

# Key Clinical, Ethical, and Policy Issues in the Evaluation of the Safety and Effectiveness of Solid Organ Transplantation in HIV-Infected Patients

**P**ATIENTS WITH human immunodeficiency virus (HIV) infection are at significant risk for end-stage kidney and liver disease, and are therefore potential candidates for solid organ transplantation.<sup>1-15</sup> However, they have been considered poor transplant candidates. In this era of effective antiretroviral therapy, preliminary experience with transplantation appears promising, although critical clinical and ethical questions remain. Thus, it is timely to perform a safety and efficacy study of transplantation in HIV-infected patients. Key clinical issues in the design of such a study include consideration of the patients' history of opportunistic complications and hepatitis C coinfection, and their ability to tolerate antiretroviral drugs when defining selection criteria for study subjects. The ethical questions of resource allocation and the risks and benefits associated with living and cadaveric organ donation must also be carefully considered. To address the concerns of utility and effectiveness for each intervention, the minimum acceptable patient and graft survival rates must be chosen on the basis of current transplant practices. Clinical outcomes data from well-designed trials are critical to ensure adherence to the principle of justice in the organ allocation process.

Patients infected with HIV have been considered poor transplantation candidates for 2 reasons. First, HIV-associated mortality may make the use of a scarce resource seem unjustified; and second, posttransplant immunosuppression might ac-

celerate HIV disease progression.<sup>16-20</sup> Mortality has decreased dramatically with the use of highly active antiretroviral therapy (HAART).<sup>21-32</sup> Thus, restricting access to transplantation because of poor survival rates is no longer justified in the HAART era. To assess the impact of immunosuppression on HIV disease progression, a pilot multisite clinical trial was initiated in June 2001.<sup>33</sup> A multisite study of 275 subjects who underwent kidney or liver transplantation has since been funded and the enrollment process is expected to begin in the fall of 2003. In this study, we describe the key clinical, ethical, and policy issues related to the study of transplantation in HIV-infected patients.

## RESOURCE ISSUES

Organs are in high demand and availability is scarce. Despite the 21 516 transplantations performed in the United States in 1999, 72 110 patients remained on waiting lists for cadaveric organs and 6143 of these died without transplantation.<sup>34</sup> Expanding populations are considered eligible for transplantation, and this raises ethical concerns because more patients are likely to die while waiting for organs. Such concerns are increased if the patients added to waiting lists do not have outcomes comparable to those already considered eligible.

To guide the just allocation of scarce resources, several distinct principles of justice have been evoked. Some people believe that justice requires prioritizing on the basis of need, while others believe

in utilitarian allocation based on best predicted outcomes. The United Network for Organ Sharing, which develops policies governing the transplantation community, does not prohibit HIV-infected patients from receiving organs.

Utilitarians have argued that diverting organs from a group known to be likely to benefit from transplantation to a group whose likelihood to benefit is unknown could result in deaths among patients on waiting lists without benefiting the organ recipients; their conclusion, therefore, is that a clinical trial of HIV-infected patients is not justified. However, to give priority to those most likely to benefit, and to give patients with similar outcomes similar priority, outcomes data are needed. It would be unjust to exclude from the waiting list patients with a new indication for transplantation simply because no one knows how their posttransplant outcomes will compare with the outcomes of patients with currently accepted indications. The outcome of each new potential indication for transplantation, including cirrhosis and hepatocellular carcinoma associated with hepatitis B or hepatitis C, was unknown until it was evaluated. We believe that the question of transplantation in HIV-infected patients should be decided according to rigorous clinical data. Therefore, we have initiated a "proof of concept" clinical trial of liver and kidney transplantation in selected HIV-infected patients. The goals of this trial are to evaluate the impact of both posttransplant immunosuppression on survival and HIV disease progression, and HIV infection on graft survival.

## RISKS AND BENEFITS OF DIFFERENT DONOR POOLS

Additional ethical issues arise in the selection of donors. Some believe that cadaveric organs should never be used in an investigational context. Concerns have also been raised that public support for organ donation may decline if it is known that organs are allocated to HIV-infected patients, just as concerns were raised about organ allocation to patients with alcoholic cirrhosis. While some individuals continue to stigmatize persons with HIV infection, this problem needs to be addressed through greater public discussion of the potential benefits of transplantation in this group, not by excluding patients from transplantation.

