

# Solid Organ Transplantation: Referral, Management, and Outcomes in HIV-Infected Patients

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*Advances in HIV management make it difficult to deny solid organ transplantation to HIV-infected patients based on futility arguments. Preliminary studies suggest that both patient and graft survival are similar in HIV-negative and HIV-positive transplant recipients. While there has been no significant HIV disease progression, substantial interactions between immunosuppressants and antiretroviral drugs necessitate careful monitoring. The evaluation and management of HIV-infected transplant candidates and recipients require excellent communication among a multidisciplinary team, the primary HIV care provider, and the patient. Timely referral for transplant evaluation will prevent unnecessary mortality during the pre-transplant evaluation process. [AIDS Reader. 2006;16:664-668, 675-678]*

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Because HIV-infected patients are living longer, health care providers must increasingly manage end-stage liver and kidney disease and the morbidity and mortality associated with these conditions.<sup>1-18</sup> With deceased donor organs for transplantation in such short supply and the high mortality associated with untreated HIV disease, these patients were traditionally considered poor transplant candidates. However, the advances in HIV management in recent years have made it difficult to deny transplant consideration to this population based on futility alone.<sup>19-24</sup> The main concern in the current treatment era has been, understandably, that post-transplant immunosuppression may accelerate HIV disease progression.

Preliminary studies suggest that HIV disease progression is relatively stable following liver and kidney transplantation.<sup>25-30</sup> Unexpectedly,

kidney allograft rejection is more frequent among HIV-positive than among HIV-negative transplant recipients. Potent rejection treatment is often associated with the development of serious non-AIDS-defining infections.<sup>31</sup> In addition, interactions between immunosuppressant and antiretroviral agents require careful monitoring and frequent dose adjustments.<sup>32</sup> Given the need for clinical guidance, pre-transplant evaluation and post-transplant management standards are being developed and evaluated in an ongoing NIH-sponsored study at 20 transplant centers in the United States.

### WHAT IS THE PROGNOSIS FOR HIV-INFECTED PATIENTS WITH A TRANSPLANT?

Most HIV-infected patients who received transplants before the HAART era acquired HIV infection in the peritransplant period or were

not known to be HIV-infected at the time of transplantation. Overall, HIV disease progression was probably accelerated in many of these patients, although one important analysis suggested that transplant recipients who were treated with cyclosporine had outcomes similar to those of HIV-negative recipients.<sup>33-40</sup> Outcomes in the HAART era have been consistently much more promising, with patient and graft survival rates similar to those of HIV-negative transplant recipients.<sup>25-30</sup>

### Overview of Studies in the HAART Era

Some studies describe both liver and kidney transplant recipients, while others include only one or the other. There is also a single case report of an HIV-infected heart transplant recipient.<sup>41</sup> Unfortunately, many of the published reports include some of the same subjects, so it is difficult to determine the total number of recipients and thus the overall incidence of some important outcomes, such as hepatitis C-associated deaths and AIDS-defining opportunistic infections.

The longest prospective study of both liver and kidney transplant recipients in the HAART era was initiated in 1999,<sup>25,26</sup> and 29 participants were enrolled at 4 transplant centers through 2003 ("Multisite Pilot Study"). At that time, a 20-center study with a targeted enrollment of 125 liver and 150 kidney transplant recipients began ("Multisite U01 Study"). Preliminary data from 53 transplant recipients who received their transplants at one of the collaborating study centers during or before the initiation of the Multisite

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Pilot Study ("Multisite Retrospective/Prospective Analysis") supported the funding of the current study.<sup>27</sup>

A related multisite analysis of HIV-infected liver transplant recipients was led by investigators at the University of Pittsburgh ("Multisite Liver Transplant Outcomes Analysis").<sup>28</sup> Additional reports of liver transplants include 14 cases from King's College in London, 12 cases from Germany, 8 cases from Spain, and 1 case from the Netherlands.<sup>42-47</sup>

Four reports describe the outcomes of HIV-infected kidney transplant recipients, including a retrospective review of 47 HIV-infected patients in the United States Renal Data System ("Retrospective Kidney Study"), a prospective analysis of 40 patients from Drexel University ("Prospective Kidney Study"), 4 cases from the University of Pittsburgh, and 1 case from Switzerland.<sup>29,30,48,49</sup>

### **Patient and Graft Survival, Hepatitis C Recurrence, and Kidney Rejection**

Patient and graft survival were similar to those in the Organ Procurement and Transplantation Network database in the Multisite Retrospective/Prospective and Multisite Liver Outcomes Analyses.<sup>27,28</sup> One of the 4 deaths among liver recipients in the first study was due to recurrent hepatitis C virus (HCV) infection. Another resulted from a severe rejection episode precipitated by antiretroviral therapy discontinuation leading to very low immunosuppressant levels. The others were related to postoperative pancreatitis and *Rhizopus* infection 4.5 years post-transplant.<sup>25</sup> Five of 7 patients from King's College who were coinfecting with HCV died—3 directly from HCV-associated complications and 1 in the setting of significant HCV infection recurrence—a median of 161 days post-transplantation. There was no recurrence of hepatitis B virus (HBV) infection among 4 patients.

Although HCV infection was also associated with poorer survival in the Multisite Liver Transplant Outcomes Analysis (50% vs 100% in those without HCV infection;  $P = .023$ ), the difference in survival between HCV-monoinfected and HCV-HIV-coinfected persons did not reach statistical significance at the  $P < .05$  level ( $P = .058$ ). There have been 5 additional deaths reported among the European liver transplant studies, including 2 from recurrent HCV infection, 1 from hepatic artery thrombosis and sepsis, 1 from chemotherapy-induced liver damage, and 1 from a procedural complication.

