

Liver Transplantation in HIV-Infected Recipients

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ABSTRACT

Although human immunodeficiency virus (HIV)-infected patients are living longer and dying less often from complications related to acquired immunodeficiency syndrome (AIDS), they are experiencing significant morbidity and mortality related to end-stage liver disease. Advances in the management of HIV disease have made it difficult to continue denying transplantation to this population based upon futility arguments alone. Patient and graft survival rates in HIV-infected study subjects appear similar to those in large transplant databases. There are no reports suggesting significant HIV disease progression. There are substantial interactions between immunosuppressants and antiretroviral drugs that require careful monitoring and dose adjustment. The evaluation and management of HIV-infected transplant candidates and recipients require excellent communication among a multidisciplinary team and the primary HIV care provider. It is critical that HIV clinicians and hepatologists are aware that liver transplantation is an option for HIV-infected patients at many transplant centers as delays in referral result in unnecessary mortality during the pretransplantation evaluation process.

KEYWORDS: Transplantation, human immunodeficiency virus, hepatitis, end-stage liver disease

Although human immunodeficiency virus (HIV)-infected patients are living longer and dying less frequently from complications related to acquired immunodeficiency syndrome (AIDS), they are experiencing significant morbidity and mortality related to end-stage liver disease.¹⁻¹⁸ Prior to the advent of highly active antiretroviral therapy (HAART), HIV-infected patients were usually not considered reasonable transplant candidates because of the poor prognosis of their underlying disease and logical concerns regarding the potential detrimental effects of immunosuppression on viral control and immune status. However, with the significant HAART-associated improvements in morbidity and mortality, increasing numbers of HIV-infected patients with end-stage liver disease are potential candidates for transplantation.¹⁹⁻²¹ The advances in

HIV management have made it difficult to continue denying solid organ transplantation to this population based upon futility arguments alone.²²⁻²⁴ However, concerns that post-transplantation immunosuppression may result in accelerated progression of HIV disease have prevented the majority of transplant centers from offering solid organ transplantation. This question and others are being evaluated in an ongoing National Institutes of Health (NIH)-sponsored study at 20 transplant centers in the United States.

THE NEED: VIRAL HEPATITIS IN HIV-INFECTED PATIENTS

Because of shared transmission modes, HIV-infected patients are at significant risk for acquiring hepatitis C

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(HCV) and B (HBV) virus infections. The prevalence of HCV among HIV-infected patients is estimated to be between 23 and 33%.²⁵⁻²⁷ Up to 240,000 people are estimated to be coinfecting with HCV and HIV.²⁵⁻²⁷ The prevalence of chronic HBV infection is about 9% in HIV-infected patients in the United States.²⁵⁻²⁷

The risk of developing end-stage liver disease from viral hepatitis is higher for HIV-infected compared with HIV-uninfected patients.¹⁻¹⁸ End-stage liver disease progression may be complicated by HIV infection itself, antiretroviral toxicity, immune restoration-induced hepatitis, or the development of lamivudine-resistant HBV.²⁸⁻⁴⁰ In the case of accelerated viral hepatitis disease progression, distinguishing between immune reconstitution effects and direct hepatotoxicity from antiretroviral therapy can be challenging.^{33,34,36} Hepatocellular carcinoma also appears to be more aggressive and pretransplantation mortality higher in HIV-infected patients.^{3,6,16}

As AIDS-related mortality declines, mortality secondary to end-stage liver disease, non-AIDS-associated infections and malignancy, chronic obstructive pulmonary disease, and coronary artery disease have increased in several cohorts in the United States.^{10,11} In a French study, 28% of non-AIDS-related deaths were attributed to end-stage liver disease.⁴ A Spanish group reported that 16% of hospital admissions and 45% of in-hospital deaths were attributed to end-stage liver disease.² In a recent analysis of a large prospective European cohort with more than 50,000 person-years of follow-up, the death rate from end-stage liver disease, adjusted for CD4 + T cell count, increased by 13% per year since the introduction of HAART.⁵