The use of living donors has been advocated to reduce the impact of the increase in organ demand on the pool of cadaveric organs. However, some believe that it is unethical to subject a living donor to risk when the benefits of the transplantation are uncertain. Issues of informed consent are complex with living donation. Potential donors have the right to know the expected durability of their gift, and potential recipients have the right to privacy. Study investigators advocate for voluntary disclosure of the potential recipient's HIV status to the potential donor (HIV disclosure without consent is illegal in many states).

The use of "marginal" or of "high-risk" organs has been considered in the study. A marginal organ is one that is not expected to function as well as a more ideal organ. A high-risk organ comes from a donor who is considered to be at increased risk of having preseroconversion HIV infection, hepatitis B, or hepatitis C that would not be detected with screening assays (ie, donors known to have recently used injection drugs, men who have sex with men, sex workers, and those who have been recently incarcerated). In a research setting, the goal of gaining knowledge may be compromised if marginal organs are used; if the study showed worse outcomes in HIV-infected patients than in patients with accepted indications for transplantation, these

poor outcomes might be due to the use of marginal organs. Hence, marginal organs are not used in the study. Although study subjects have the same access to the donor pool as HIV-uninfected patients, at some study sites recipients have the option to accept high-risk organs to gain earlier access to transplantation.

Some have advocated for the use of organs from HIV-infected donors in this study. The phenomenon of superinfection with a new strain or with new strains of HIV has only recently been documented,<sup>35,36</sup> and is under study. If superinfection occurred soon after transplantation, transmission of more virulent or resistant HIV strains would be of serious concern for patients with well-controlled HIV infection. Given this risk, we feel that this question should be addressed after the safety of transplantation is established.

## STUDY SUBJECT SELECTION CRITERIA

The goals of study selection criteria are to protect potential subjects by excluding those who are very unlikely to benefit from a transplantation; to be fair to potential subjects by not unjustly excluding them from a potentially beneficial intervention; to maximize knowledge gained; and to ensure the rational use of a scarce resource. The tension between broad and narrow access to a study is inherent in clinical research. Broad inclusion criteria provide more generalizable results and greater access to a potentially beneficial intervention. However, broader inclusion criteria may result in misleadingly negative findings. If patients with severe HIV-induced immunosuppression have very poor outcomes, negative results might be mistakenly generalized to all HIV-infected patients, even though patients with less HIV-induced immunosuppression might have good outcomes. Thus, we have adopted a "proof of principle" approach to subject selection that provides the best chance for a successful study outcome, and ultimately the potential for the broadest long-term access to transplantation. The

study is evaluating the hypothesis that immunosuppression neither accelerates the progression of HIV disease nor reduces survival in subjects with a relatively intact immune system and good HIV suppression. If such a population has a good outcome, selection criteria will be modified as the study progresses to test the same hypothesis in patients with more advanced immune dysfunction (eg, a history of opportunistic disease or a lower CD4 T-cell count) and/or less well-controlled HIV replication.

In most cases we select subjects with the best prognostic indicators, except when patient need takes priority. Four key examples of the tension between broad and narrow inclusion criteria include (1) asymptomatic patients with a remote history of an AIDS-defining opportunistic infection or neoplasm; (2) candidates for liver transplantation who are HIV infected and unable to tolerate antiretroviral therapy; (3) patients with hepatitis C infection seeking liver transplantation; and (4) patients with hepatitis C infection seeking kidney transplantation. In some cases, eg, in the case of a history of opportunistic complication and plasma HIV RNA, we adopted more conservative selection criteria, developed a plan to reassess and consider broadening the criteria after outcomes data became available, and made such revisions. In other cases, we have elected to define the criteria more broadly from the beginning, eg, in the case of hepatitis C virus (HCV) coinfection. The distinct approaches to each of these potential comorbidities have been developed according to clinical concerns, data in the transplantation and HIV literature, and the prevalence of comorbid conditions, as outlined in the following sections.

