50 to 115,776 copies/mL, with a median below 50 copies/mL.

The results are summarized in Table 1. Median follow-up was 314 days. CD4+ cell counts were maintained and HIV RNA levels largely remained suppressed, with levels below 50 or 75 copies/mL maintained in the vast majority of patients. Two kidney recipients and 4 liver recipients died during follow-up. Of the 2 kidney recipients who died, one had an ischemic bowel episode and enterococcal sepsis 6 months after transplantation and the other developed staphylococcal sepsis 2 months after returning to dialysis after chronic rejection. Of the 4 liver recipients who died, one died with recurrent hepatitis C virus (HCV) infection 15 months after transplantation, one from postoperative pancreatitis, and one from Rhizopus cavernous sinus thrombosis, an uncommon posttransplantation or HIV-associated complication, 4.5 years after transplantation. The fourth patient died from a rejection episode. The patient was taking very low-dose immunosuppressant therapy because of pharmacokinetic interaction with his protease inhibitor (PI) treatment; however, when he later was put on an antiretroviral drug holiday, that information was not communicated to the transplant physicians, and the patient was thus left virtually without immunosuppressant therapy.

Opportunistic infections were infrequent: a liver transplant patient who died from recurrent HCV infection developed cytomegalovirus (CMV) esophagitis at a relatively high CD4+ cell count of 200/μL, and a kidney transplant recipient with diabetes mellitus developed candidal esophagitis, which was easily managed.

The rejection rate of 38% among kidney recipients is relatively high; additional follow-up in this cohort has shown even higher kidney rejection rates (approximately 70%), and the explanation for the high rate of rejection remains uncertain. Nevertheless, as shown in Table 2, patient survival rates and graft survival rates in this small cohort of patients are at least consistent with that observed at 1 year among patients in the United Network of Organ Sharing (UNOS) database. Among the ineligible patients, 2 with very advanced HIV dis-

ease died shortly after transplantation, one (ineligible because of undiagnosed HIV disease and a low CD4+ cell count) with *Mycobacterium avium* complex (MAC) disease and progressive multifocal leukoencephalopathy (PML) and the other (ineligible because of incompletely evaluated altered mental status) with PML alone. The 2 cases of PML in this setting is troubling, and the condition is considered an exclusion criterion for transplantation in the ongoing study. In 2 patients who were ineligible because of history of opportunistic infection, no recurrences were observed; one had a history of *Pneumocystis carinii* pneumonia (PCP; now named *Pneumocystis jiroveci* pneumonia) and CMV disease and another had a history of Kaposi's sarcoma and CMV disease. On the basis of these observations and other anecdotal experience, the ongoing study is now permitting enrollment of patients with histories of many opportunistic diseases. In other patients considered ineligible because of CD4+ cell counts just under the inclusion criteria or very low detectable HIV RNA levels, CD4+ cell counts were at least maintained and HIV RNA levels were well controlled.

Thus, the overall findings in both the eligible and ineligible patients indicate that in carefully selected patients, baseline immunologic and virologic values can be maintained and that opportunistic complications are infrequent; they also suggest that progression of HIV disease does occur in those patients with advanced disease.

Updated information is available from a group of 24 patients treated at the University of California San Francisco (UCSF), consisting of patients included in the above analysis and patients subsequently enrolled in the pilot multicenter study. Of these 24 patients, 14 were kidney recipients, 9 were liver recipients, and 1 received both organs. Four patients (17%) have a history of opportunistic infection (CMV disease, MAC, cryptococcosis, and Kaposi's sarcoma); 4 of the kidney recipients (29%) and 4 of the liver recipients (40%) have HCV coinfection. Median follow-up is 480 days (range, 8-1254 days). Two patients have died, one from recurrent HCV infection as mentioned above, and another (kidney recipient) from congestive heart failure.

No new AIDS-defining opportunistic infections have been observed. Overall,

Table 1. Outcomes of Transplantation in 45 HIV-Infected Patients (26 Kidney Recipients, 19 Liver Recipients)

Median follow-up	314 days (range, 3-1696)
Deaths	2 kidney recipients 4 liver recipients
Opportunistic complications	1 kidney recipient (Candida esophagitis) 1 liver recipient (cytomegalovirus esophagitis)
CD4+ cell count, median (range)	
Kidney recipients	Baseline: 441/μL Posttransplantation: 436/μL (3-975/μL)
Liver recipients	Baseline: 280/μL Posttransplantation: 218/μL (110-992/μL)
Plasma HIV RNA, median (range)	
Kidney recipients	Baseline: <50 copies/mL Posttransplantation: <50 copies/mL (50-533 copies/mL)
Liver recipients	Baseline: <50 copies/mL Posttransplantation: <50 copies/mL (<50-9600 copies/mL)
Retransplantation	1 liver recipient (small-for-size graft lesion)
Additional graft loss	3 kidney recipients (2 rejection, 1 thrombosis)
Total rejection	38% of kidney recipients 21% of liver recipients