NONVIRAL LIVER DISEASE IN HIV

Current antiretroviral treatment generally includes two or more nucleoside analogue reverse transcriptase inhibitors in combination with a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor, or both. Nucleoside analogue toxicity, regardless of viral hepatitis infection status, can cause fulminant hepatic failure with lactic acidosis and massive hepatic steatosis, although this is rare.^{35,37,38} The nonnucleoside analogue agents, particularly nevirapine, can also cause significant hepatotoxicity and even death. The risk of the immune-mediated variant of nevirapine toxicity is higher in women, during pregnancy, and in persons with relatively high CD4 + T cell counts.^{39,41-43} All the protease inhibitors can be hepatotoxic. The overall impact of HAART on mortality due to end-stage liver disease is not clear. In some studies, HAART is associated with reductions in liver-related mortality.¹³ In the large European cohort described previously, each year of exposure to HAART was associated with a 12% increase in the liver-related death rate.⁵

THE OPPORTUNITIES: IMMUNOSUPPRESSANT THERAPY IN HIV

One logical concern that has limited transplantation in people with HIV infection is that immunosuppressive agents may exacerbate the already immunocompromised state. Intriguingly, immunosuppressive agents may actually be useful in the treatment of HIV infection through antiviral, immune-modulating, coreceptor down-regulation, or pharmacokinetic mechanisms.⁴⁴⁻⁵⁹ Cyclosporine has several different antiviral properties, including a direct effect on viral replication by binding to cyclophilin A. Cyclophilin A, the binding target of cyclosporine, is known to modulate HIV-1 infectivity by forming a complex with the HIV gag protein. The interference with this interaction can inhibit the nuclear import of HIV-1 DNA in activated T cells. Cyclosporine may also indirectly suppress viral replication by inhibiting interleukin 2 (IL-2)-dependent CD4 + T cell activation and proliferation, resulting in improved CD4 + T cell number function and clinical outcomes.^{45-49,51,56,60} In a retrospective review from the pre-HAART era, HIV-infected transplant recipients using cyclosporine progressed to AIDS at the same frequency as HIV-infected patients who did not receive a transplant or immunosuppression. However, the transplant recipients who did not receive cyclosporine progressed to AIDS more quickly than the nontransplanted HIV-positive cohort.⁶⁰ In a randomized controlled treatment trial, low-dose cyclosporine in HIV-infected subjects failed to cause a significant increase in CD4 + T cells.⁵⁶ However, subjects who received protease inhibitor-containing HAART and cyclosporine immediately after diagnosis of acute HIV infection achieved a larger rise in CD4 + T cells than control subjects who received HAART alone.⁴⁹ Because protease inhibitors increase cyclosporine levels, these subjects achieved trough levels similar to those used in the transplant setting. Thus, "typical" cyclosporine levels may be required to produce beneficial immunologic effects in HIV-infected patients.

Mycophenolate mofetil, an antiproliferative immunosuppressant commonly used following solid organ transplantation, has also been examined for use in the treatment of HIV infection. Mycophenolate mofetil is hydrolyzed to form mycophenolic acid, a potent inhibitor of inosine monophosphate dehydrogenase, an enzyme involved in the synthesis of deoxyguanosine triphosphate (dGTP). In *in vitro* studies, mycophenolic acid synergistically increased the antiretroviral effect of the nucleoside analogues abacavir, didanosine, and tenofovir and was associated with reductions in immune activation markers.^{52,54,55,57,59,61} It is hypothesized that reduction in intracellular dGTP concentrations increases the antiretroviral activity of guanosine analogues such as abacavir. Antagonism, probably due to inhibition of thymidine kinase, was observed with

mycophenolic acid plus the thymidine analogues zidovudine and stavudine.