Kidney rejection has occurred more frequently than expected in some cohorts, although there have been few graft losses.<sup>25-27,29</sup> Renal function is often preserved despite these rejection episodes. In contrast, rejection episodes were less common, but renal function perhaps poorer, in the Prospective Kidney study described above.<sup>30</sup> The lower rejection rates in this cohort may have come at some cost in terms of renal toxicity related to higher levels of calcineurin inhibitors and/or calcineurin metabolites.

### **HIV Disease Progression**

Three patients described in these reports developed an AIDS-defining opportunistic infection or neoplasm, including one case each of Cytomegalovirus (CMV) and *Candida* esophagitis.<sup>26,27</sup> A patient with Kaposi sarcoma (KS) and multicentric Castleman disease was in complete remission at 31 months post-transplantation.<sup>45</sup> CD4<sup>+</sup> T-cell counts have been stable over time, except following the treatment of kidney rejection with thymoglobulin.<sup>25,30,31</sup> Despite significant drug interactions and modifications in immunosuppressant dosing, HIV RNA has been well controlled in all the published studies describing patients who received antiretroviral therapy.

## **WHO SHOULD BE REFERRED FOR TRANSPLANT EVALUATION AND WHEN?**

### **End-stage Liver Disease**

As AIDS-related mortality has declined, mortality secondary to end-stage liver disease has increased.<sup>2,4,5,10,11</sup> HIV-infected patients are at significant risk for acquiring infection with HCV and HBV, and the risk of development of end-stage liver disease from viral hepatitis is higher in this population.<sup>1-18</sup> Hepatocellular carcinoma also appears to be more aggressive, and pre-transplantation mortality higher, in HIV-infected patients.<sup>3,6,16</sup> Nucleoside analogue toxicity can rarely cause fulminant hepatic failure with lactic acidosis and massive hepatic steatosis.<sup>50-52</sup> Nevirapine also can cause significant hepatotoxicity and even death.<sup>53-56</sup>

In general, referral for transplant evaluation follows the same criteria established for all potential transplant candidates at a given institution (Table 1). Patients with liver disease should be referred for liver transplant evaluation after initial clinical decompensation with hepatic encephalopathy, ascites, or variceal bleeding. A patient with known cirrhosis and evidence of liver synthetic dysfunction with a low albumin level and an elevated prothrombin time may also be referred. A Child-Turcotte-Pugh (CTP) score of 7 or greater is a good indicator for referral for transplant evaluation. Each of 5 parameters is assigned a score from 1 to 3. It is critical that HIV clinicians, hepatologists, and patients be aware that liver transplantation is an option for HIV-infected patients at many transplant centers, because delays in referral result in unnecessary mortality during the pre-transplant evaluation process.<sup>6,16</sup>

### **Chronic Kidney Disease**

Both end-stage renal disease and dialysis are associated with substan-

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**Table 1. When to Refer Patients for Transplant Evaluation**

Kidney transplant candidates	Liver transplant candidates			
Hemodialysis	Ascites			
Peritoneal dialysis	Hepatic encephalopathy			
Glomerular filtration rate < 25 mL/min/1.73m <sup>2</sup> or creatinine clearance < 25 mL/min	Esophageal or gastric varices			
	Elevated bilirubin level, international normalized ratio (INR), and decreased albumin level in setting of radiographic or histologic evidence of cirrhosis and portal hypertension			
	Child-Turcotte-Pugh score $\geq$ 7			
	<b>Score</b>	<b>1</b>	<b>2</b>	<b>3</b>
	INR	< 1.7	1.7 - 2.3	> 2.3
	Bilirubin (mg/dL)	< 2	2 - 3	> 3
	Albumin (g/dL)	> 3.5	3.5 - 2.8	< 2.8
	Ascites	Absent	Mild	Severe
	Encephalopathy	Absent	Mild	Severe

Note: A patient meeting any one of the above criteria would be a candidate for transplant evaluation.

tial morbidity and mortality, especially in HIV-infected patients.<sup>57-59</sup> The impact of effective antiretroviral therapy on the survival of patients receiving dialysis is unclear.<sup>60,61</sup> Potentially eligible patients receiving hemodialysis or peritoneal dialysis should be referred for kidney transplant evaluation. Before dialysis, those with a creatinine clearance or glomerular filtration rate (GFR) of less than 25 mL/min/1.73m<sup>2</sup> should be referred for evaluation, although they will not start to accumulate time on the United Network for Organ Sharing (UNOS) transplant waiting list until their GFR is less than 20 mL/min/1.73m<sup>2</sup>. The specific referral criteria may vary outside the United States.

### HIV-Specific Criteria

In general, transplantation should be offered to persons with a relatively intact immune system and controllable HIV viremia. While we currently recommend the following HIV-specific criteria for transplantation based on our clinical trial experience, these criteria are likely to

evolve with our increasing knowledge of HIV infection in the context of transplantation (Table 2).

For kidney transplant candidates, we recommend that CD4<sup>+</sup> T-cell counts be 200/ $\mu$ L or greater before transplantation. For liver transplant candidates who have never had an AIDS-related opportunistic infection, the CD4<sup>+</sup> T-cell count should be 100/ $\mu$ L or greater before transplantation and greater than 200/ $\mu$ L for those with such a history.