### Example 1: History of Opportunistic Infections

Patients with a history of neoplastic complications or infectious opportunistic infections (OIs) were excluded during the first phase of the study. However, protective immune reconstitution occurs with HAART<sup>25-30,32,37-47</sup> and many poten-

tial transplant recipients may have a remote OI history. Thus, this exclusion was reevaluated after the first 20 subjects were followed up for 6 months. Given the low incidence of OIs, the inclusion criteria were modified to include subjects with specific OI histories. Opportunistic infections that are not treatable in the context of immunosuppression alone, such as disseminated coccidioidomycosis, will still be excluded; and OIs that cannot be avoided with prophylaxis, such as cryptosporidiosis, Kaposi sarcoma, and progressive multifocal leukoencephalopathy, are still generally excluded.<sup>48</sup>

### Example 2: Plasma HIV RNA and Liver Transplantation

Kidney transplantation candidates must have undetectable plasma HIV RNA while receiving stable antiretroviral therapy, but patients with end-stage liver disease may not be able to tolerate HAART.<sup>49-55</sup> Such patients may respond well to HAART after liver transplantation, however, provided that their virus is sensitive to antiretroviral agents. The study allows participating transplantation centers to determine whether to accept liver transplantation candidates with detectable plasma HIV RNA (if the study HIV specialist deems it probable that HIV RNA can be fully suppressed after transplantation). Alternatively, a center may require full suppression of HIV replication prior to transplantation. If initial subjects who have detectable HIV RNA but are not treated with HAART before transplantation are able to suppress HIV replication after transplantation, this criterion will be adopted at all participating centers.

Uncontrolled posttransplant replication of HCV, hepatitis B virus (HBV), cytomegalovirus, and Epstein-Barr virus is associated with increased morbidity and mortality. Thus, posttransplant control of HIV may be critical to a successful clinical outcome. While the goal of HAART is to maintain an undetectable HIV RNA level, recent data suggest that even partial control of HIV replication while using HAART provides at least short-term immunologic and clinical benefit.<sup>39,40,56</sup> Whether this benefit persists with the

use of immunosuppression therapy is unknown, as posttransplant immunosuppression therapy may up-regulate, down-regulate, or have no impact on HIV replication. As preliminary outcomes data are accumulated, we will continue to reassess the exclusion of patients with drug-resistant HIV who are not predicted to fully suppress viral replication after transplantation.

### Example 3: Hepatitis C and Liver Transplantation

Liver transplantation in patients with HIV but no HCV is complicated by infection of the graft, which can result in rapid progression to cirrhosis.<sup>57-59</sup> In addition, HCV's natural history is accelerated in HIV-infected patients, particularly in those with lower CD4 T-cell counts.<sup>7,60-69</sup> Survival data in HIV/HCV coinfecting transplant recipients in the HAART era are variable. At the University of Pittsburgh, 4 of 6 HIV/HCV coinfecting patients are alive, with a follow-up of more than 42 months and the 2 deaths not related to HCV infection.<sup>70</sup> In contrast, investigators at King's College in London have reported deaths in the 4 HIV/HCV coinfecting liver recipients they were following up, while 4 HIV/HBV coinfecting recipients are alive.<sup>19</sup> A death from cholestatic hepatitis in an HIV/HCV coinfecting recipient was recently reported.<sup>71</sup> An HCV-infected liver recipient at the University of California at San Francisco died of recurrent HCV 14.5 months after transplantation.

We include HCV-infected subjects in this trial because the high prevalence of HCV/HIV coinfection makes the question of the safety and efficacy of transplantation in this population a pressing issue.<sup>3,72,73</sup> If early data show a strong trend toward poor outcomes in HIV/HCV coinfecting subjects, we will use an early stopping rule if the 99.9% confidence interval for the 1-year survival rate excludes the Medicare threshold of 77%.

### Example 4: Hepatitis C and Kidney Transplantation

Some studies show worse patient and graft survival outcomes in renal trans-

plant recipients who are infected with HCV than in those who are not.<sup>74,75</sup> Renal transplant recipients who are infected with HCV may have a better chance of survival than those who remain treated with dialysis, despite data demonstrating acceleration of liver disease in kidney recipients.<sup>76,77</sup> Thus, only renal transplantation candidates with advanced liver disease are excluded from the current study. We considered, but rejected, excluding HIV/HCV coinfecting kidney transplantation candidates. Because there are so many HIV-infected patients with end-stage renal disease who also have HCV infection, it is important to determine whether renal transplantation is effective in these patients.