Rapamycin, a potent target of rapamycin (TOR) inhibitor that blocks the effect of IL-2 on the cell cycle, is a more recent addition to the immunosuppressive armamentarium that also reduces CCR5 expression on CD4 + T cells. The CCR5 receptor on CD4 + T cells is one of the two coreceptors utilized by HIV to enter cells, and its down-regulation could theoretically curtail HIV entry into the T lymphocyte.⁵⁸ Rapamycin also inhibits vascular endothelial growth factor and has proved to be highly effective in the treatment of Kaposi's sarcoma (KS).⁶² For HIV-positive transplant recipients who have a history of KS or develop KS following transplantation, rapamycin may control the alloimmune response and at the same time curtail KS.

TRANSPLANTATION OUTCOMES IN HIV-INFECTED RECIPIENTS

Many HIV-infected patients received transplants prior to the HAART era, although most were not known to be HIV infected at the time of transplantation or acquired HIV infection in the peritransplantation period. Some transplant centers reported good outcomes following transplantation in HIV-infected patients at that time; however, other reports have been less favorable.⁶³⁻⁶⁹

Publications in the HAART era describe relatively small numbers of subjects, and subjects from some centers may be included in more than one report. The longest prospective study of HIV-infected liver and kidney transplant recipients in the HAART era was initiated at the University of California, San Francisco (UCSF) in 1999.⁷⁰⁻⁷² We described the initial outcomes of 14 subjects, including 4 liver transplant recipients who were observed for a mean of 380 days.⁷⁰ Prior to transplantation, this group had no history of opportunistic infections, CD4 + T cell counts of more than 100 cells/mL for liver recipients, and undetectable HIV RNA or predicted suppression of HIV RNA with HAART following transplantation. Two liver recipients had HBV infection, and one had fulminant liver failure due to hepatitis A infection. The one HCV-coinfected liver recipient died 445 days after transplantation from complications of recurrent HCV infection. Despite significant drug interactions requiring modifications in immunosuppressant doses, HIV RNA was controlled in subjects who maintained antiretroviral therapy.

This single-center pilot study progressed to a four-center pilot study that enrolled 29 subjects between 1999 and 2003, including the 14 described previously, with follow-up ongoing.⁷³ The early promising results from this pilot trial provided the preliminary data and guided protocol development for a larger NIH-

sponsored 20-center multisite study that began enrollment in 2003 (www.hivtransplant.com).

A multisite analysis of HIV-infected liver transplant recipients led by investigators at the University of Pittsburgh included patients from the UCSF pilot trials,⁷⁰⁻⁷² the University of Miami,⁷⁴ King's College,⁷⁵ the University of Minnesota, and the University of Pittsburgh. Among 24 HIV-infected liver transplant recipients, the cumulative survival at years 1, 2, and 3 (87%, 73%, and 73%) was similar to that of age- and race-matched HIV-negative recipients from the United Network for Organ Sharing (UNOS) database (87%, 82%, and 78%). In a multivariate analysis, death was associated with a post-transplantation CD4 + T cell count of less than 200 or detectable HIV RNA but not with pretransplantation CD4 + T cell count or detectable HIV RNA. Although HCV infection was also associated with poorer survival in this cohort (50% versus 100% in those without HCV; $p = 0.023$), the difference in survival between HCV monoinfected and HCV-HIV-coinfected individuals did not reach statistical significance at the $p < 0.05$ level ($p = 0.058$). The impact of HIV infection on survival in HCV-infected liver transplant recipients is not yet well understood.

Investigators from King's College in London reported in 2001 on the outcomes of five HIV-infected liver transplant recipients.⁷⁵ The three individuals with hepatitis C infection died of complications from recurrent HCV infection at 6 to 25 months after transplantation; the other two patients were doing well at the time of the report. This group subsequently updated their series in 2004, reporting on 14 recipients (9 in addition to the prior report), 7 of whom had hepatitis C infection.⁷⁶ Five of these patients died, four from HCV-associated complications, a median of 161 days after transplantation. All the patients with hepatitis B infection were doing well, with no recurrence of hepatitis B. These authors concluded that "longer follow-up in larger series is required before a conclusive directive can be provided for HCV-HIV-coinfected patients requiring liver transplantation."