Because many patients with end-stage liver disease, similar to those with severe acute illnesses, experience an acute decline in CD4<sup>+</sup> T-cell count in the days and weeks before transplantation, it is reasonable to apply this requirement at some point in the 3 to 4 months before transplantation.<sup>62</sup> Interferon treatment of HCV infection will cause a transient decline in CD4<sup>+</sup> T-cell count. This should be taken into account when determining the appropriate time frame for the CD4<sup>+</sup> T-cell criteria (eg, it may be reasonable to require this level only before initiation of HCV therapy).

In addition, the HIV RNA level should ideally be undetectable in those receiving antiretroviral therapy. For liver transplant candidates who are unable to tolerate or have recently begun receiving antiretroviral therapy, an experienced HIV clinician should confidently predict full suppression once therapy has been started, based on review of the antiretroviral treatment history, HIV RNA level history, and available antiretroviral resistance tests.

Although most studies and transplant programs exclude patients with multidrug-resistant HIV and a detectable HIV RNA level but relatively high CD4<sup>+</sup> T-cell counts, it may not be unreasonable to consider such patients on a case-by-case basis. Long-term nonprogressors who have never had a detectable HIV RNA level may not need to start antiretroviral therapy before or after transplantation, but they should be monitored very closely.<sup>48</sup>

Any AIDS-related opportunistic infections or cancers should be completely treated before transplantation. The Multisite U01 Study con-

tinues to exclude those persons with diseases for which there is no reliable therapy should disease recur post-transplantation (eg, progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, and multidrug-resistant systemic fungal infections); it currently allows persons with a history of resolved cutaneous KS but not visceral KS.

### **HOW DOES THE EVALUATION PROCESS WORK?**

Each transplant center has its own procedures. We describe the typical pre-transplantation evaluation process followed at the University of California, San Francisco (UCSF), as an example (Table 2).

#### **Liver Transplant Candidates**

Most referrals to a transplant center are initially screened by a transplant hepatologist. The Model for End-Stage Liver Disease (MELD) score at the time of referral will dictate the initial appointment type. The MELD severity scale is predictive of the risk of dying as a result of liver disease. It is calculated using the bilirubin level, international normalized ratio, and creatinine level (<http://www.unos.org/resources/meldPeldCalculator.asp>).

Generally, patients who have a MELD score of 15 or greater will be seen for a phase 1 evaluation; those who have a MELD score of 10 to 14 will see only a hepatologist, initially. Symptoms of liver decompensation may influence the timing and phase of initial evaluation. It is possible that the MELD score will not adequately predict overall disease severity and progression to death in HIV-infected liver transplant candidates, and this is an area that is under active investigation.<sup>6,16</sup>

A typical phase 1 evaluation includes appointments with the nurse coordinator, hepatologist, surgeon, and social worker. Testing includes abdominal ultrasonography and

blood work. The patient's medical history, drug and alcohol use, and social situation are then presented at a selection committee, and if the patient is considered a probable transplant candidate, he or she is listed with UNOS.

The timing of the phase 2 workup depends on the severity of the liver disease. This evaluation generally consists of routine blood work, abdominal CT, cardiac workup, arterial blood gas analysis, chest radiograph, colonoscopy, mammography, Papanicolaou (Pap) smear, prostate specific antigen determination, purified protein derivative (PPD) test, and vaccination against hepatitis A and B and pneumococcus. These studies and procedures can be performed at the transplant center or coordinated through the patient's primary care provider.

#### **Kidney Transplant Candidates**

The initial evaluation for a kidney transplant candidate takes approximately 4 hours. In addition to a transplant education class, the patient will see a surgeon or nephrologist, nurse coordinator, social worker, and financial counselor. Testing includes blood work, tissue typing, and blood typing.

After the case is presented at the selection committee, the patient is listed with UNOS. It is not necessary that all transplant criteria be met to initiate the listing process if it is believed that these criteria are likely to be met before transplantation. It is important for the patient to start accruing time on the waiting list as soon as possible.

The likely organ donor option determines the next phase. Those with a living donor or considering a "high infectious risk" donor (one who is serologically negative for HIV, HCV, and HBV but has recently engaged in behavior that puts the donor at risk for being in the window period for infection) will begin

their medical workups. Those waiting for a deceased donor, which can take 4 to 6 years at UCSF, will complete the workup when they are closer to the top of the list.

#### **All Candidates**

The medical, psychosocial, financial, and social support evaluations are described in Table 2. Evaluation of the patient's coping style includes a discussion about expectations and an evaluation of how the patient will adjust to post-transplantation realities.

#### **HOW DOES ORGAN ALLOCATION WORK?**

In the United States, liver allocation is based on severity of illness, with the sickest patients receiving priority according to MELD score. Hepatocellular carcinoma increases the MELD score through "exception points." The average MELD score at the time of transplantation varies by region and blood type. Kidney allocation in northern California is based mainly on time on the UNOS transplant waiting list and blood type.

#### **Pre-Transplantation Challenges**

Transplant candidates often do not understand the pre-transplantation process. They are challenged by the long waiting times associated with the organ allocation process. The insufficient supply of organs can create a fear of dying or of developing a medical contraindication before transplantation.

While waiting for an organ to become available, the patient may experience deteriorating health, fatigue, medication side effects, and/or adherence difficulties. Common psychosocial challenges include the fear of dying, worry about becoming a burden to loved ones, guilt about wishing for an organ at the expense of someone else's life, and withdrawal of loved ones who do not want to be donors. ➤

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### HOW ARE TRANSPLANT RECIPIENTS MANAGED POST-TRANSPLANTATION?

Post-transplant management includes immunosuppressant therapy, antiretroviral therapy, prophylaxis to prevent opportunistic infections associated with transplant immunosuppressants and/or HIV infection, routine health care maintenance, and specific therapy for HBV and/or HCV infection in coinfecting or tri-infected patients (Table 3). A significant portion of the post-transplant management depends on communication among members of a very large multidisciplinary team.