Table **2.** Patient and Graft Survival in Current Cohort* Compared With 1-year Outcomes in United Network of Organ Sharing (UNOS) Database

	Current HIV cohort	UNOS database, 1-year rates
Patient survival		
Kidney recipients	92% of all recipients; 91% at 1 year (n=11)	94.8% deceased donor 97.6% living donor
Liver recipients	79% of all recipients; 92% at 1 year (n=12)	87.9%
Graft survival		
Kidney recipients	85% of all recipients; 71% at 1 year (n=14)	89.4% deceased donor 94.5% living donor
Liver recipients	79% of all recipients; 83% at 1 year (n=12)	81.4%

*Data from current cohort from all patients and from those dying before 1 year or with at least 1 year of follow-up.

rejection has occurred in 10 (71%) of the kidney recipients, with no clear pattern in type or timing of rejection, and in 1 liver recipient. Graft loss has occurred in 1 kidney recipient (graft rejection) and in 1 liver recipient (retransplantation required due to a "small-for-size" graft lesion from a living donor). Evidence of recurrent HCV infection has been observed in 2 liver recipients and in none of the kidney recipients. The median CD4+ cell count in these patients decreased from 407/µL (range, 104-973/µL) to 255/µL (range, 8-902/µL); this decrease likely reflects the effects of immunosuppressant treatment for acute rejection episodes. The median HIV RNA level is below 75 copies/mL (range, <75-9600 copies/mL).

Special Clinical Considerations in HIV-Infected Patients

Viral Coinfection

Prior to the availability of effective antiviral therapy, hepatitis B virus (HBV) infection was a contraindication to transplantation, since reinfection is universally rapid and fatal in the absence of viral control. Current posttransplantation management of HBV infection relies on hepatitis B immune globulin and lamivudine treatment, but there is concern that many HIV-infected patients will have lamivudine-resistant HBV because the drug has been used in their antiretroviral regimens. However, there is hope that adefovir or tenofovir can provide adequate control of lamivudine-resistant HBV in the posttransplantation period. Thus far, posttransplantation management of a very few patients with lamivudine-resistant HBV has been successful.

HCV coinfection is common in patients with HIV infection. Unfortunately, HCV infection is associated with relatively poor outcomes in HIV-uninfected transplant recipients, with universal infection of the transplant graft. HIV/HCV coinfection prompts additional concern since HCV disease has an accelerated natural history in the setting of HIV infection. Experience to date with transplantation in HIV/HCV-coinfected patients is variable, with some centers reporting very bad outcomes and some reporting outcomes similar to those in HIV-uninfected patients. Further study of this issue is needed. According to the current transplant study protocol, HCV treatment is not to be instituted preemptively in the posttransplantation period because there are no data to indicate that HCV clearance rates are improved by this practice and to minimize drug interactions and toxicity in the posttransplantation period. HCV treatment should be initiated if biopsy shows severe or progressive recurrent HCV disease, with the decision whether and when to treat being made by the treating physician. A nested randomized study of preemptive versus histologically indicated therapy may be incorporated into the ongoing multicenter study.

Human papilloma virus (HPV)-related cervical and anorectal disease is more common in HIV-infected than HIV-uninfected persons, and there is concern that the incidence may increase with immunosuppression in the posttransplantation period. The ongoing study of transplantation includes a substudy of baseline and posttransplantation disease characteristics to ascertain the potential effect of iatrogenic immunosuppression on disease progression. Observations thus far in the small group of patients treated at UCSF suggest that progression rates are similar to those in patients not undergoing transplantation.

There is also considerable concern that posttransplantation immunosuppression could exacerbate Kaposi's sarcoma or other human herpesvirus-8-associated disease. Transplant-associated Kaposi's sarcoma in kidney recipients requires sacrifice of the kidney transplant to stop Kaposi's sarcoma progression. Thus far, transplantation has occurred in 2 patients who were known to have visceral (pulmonary) Kaposi's sarcoma, and these patients have had no recurrence of the disease. No new occurrence of Kaposi's sarcoma has been observed in transplant patients to date. The ongoing transplant study is now permitting enrollment of patients with a history of cutaneous Kaposi's sarcoma but not visceral disease, and this issue will be monitored closely in the study.