Additional reports include four cases each from Madrid and Barcelona, Spain; five cases from Essen, Germany; seven cases from Bonn, Germany; and one case from The Netherlands.⁷⁷⁻⁸¹ Among these 21 patients, 14 were infected with HCV, 5 with HBV, and 2 with both HCV and HBV. There were five reported deaths; two resulted from recurrent HCV, one from hepatic artery thrombosis with intra-abdominal abscesses and sepsis, one from chemotherapy induced liver damage (Hodgkin's disease), and one from an intrathoracic hemorrhage following the placement of a thoracic drain. Three rejection episodes that were successfully treated were described. A single opportunistic complication, a case of KS and multicentric Castleman's disease, was in complete remission at 31 months after

transplantation. There were no reports of HIV or HBV virologic breakthrough.

The King's College group more fully described a previously reported case of fatal HAART-induced hepatotoxicity, and a French group described a case requiring retransplantation because of HAART-induced drug toxicity.^{82,83} Both of these patients were using antiretroviral combinations, specifically didanosine and stavudine, that are no longer commonly used because of the known increased potential for lactic acidosis and massive hepatic steatosis.⁸⁴⁻⁸⁶ The patient who was retransplanted has done well for 4 years on a new antiretroviral regimen. On a more optimistic note, the group from Madrid described an uneventful pregnancy in an HIV-infected liver transplant recipient.⁸⁷

ONGOING CLINICAL STUDIES

The primary aim of an ongoing prospective, multicenter cohort study of HIV-infected patients who undergo kidney or liver transplantation is to evaluate the safety and efficacy of solid organ transplantation in people with HIV disease. The long-range goals are (1) to provide patients and clinicians with information regarding the HIV-specific risks of transplantation, (2) to provide clinicians with information necessary to manage immunosuppressive and antiretroviral medications together, and (3) to understand underlying basic science mechanisms that explain patients' outcomes so that clinical management may be adjusted to maximize these outcomes. This NIH-sponsored study plans to enroll 125 liver and 150 kidney transplant recipients at 20 transplant centers (www.HIVTransplant.com).

KEY PRETRANSPLANTATION SELECTION AND EVALUATION ISSUES

Selection criteria for clinical studies of solid organ transplantation in HIV-infected patients have evolved since these studies started in the late 1990s. The general principle has been to offer transplantation to individuals with a relatively intact immune system and controllable HIV viremia. The following HIV-specific criteria for transplantation are recommended, recognizing that these criteria are likely to evolve with increasing knowledge of HIV treatment and HIV management in the context of transplantation (Table 1). First, CD4 + T cell counts should be greater than or equal to 100 cells/mL prior to transplantation for patients who have never had an AIDS-related opportunistic infection and greater than 200 cells/mL for those with such a history. Unfortunately, many patients experience an acute decline in their CD4 + T cell count in the days and weeks prior to transplantation; thus, it is reasonable to limit this requirement to some point in the 3 to 4 months prior to transplantation. In addition, the use of interferon to treat

HCV causes a transient decline in CD4 + T cell count. This should be taken into account when determining the appropriate time frame for the CD4 + T cell criteria (i.e., it may be reasonable to require this level only prior to initiation of HCV therapy). Acceptable CD4 + T cell counts or percentages in children need to be adjusted on the basis of age (Table 1).

Second, the HIV RNA should be undetectable in those receiving HAART. For patients who are unable to tolerate or have recently initiated HAART, an experienced HIV clinician should confidently predict full suppression after HAART is initiated. This prediction is based upon review of the antiretroviral treatment history, HIV RNA history, and available antiretroviral resistance tests. A substantial number of patients with HIV infection have multidrug-resistant HIV with detectable HIV RNA but relatively high CD4 + T cells. Although most studies and programs would exclude such patients from transplantation, they may actually do well and it is not unreasonable to consider them on a case-by-case basis.