### Drug Interactions

There are substantial interactions between the common immunosuppressant medications (eg, cyclosporine, tacrolimus, and sirolimus) and antiretroviral protease inhibitors as a result of metabolism by cytochrome P-450 3A enzymes.<sup>32,63-65</sup> Initial immunosuppressant dosages are much lower in patients taking protease inhibitors and are often further reduced over time if cyclosporine is used. Efavirenz is a P-450 3A inducer; thus, immunosuppressant dosages are usually increased when used with efavirenz. When both a protease inhibitor and an NNRTI are

used, immunosuppressant dosages are similar to those used with protease inhibitors alone. Care must be taken when considering antibiotics, antifungals, and other agents that are metabolized by the hepatic P-450 system, and these medication changes should always be discussed with the transplant team before implementation.

Some transplant centers try to avoid protease inhibitors or use NRTI-only regimens. In contrast, we recommend continuing the antiretroviral regimen that makes the most sense from an HIV suppression perspective. However, atazanavir should

**Table 2. Transplant Evaluation, Listing, and Organ Allocation**

	All candidates	Kidney candidates	Liver candidates
Evaluation	<p><i>Routine tests</i> ECG, chest radiograph, stool guaiac, prostate specific antigen, cervical Pap smear, mammogram, dental screening; some or all of the following: pulmonary function tests, echocardiogram, nuclear medicine cardiac scan, cardiac catheterization, endoscopy/colonoscopy, abdominal ultrasonogram, liver biopsy</p> <p><i>Psychosocial evaluation</i> History of substance abuse; financial resources; return to work; social support</p>	<p><i>Suggested HIV criteria</i> CD4<sup>+</sup> T cell <math>\geq</math> 200/mL* Receiving antiretroviral therapy<sup>†</sup> HIV RNA level undetectable using an ultrasensitive assay<sup>‡</sup></p>	<p><i>Suggested HIV criteria</i> CD4<sup>+</sup> T cell <math>\geq</math> 100/mL or <math>\geq</math> 200/mL if there is a history of opportunistic complication* HIV RNA level undetectable using an ultrasensitive assay<sup>‡</sup> If not receiving, recently started, or reinitiated antiretroviral therapy, may have detectable HIV RNA level if an HIV clinician confidently predicts HIV suppression post-transplant</p>
UNOS listing <sup>§</sup>		Receiving dialysis or glomerular filtration rate $\leq$ 20 mL/min/1.73m <sup>2</sup>	Child-Turcotte-Pugh score $\geq$ 7
Organ allocation <sup>§</sup>		Length of time waiting <sup>  </sup>	MELD score <sup>¶</sup> (bilirubin, INR, and creatinine [ <a href="http://www.unos.org/resources/meldPeldCalculator.asp">http://www.unos.org/resources/meldPeldCalculator.asp</a> ])

UNOS, United Network for Organ Sharing; MELD, Model for End-Stage Liver Disease; INR, international normalization ratio; UCSF, University of California, San Francisco.

\*Children: 1 - 2 y, CD4%  $\geq$  30%; 2 - 10 y, CD4%  $\geq$  20%.

<sup>†</sup>Long term nonprogressors who have never had detectable HIV RNA may elect not to initiate antiretroviral therapy with close monitoring post-transplant.

<sup>‡</sup>Intermittent elevations to 1000 copies/mL, if not persistent on more than 2 sequential measures and followed by undetectable levels, are likely to be blips and may be allowed.

<sup>§</sup>Current US criteria.

<sup>||</sup>Some centers may offer high-infectious risk or extended-donor organs as an option.

<sup>¶</sup>MELD score at time of transplant varies by region and blood type. At UCSF, the average MELD score at the time of transplantation is approximately 30. Patients with hepatocellular carcinoma will have their score increased.

be avoided when possible because proton pump inhibitors are nearly universally used post-transplantation. The additive myelotoxicity of zidovudine and the post-transplantation immunosuppressive and prophylactic medications should also be considered. When possible, it is reasonable to limit the use of zidovudine and stavudine when mycophenolate mofetil is used because of the in vitro antiretroviral antagonism seen with these agents.<sup>66-71</sup>

### Hepatitis B Management

The dual management of infection with HIV and HBV requires consideration of virologic suppression and drug resistance with both viruses. Lamivudine, emtricitabine, and tenofovir have activity against both HIV and HBV. Thus, these agents should only be used in the context of a fully suppressive HIV treatment regimen to avoid the development of resistance. Adefovir and entecavir are active only against HBV and may be used to treat hepatitis B when HIV

therapy must be withheld.

HBV resistance must also be considered when selecting these regimens. In the context of HBV monotherapy, lamivudine-resistant HBV can develop within 6 months and is seen in 50% of patients after 3 years. Fortunately, HBV-HIV-coinfected patients, who are at high risk for having lamivudine-resistant HBV, usually have ongoing suppression of HBV in the post-transplant period.<sup>72</sup> In addition to the antiviral agents discussed above, high-dose hepatitis B immune globulin is used intravenously once a month for 6 months and then intramuscularly or intravenously once a month indefinitely.

### Hepatitis C Management

Because there are no data available to suggest that HCV RNA clearance rates are higher when antiviral therapy is started preemptively post-transplantation as opposed to waiting until recurrent HCV disease is documented, many transplant cen-

ters do not initiate HCV treatment until there is liver biopsy documentation of recurrent HCV infection with severe or progressive disease. The introduction of interferon and ribavirin often results in the need for granulocyte colony-stimulating factor, erythropoietin, or both—as well as for an antidepressant—and adds to an already complicated medication and clinical follow-up regimen.