Immunosuppression-Related Issues

A number of transplant patients have developed metabolic complications, including insulin resistance, frank diabetes, hyperlipidemia, osteopenia, osteoporosis, and fracture. Iatrogenic immunosuppression, the antiretroviral treatment, and HIV infection itself can contribute to these abnormalities. The interactions among these conditions are unknown; these complications may occur at higher rates in the context of HIV infection and should be monitored carefully.

Drug Issues

Antiretroviral treatment interruptions in the posttransplantation period (eg, to permit organ function to stabilize or

for recurrent HCV infection) have resulted in minimal and delayed rebound of HIV RNA levels in some patients. This observation suggests that immunosuppressive therapies—in particular, cyclosporine and mycophenolate mofetil—may have direct or immune-mediated antiretroviral activity. Cyclosporine and tacrolimus may have different mechanisms of activity with regard to anti-HIV effects, and analyses are planned in the ongoing transplant study to attempt to determine whether different immunosuppressant regimens have different effects on virus levels in plasma and other viral reservoirs.

The pharmacokinetic interactions of hepatically metabolized antiretroviral and immunosuppressant drugs need to be characterized in the transplantation setting. The ongoing transplant study includes 12- to 24-hour pharmacokinetic evaluations of immunosuppressant drug, PI, and nonnucleoside reverse transcriptase inhibitor (NNRTI) levels at pretransplantation; at 2 and 12 weeks, 6 months, and 1, 2, and 5 years posttransplantation; and when there is a significant change in antiretroviral treatment or immunosuppressant treatment, or when an opportunistic infection occurs. It is already recognized that cyclosporine must be given at low doses when used together with PIs or PI/NNRTI combinations and at low to typical doses when used together with NNRTIs to achieve adequate plasma cyclosporine levels and adequate immunosuppression. Findings with tacrolimus and sirolimus have been similar to those with cyclosporine. PI and NNRTI concentrations are also affected by the coadministration of the immunosuppressants, but generally have remained within adequate therapeutic ranges. It remains unclear precisely how to integrate these observations into optimizing treatment, and it is hoped that the pharmacokinetic studies will provide guidance in this regard.

Prospective Study in Transplantation

The ongoing multicenter prospective study has a target enrollment of 150 kidney transplant recipients and 125 liver transplant recipients (see Table 3).

Table 3. Participating Centers of the Solid-Organ Transplant in HIV Multisite Study

Kidney and Liver

- Beth Israel Deaconess Medical Center, Boston, MA
- Georgetown Medical Center, Washington, DC
- Mount Sinai School of Medicine, New York, NY (adult, both; pediatrics, kidney)
- University of California San Francisco (adult and pediatrics, both)
- University of Chicago (adult and pediatrics, both)
- University of Cincinnati
- University of Minnesota
- University of Pennsylvania
- University of Pittsburgh
- University of Virginia

Kidney

- Drexel University, Philadelphia, PA
- University of Maryland
- University of Miami
- Washington Hospital Center, Washington, DC

Liver

- Cedars-Sinai Medical Center, Los Angeles, CA
- Columbia University, New York, NY (adult and pediatrics)

Visit the study Web site, http://spitfire. emmes.com/study/htr/ for further information, including contact information and listings of additional centers and changes.

Primary aims of the study are to assess the impact of iatrogenic immunosuppression on patient survival and to assess the impact of HIV infection and antiretroviral treatment on graft survival, including in the settings of HBV or HCV coinfection and HIV-associated nephropathy. Secondary aims include assessment of the effect of immunosuppressant therapy on CD4+ cell counts, HIV RNA levels, and opportunistic complications; exploration of the relationships among disease development, the host immune response, and viral evolution with regard to HBV, HCV, CMV, human herpesvirus-8, and HPV; assessment of the impact of HIV infection on alloimmune response and graft rejection rates; and analysis of pharmacokinetic interactions between immunosuppressant drugs and hepatically metabolized antiretroviral agents.

Initial experience in managing HIV-infected transplant recipients has highlighted the need for a multidisciplinary health care team to participate actively in patient monitoring and management, with excellent communication among team members being crucial to patient safety. Effective and timely communication is particularly important regarding medication changes and evaluation of symptoms and laboratory abnormalities.

Suggested Reading

Calabrese LH, Albrecht M, Young J, et al. Successful cardiac transplantation in an HIV-1-infected patient with advanced disease. *N Engl J Med.* 2003;348:2323-2328.

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