Because of the possibility of accelerated progression of HCV after transplantation, we considered excluding patients with untreated disease. The ethical concern is to ensure that the risk-benefit ratio in HIV/HCV coinfecting subjects with end-stage renal disease is appropriate. Current treatments for HCV have relatively poor efficacy and considerable side effects. However, delaying treatment until after transplantation may be dangerous because interferon may increase the risk of rejection—although some renal transplant recipients are tolerating interferon well (William Amend, Jr, oral communication, 2001). Thus, we recommend but do not require pretransplantation HCV therapy, leaving the decision to the primary care provider and the patient.

### REIMBURSEMENT POLICIES

Reimbursement by third-party payers for experimental procedures is not assured. The definition of *experimental procedure* has been recently debated in the legal cases of 2 HIV-infected liver transplantation candidates in the Boston area.<sup>78,79</sup> The Social Security Act restricts Medicare coverage to that which is found "reasonable and necessary" for the treatment of illness or injury. Medicare coverage decisions rely on evidence of effectiveness. One of the goals of this study is to provide rigorous data that can be used to meet this requirement. No Medicare rule specifically pro-

cludes transplantation coverage for HIV-infected individuals.

Study investigators believe that private and public insurance should cover the clinical costs associated with this study. Without such a policy, case-by-case determinations of insurance coverage will be made in the face of clinical uncertainty. There are precedents of patients who obtained insurance coverage for nonstandard treatments through lawsuits or because of publicity, without any data collection to answer the question of efficacy, only to find later that the intervention was not effective (eg, autologous bone marrow transplantation for metastatic breast cancer). It would be preferable for insurers to pay the clinical costs associated with the trial and contribute to the acquisition of the safety and efficacy data required to make general reimbursement policy decisions.

#### OFF-STUDY TRANSPLANT OPTIONS

Some centers participating in the study are willing to perform transplantations for patients who do not meet study criteria or who do not wish to participate in the study, and some centers not participating in the study will offer transplantation to HIV-infected patients. These centers believe that all patients who decide that they could benefit from transplantation have a right to be placed on the waiting list and receive a transplant. According to this viewpoint, off-protocol access must be an option given study exclusion criteria and geographical limitations.

A different viewpoint is that performing transplantations off-study on patients who are eligible for the study would delay results that could convince insurers to cover this indication and transplantation centers to provide it, and therefore harm future HIV-infected patients. And if the intervention were not successful, this practice could also harm other patients on the waiting list. To the extent that transplantation research improves the justice of allocation policies associated with organ transplantation, every patient who receives a transplant outside of a study represents a loss of knowledge that

could benefit those who will need transplantation later on. However, study investigators recognize that transplantation centers will make autonomous decisions in this area.

#### CONCLUSIONS

Preliminary experience with transplantation in the HAART era appears promising, although critical clinical and ethical questions remain. With improvements in the management of HIV infection, it is timely to perform a safety and efficacy study of transplantation in HIV-infected patients. To address the concerns of utility and effectiveness of a transplantation procedure, the minimum patient and graft survival rates deemed acceptable, based on current transplantation practices, must be defined. Clinical outcomes data from well-designed trials are critical to promote adherence to the principle of justice in the organ allocation process. The process of including HIV-infected patients in a clinical trial should occur as publicly as possible. In this way, all stakeholders will be able to participate in discussions focused on excellence in patient care and driven by well-designed and ethical clinical and basic research.

*Michelle E. Roland, MD  
Positive Health Program  
Department of Medicine  
University of California,  
San Francisco  
Ward 84, San Francisco  
General Hospital  
995 Potrero Ave  
San Francisco, CA 94110  
(e-mail: mroland@php.ucsf.edu)  
Bernard Lo, MD  
Jeffrey Raff, DrPH  
Berkeley, Calif  
Peter G. Stock, MD, PhD  
San Francisco*

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### Correction

**Error in Text, Tables, and Figures.** In the Original Investigation by Cosmi et al titled "Role of Family History in Identifying Women With Thrombophilia and Higher Risk of Venous Thromboembolism During Oral Contraception," published in the May 12 issue of the ARCHIVES (2003;163:1105-1109), the abbreviation for the mutation of the prothrombin gene was inadvertently given as "G20120A" throughout the text, tables, and figures, instead of the correct abbreviation "G20210A."