### Opportunistic Infection Prophylaxis and Health Care Maintenance

Opportunistic infection prophylaxis includes standard post-transplantation prophylaxis and HIV-related prophylaxis with additional consideration given to the potential increased vulnerability to opportunistic infections in this population. Of note, we recommend that *Pneumocystis jiroveci* prophylaxis be continued for life, regardless of CD4<sup>+</sup> T-cell count (Table 3).

Transplantation is not commonly associated with the development

**Table 3. Post-transplant Management**

Treatment	General principles	Comments
Immunosuppression	Combinations of a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative agent (mycophenolate mofetil or sirolimus), and prednisone	Substantial interactions between many immunosuppressants and protease inhibitors and efavirenz as a result of cytochrome P-450 3A metabolism
Antiretroviral therapy	Usually continue the pre-transplant antiretroviral regimen, except: (1) atazanavir should be avoided because proton pump inhibitors are usually used and (2) the additive myelotoxicity of zidovudine and immunosuppressive and prophylactic medications should be considered	Some experts try to limit the use of zidovudine and stavudine when mycophenolate mofetil is used because of the in vitro antiretroviral antagonism seen with these agents <sup>66-71</sup>
HIV-specific prophylaxis	<i>Pneumocystis jiroveci</i> pneumonia prophylaxis is recommended for life in ongoing clinical trials; other primary and secondary OI prophylaxis should be guided by DHHS CD4 <sup>+</sup> T-cell count CD4 <sup>+</sup> criteria <sup>73</sup>	For patients with a history of opportunistic infections, consider secondary prophylaxis reinstatement immediately post-transplantation for 1 month and for 1 month following completion of acute rejection therapy; if the T-cell count is suppressed, continuation should be guided by the CD4 <sup>+</sup> T-cell count <sup>73</sup>

OI, opportunistic infection; DHHS, Department of Health and Human Services.

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of *Mycobacterium avium-intracellulare* complex. HIV-infected transplant recipients with low CD4<sup>+</sup> T-cell counts should receive macrolide prophylaxis with weekly azithromycin because it has less potent drug interaction potential than does clarithromycin.<sup>73</sup> CMV retinitis is not a typical post-transplant manifestation of CMV disease; patients with CD4<sup>+</sup> T-cell counts below 50/ $\mu$ L should be advised about the symptoms of CMV retinitis and have regular ophthalmologic examinations.<sup>73</sup>

Patients with a history of opportunistic infection need to receive secondary prophylaxis based on their CD4<sup>+</sup> T-cell counts.<sup>73</sup> Secondary prophylaxis should probably also be re-instituted in the immediate post-transplant period and in the case of treatment for acute rejection.

Before transplantation, patients should be vaccinated against hepatitis A and B and pneumococcus, if they are not already immune, as is standard practice at our transplant center. There is no consensus about influenza vaccination in the context of transplantation, although it is recommended for HIV-infected patients. HIV-infected patients should have PPD screening every 6 months or according to local HIV/tuberculosis prevention standards; those with a positive PPD result should receive 9 months of treatment. Treatment can be initiated pre-transplantation and completed post-transplantation.

Patients should also undergo comprehensive dental screening and care before transplantation whenever possible. Women should have a cervical Pap smear or colposcopy screening at least every 6 to 12 months.<sup>73</sup> Both women and men with HIV infection are at risk for the development of human papillomavirus-associated anorectal cancers, and they should be screened with anal Pap smears and colposcopy where available.<sup>74</sup>

Skin cancer is more common fol-

lowing transplantation; thus, careful dermatologic monitoring is important. Other cancers can occur after 5 to 10 years in non-HIV-infected transplant recipients, again emphasizing the need for ongoing monitoring of these patients.

### Post-Transplantation Challenges

It is common for transplant candidates and recipients to overestimate the benefits and minimize the new challenges associated with transplantation. Unmet expectations can be very disappointing. Multiple medications, side effects, potential drug interactions, and frequent laboratory monitoring and other testing can be very stressful. Temporary relocation closer to a transplant center in the peritransplant period creates emotional, financial, and support issues.

Adjusting pre-transplantation expectations to post-transplantation realities may result in situational depression. Chronic depression can arise when the patient realizes that the transplant did not solve all of his medical or psychosocial problems. Living with a chronic illness can transform life in a positive way or lead to despair. Persons who have HIV infection may be better equipped to deal with many of these challenges than the typical transplant recipient because they have lived with HIV disease before taking on the additional demands associated with organ transplantation.

### ONGOING CLINICAL STUDIES

The long-range goals of the ongoing prospective multicenter cohort study of HIV-infected patients who undergo kidney or liver transplantation include providing patients and clinicians with information regarding the HIV-specific risks of transplantation and providing clinicians with information necessary to manage complex drug interactions and assess and manage medical and psychoso-

cial complications in this population. The study also aims to explore the underlying basic science mechanisms that explain patient outcomes so that clinical management may be adjusted to improve these outcomes. The study intends to enroll 125 liver and 150 kidney transplant recipients in 20 US transplant centers ([www.HIVTransplant.com](http://www.HIVTransplant.com)).

### ETHICS AND POLICY

It is difficult to deny transplantation to select persons based on HIV infection status alone.<sup>22-24,75</sup> UNOS policy does not consider HIV infection to be a contraindication for transplantation. Third-party payers increasingly have policies or are being compelled by legislation or legal decisions to cover these costs. The United States Veterans Affairs Administration policy now allows transplantation for HIV-infected patients.<sup>76</sup> Spain and the United Kingdom have published guidelines for liver transplantation in patients infected with HIV.<sup>77,78</sup>

### CONCLUSIONS

The need for transplantation in HIV-infected persons is significant and is likely to grow. Preliminary data in the HAART era suggest that transplantation is safe. Similar patient and graft survival rates compared with those in the general transplantation population suggest that this intervention is also effective. As in the non-HIV-infected population, HCV-HIV-coinfected patients appear to have variable outcomes. The evaluation and management of HIV-infected transplant candidates and recipients require excellent communication among members of a multidisciplinary team of health care providers, the primary HIV care providers, and the patients. It is critical that HIV clinicians, hepatologists, nephrologists, and patients be aware that transplantation is an option for HIV-infected patients at many transplant centers, because delays in refer-

ral can result in avoidable mortality during the pre-transplant evaluation process.<sup>16</sup>

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## References

1. Puoti M, Spinetti A, Ghezzi A, et al. Mortality from liver disease in patients with HIV infection: a cohort study. *J Acquir Immune Defic Syndr*. 2000;24:211-217.
2. Martin-Carbonero L, Soriano V, Valencia E, et al. Increasing impact of chronic viral hepatitis on hospital admissions and mortality among HIV-infected patients. *AIDS Res Hum Retroviruses*. 2001;17:1467-1471.
3. Puoti M, Bruno R, Soriano V, et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS*. 2004;18:2285-2293.
4. Rosenthal E, Poiree M, Pradier C, et al. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). *AIDS*. 2003;17:1803-1809.
5. Mocroft A, Soriano V, Rockstroh J, et al. Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? *AIDS*. 2005;19:2117-2125.
6. Ragni MV, Eghtesad B, Schlesinger KW, et al. Pre-transplant survival is shorter in HIV-positive than HIV-negative subjects with end-stage liver disease. *Liver Transpl*. 2005;11:1425-1430.
7. Gebo KA, Fleishman JA, Moore RD. Hospitalizations for metabolic conditions, opportunistic infections, and injection drug use among HIV patients: trends between 1996 and 2000 in 12 states. *J Acquir Immune Defic Syndr*. 2005;40:609-616.
8. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis*. 2001;32:492-497.
9. Cacoub P, Geffray L, Rosenthal E, et al. Mortality among human immunodeficiency virus-infected patients with cirrhosis or hepatocellular carcinoma due to hepatitis C virus in French departments of internal medicine/infectious diseases, in 1995 and 1997. *Clin Infect Dis*. 2001;32:1207-1214.
10. Jain MK, Skiest DJ, Cloud JW, et al. Changes in mortality related to human immunodeficiency virus infection: comparative analysis of inpatient deaths in 1995 and in 1999-2000. *Clin Infect Dis*. 2003;36:1030-1038.
11. Louie JK, Hsu LC, Osmond DH, et al. Trends in causes of death among persons with acquired immunodeficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994-1998. *J Infect Dis*. 2002;186:1023-1027.
12. Monga HK, Rodriguez-Barradas MC, Breaux K, et al. Hepatitis C virus infection-related morbidity and mortality among patients with human immunodeficiency virus infection. *Clin Infect Dis*. 2001;33:240-247.
13. Qurishi N, Kreuzberg C, Luchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. *Lancet*. 2003;362:1708-1713.
14. Ragni MV, Belle SH. Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection. *J Infect Dis*. 2001;183:1112-1115.
15. Thio CL, Seaberg EC, Skolasky R Jr, et al; Multi-

center AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002;360:1921-1926.

16. Stock PG. Rapid deterioration of HIV co-infected patients waiting for liver transplantation is not predicted by MELD. *Liver Transpl*. 2005;11:1315-1317.
17. Staples CT Jr, Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta VA (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. *Clin Infect Dis*. 1999;29:150-154.
18. Soriano V, Garcia-Samaniego J, Valencia E, et al. Impact of chronic liver disease due to hepatitis viruses as cause of hospital admission and death in HIV-infected drug users. *Eur J Epidemiol*. 1999;15:1-4.
19. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853-860.
20. Feinberg MB. Changing the natural history of HIV disease. *Lancet*. 1996;348:239-246.
21. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2000;30(suppl 1):S5-S14.
22. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med*. 2002;347:284-287.
23. Roland ME, Havlir DV. Responding to organ failure in HIV-infected patients. *N Engl J Med*. 2003;348:2279-2281.
24. Roland ME, Lo B, Braff J, Stock PG. Key clinical, ethical, and policy issues in the evaluation of the safety and effectiveness of solid organ transplantation in HIV-infected patients. *Arch Intern Med*. 2003;163:1773-1778.
25. Stock PG, Roland ME, Carlson L, et al. Kidney and liver transplantation in human immunodeficiency virus-infected patients: a pilot safety and efficacy study. *Transplantation*. 2003;76:370-375.
26. Roland ME, Adey D, Carlson LL, Terrault NA. Kidney and liver transplantation in HIV-infected patients: case presentations and review. *AIDS Patient Care STDS*. 2003;17:501-507.
27. Roland ME, Stock PG. Review of solid-organ transplantation in HIV-infected patients. *Transplantation*. 2003;75:425-429.
28. Ragni MV, Belle SH, Im K, et al. Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis*. 2003;188:1412-1420.
29. Abbott KC, Swanson SJ, Agodoa LY, Kimmel PL. Human immunodeficiency virus infection and kidney transplantation in the era of highly active antiretroviral therapy and modern immunosuppression. *J Am Soc Nephrol*. 2004;15:1633-1639.
30. Kumar MS, Sierka DR, Damask AM, et al. Safety and success of kidney transplantation and concomitant immunosuppression in HIV-positive patients. *Kidney Int*. 2005;67:1622-1629.
31. Carter JT, Melcher ML, Carlson LL, et al. Thymoglobulin-associated Cd4+ T-cell depletion and infection risk in HIV-infected renal transplant recipients. *Am J Transplant*. 2006;6:753-760.
32. Frassetto L, Baluom M, Jacobsen W, et al. Cyclosporine pharmacokinetics and dosing modifications in human immunodeficiency virus-infected liver and kidney transplant recipients. *Transplantation*. 2005;80:13-17.
33. Dummer JS, Erb S, Breinig MK, et al. Infection with human immunodeficiency virus in the Pittsburgh transplant population. A study of 583 donors and 1043 recipients, 1981-1986. *Transplantation*. 1989;47:134-140.
34. Poli F, Scalapogna M, Pizzi C, et al. HIV infection in cadaveric renal allograft recipients in the North Italy Transplant Program. *Transplantation*. 1989;47:24-27.

35. Tzakis AG, Cooper MH, Dummer JS, et al. Transplantation in HIV+ patients. *Transplantation*. 1990;49:354-358.
36. Erice A, Rhame FS, Heussner RC, et al. Human immunodeficiency virus infection in patients with solid-organ transplants: report of five cases and review. *Rev Infect Dis*. 1991;13:537-547.
37. Bouscarat F, Samuel D, Simon F, et al. An observational study of 11 French liver transplant recipients infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 1994;19:854-859.
38. Ahuja TS, Zingman B, Glicklich D. Long-term survival in an HIV-infected renal transplant recipient. *Am J Nephrol*. 1997;17:480-482.
39. Ragni MV, Bontempo FA, Lewis JH. Organ transplantation in HIV-positive patients with hemophilia. *N Engl J Med*. 1990;322:1886-1887.
40. Schwarz A, Offermann G, Keller F, et al. The effect of cyclosporine on the progression of human immunodeficiency virus type 1 infection transmitted by transplantation—data on four cases and review of the literature. *Transplantation*. 1993;55:95-103.
41. 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.
42. Norris S, Taylor C, Muiresan P, et al. Outcomes of liver transplantation in HIV-infected individuals: the impact of HCV and HBV infection. *Liver Transpl*. 2004;10:1271-1278.
43. Moreno S, Fortun J, Quereda C, et al. Liver transplantation in HIV-infected recipients. *Liver Transpl*. 2005;11:76-81.
44. Rafecas A, Rufi G, Figueras J, et al. Liver transplantation without steroid induction in HIV-infected patients. *Liver Transpl*. 2004;10:1320-1323.
45. Vogel M, Voigt E, Schafer N, et al. Orthotopic liver transplantation in human immunodeficiency virus (HIV)-positive patients: outcome of 7 patients from the Bonn cohort. *Liver Transpl*. 2005;11:1515-1521.
46. Radecke K, Fruhauf NR, Miller M, et al. Outcome after orthotopic liver transplantation in five HIV-infected patients with virus hepatitis-induced cirrhosis. *Liver Int*. 2005;25:101-108.
47. Honkoop P, Kazemier G, Perenboom RM, et al. Liver transplantation in a HIV-positive patient receiving potent antiretroviral therapy; the first case in The Netherlands [in Dutch]. *Ned Tijdschr Geneesk*. 2004;148:2500-2504.
48. Toso C, Berney T, Oberholzer J, et al. Kidney-pancreas transplantation in a long-term non-progressor HIV-infected recipient. *Am J Transplant*. 2003;3:631-633.
49. Tan HP, Kaczorowski DJ, Basu A, et al. Living-related donor renal transplantation in HIV+ recipients using alemtuzumab preconditioning and steroid-free tacrolimus monotherapy: a single center preliminary experience. *Transplantation*. 2004;78:1683-1688.
50. Saves M, Vandentorren S, Daucourt V, et al. Severe hepatic cytolysis: incidence and risk factors in patients treated by antiretroviral combinations. Aquitaine Cohort, France, 1996-1998. Groupe d'Epidemiologie Clinique de Sida en Aquitaine (GECSA). *AIDS*. 1999;13:F115-F121.
51. Carr A, Morey A, Mallon P, et al. Fatal portal hypertension, liver failure, and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidemia. *Lancet*. 2001;357:1412-1414.
52. Chariot P, Drogou I, de Lacroix-Szmania I, et al. Zidovudine-induced mitochondrial disorder with massive liver steatosis, myopathy, lactic acidosis, and mitochondrial DNA depletion. *J Hepatol*. 1999;30:156-160.
53. Martin-Carbonero L, Rodriguez-Rosado R, Soriano V, Gonzalez-Lahoz J. Hepatotoxicity of non nucleoside analogues: nevirapine versus efavirenz. 5th International Congress on Drug Therapy in HIV Infection; October 22-26, 2000; Glasgow, UK. Abstract

## Disease Management

p164.

54. Martinez E, Blanco JL, Arnaiz JA, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS*. 2001;15:1261-1268.
55. Thorne C, Newell ML. The safety of antiretroviral drugs in pregnancy. *Expert Opin Drug Saf*. 2005;4:323-335.
56. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr*. 2003;34(suppl 1):S21-S33.
57. Dave MB, Shabih K, Blum S. Maintenance hemodialysis in patients with HIV-associated nephropathy. *Clin Nephrol*. 1998;50:367-374.
58. Perinbasekar S, Brod-Miller C, Pal S, Mattana J. Predictors of survival in HIV-infected patients on hemodialysis. *Am J Nephrol*. 1996;16:280-286.
59. Schoenfeld P, Mendelson M, Rodriguez R. Survival of ESRD patients with HIV infection. *J Am Soc Nephrol*. 1995;6:561. Abstract 2110.
60. Rodriguez RA, Mendelson M, O'Hare AM, et al. Determinants of survival among HIV-infected chronic dialysis patients. *J Am Soc Nephrol*. 2003;14:1307-1313.
61. Ahuja TS, Grady J, Khan S. Changing trends in the survival of dialysis patients with human immunodeficiency virus in the United States. *J Am Soc Nephrol*. 2002;13:1889-1893.
62. Aldrich J, Gross R, Adler M, et al. The effect of acute severe illness on CD4<sup>+</sup> lymphocyte counts in nonimmunocompromised patients. *Arch Intern Med*. 2000;160:715-716.
63. Jain A, Venkataraman R, Shapiro R, et al. The interaction between anti-retroviral agents and tacrolimus in liver and kidney transplant patients. Transplant 2002, American Transplant Congress; April 26-May 1, 2002; Washington, DC.
64. Guaraldi G, Cocchi S, Codeluppi M, et al. Role of therapeutic drug monitoring in a patient with human immunodeficiency virus infection and end-stage liver disease undergoing orthotopic liver transplantation. *Transplant Proc*. 2005;37:2609-2610.
65. Vogel M, Voigt E, Michaelis HC, et al. Management of drug-to-drug interactions between cyclosporine A and the protease-inhibitor lopinavir/ritonavir in liver-transplanted HIV-infected patients. *Liver Transpl*. 2004;10:939-944.
66. Chapuis AG, Paolo Rizzardi G, D'Agostino C, et al. Effects of mycophenolic acid on human immunodeficiency virus infection in vitro and in vivo. *Nat Med*. 2000;6:762-768.
67. Margolis DM, Kewn S, Coull JJ, et al. The addition of mycophenolate mofetil to antiretroviral therapy including abacavir is associated with depletion of intracellular deoxyguanosine triphosphate and a decrease in plasma HIV-1 RNA. *J Acquir Immune Defic Syndr*. 2002;31:45-49.
68. Hossain MM, Coull JJ, Drusano GL, Margolis DM. Dose proportional inhibition of HIV-1 replication by mycophenolic acid and synergistic inhibition in combination with abacavir, didanosine, and tenofovir. *Antiviral Res*. 2002;55:41-52.
69. Garcia F, Plana M, Arnedo M, et al. Effect of mycophenolate mofetil on immune response and plasma and lymphatic tissue viral load during and after

interruption of highly active antiretroviral therapy for patients with chronic HIV infection: a randomized pilot study. *J Acquir Immune Defic Syndr*. 2004;36:823-830.

70. Heredia A, Margolis D, Oldach D, et al. Abacavir in combination with the inosine monophosphate dehydrogenase (IMPDH)-inhibitor mycophenolic acid is active against multidrug-resistant HIV-1. *J Acquir Immune Defic Syndr*. 1999;22:406-407.
71. Margolis D, Heredia A, Gaywee J, et al. Abacavir and mycophenolic acid, an inhibitor of inosine monophosphate dehydrogenase, have profound and synergistic anti-HIV activity. *J Acquir Immune Defic Syndr*. 1999;21:362-370.
72. Terrault NA, Carter JT, Carlson L, et al. Outcome of patients with hepatitis B virus and human immunodeficiency virus infections referred for liver transplantation. *Liver Transpl*. 2006;12:801-807.
73. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. US Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). *MMWR Recomm Rep*. 1999;48(RR-10):1-59, 61-56.
74. Palefsky JH, Holly EA, Efirde JT, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. *AIDS*. 2005;19:1407-1414.
75. Roland ME, Stock PG. Comprehensive guidelines translate research findings into clinical policy for HIV-infected transplant candidates and recipients [in Spanish]. *Enferm Infecc Microbiol Clin*. 2005;23:331-334.
76. Tien PC. Management and treatment of hepatitis C virus infection in HIV-infected adults: recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office. *Am J Gastroenterol*. 2005;100:2338-2354.
77. Miro JM T-CJ, Moreno A, Tuset M, et al; HIV SOT Working Group. GESIDA/GESITRA-SEIMC, SPNS and ONT consensus document on solid organ transplant (SOT) in HIV-infected patient in Spain 2005 [in Spanish]. *Enferm Infecc Microbiol Clin*. 2005;23:353-362.
78. O'Grady J, Taylor C, Brook G. Guidelines for liver transplantation in patients with HIV infection (2005). *HIV Med*. 2005;6(suppl 2):149-153.

### Evidence-Based Medicine

Frassetto L, Baluom M, Jacobsen W, et al. Cyclosporine pharmacokinetics and dosing modifications in human immunodeficiency virus-infected liver and kidney transplant recipients. *Transplantation*. 2005;80:13-17.

Stock PG, Roland ME, Carlson L, et al. Kidney and liver transplantation in human immunodeficiency virus-infected patients: a pilot safety and efficacy study. *Transplantation*. 2003;76:370-375.

### Management Guidelines

Roland ME, Stock PG. Liver transplantation in HIV-infected recipients. *Semin Liver Dis*. 2006;26:273-284.

Roland ME, Stock PG. Solid organ transplantation is a reality for patients with HIV infection. *Curr HIV/AIDS Rep*. 2006;3:132-138.



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