The third HIV-specific selection criterion addresses the patient's history of AIDS-related opportunistic infections and cancers. All opportunistic infections and cancers must be completely treated prior to transplantation. Diseases for which there is no reliable therapy should they recur after transplantation remain an exclusion criterion. At this time, such infections include progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, and multidrug-resistant systemic fungal infections. We also exclude patients with a history of AIDS-associated primary central nervous system lymphoma. Most current clinical trials include individuals with a history of resolved cutaneous KS. Patients with this history require a recent high-resolution chest computed tomography scan without evidence of pulmonary KS.

KEY POST-TRANSPLANTATION MANAGEMENT ISSUES

Drug Interactions

Most transplant centers use triple immunosuppressant therapy with combinations of a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative agent (mycophenolate mofetil or sirolimus), and prednisone. Some centers have elected to use immunosuppression that has also been found to have anti-HIV qualities as described previously. However, there are substantial interactions between the calcineurin inhibitors, TOR inhibitors (sirolimus), and antiretroviral protease inhibitors related to cytochrome p4503A metabolism.⁸⁸⁻⁹¹ Initial immunosuppressant dosages are substantially lower in patients taking protease inhibitors, and these dosages must be further reduced over time. There are also interactions between these immunosuppressive

Table 1 Key Selection Criteria for HIV-Infected Liver Transplant Candidates (2006)

Issue	Criteria	Comments
CD4 + T cell count	Patients > 10 years old: ≥ 100/mL or ≥ 200/mL if there is a history of any opportunistic complication	Children: 1–2 years: CD4% ≥ 30 2–10 years: CD4% ≥ 20%
HIV-1 RNA	On HAART: undetectable using an ultrasensitive assay Not on HAART or recently started or reinitiated HAART: may have detectable viral load, if an HIV clinician confidently predicts HIV suppression after transplantation	
Opportunistic complications allowed	Received appropriate acute and maintenance therapy with no evidence of active disease: <ul style="list-style-type: none"> • Candidiasis of bronchi, trachea, lungs, or esophagus • Cytomegalovirus disease 	No active disease on ophthalmologic examination (intraocular implant does not imply active disease)
	<ul style="list-style-type: none"> • Herpes simplex: chronic ulcer(s) (greater than 1 month); or bronchitis, pneumonitis, or esophagitis • Isosporiasis, chronic intestinal (greater than 1 month) • Lymphocytic interstitial pneumonitis • <i>Mycobacterium avium</i> complex, disseminated or extrapulmonary • <i>Mycobacterium tuberculosis</i>, any site • <i>Mycobacterium kansasii</i>, any site • <i>Mycobacterium</i>, other species, disseminated or extrapulmonary • <i>Pneumocystis carinii</i> pneumonia • Pneumonia, recurrent • Recurrent bacterial infections • Salmonella septicemia, recurrent • Cryptococcosis, extrapulmonary • Encephalopathy, HIV-related 	Negative serum CRAG Resolved on HAART with marked improvement in mental status Must be on secondary prophylaxis regardless of CD4 count (modify if the USPHS/IDSA guidelines change ¹⁰⁰)
	<ul style="list-style-type: none"> • Histoplasmosis, disseminated or extrapulmonary • Kaposi's sarcoma (cutaneous) 	No active/vascular residual cutaneous lesions on examination and negative chest CT scan MRI without active disease
Opportunistic complications excluded	<ul style="list-style-type: none"> • Toxoplasmosis, CNS • Progressive multifocal leukoencephalopathy (PML) • Chronic intestinal cryptosporidiosis (> 1 month) • Lymphoma (brain) • Documented multidrug-resistant fungal infection not expected to respond to available oral antifungal agents (<i>krussii</i>, <i>glabrata</i>, <i>candida</i>) 	
Neoplasms	Allowed: <ul style="list-style-type: none"> • In situ anogenital carcinoma • Adequately treated basal or squamous cell carcinoma of the skin • Solid tumors treated with curative therapy and disease free for more than 5 years 	

CNS, central nervous system; CRAG, cryptococcal antigen; CT, computed tomography; HAART, highly active antiretroviral therapy; IDSA, Infectious Disease Society of America; MRI, magnetic resonance imaging; USPHS, U.S. Public Health Service.

agents and the nonnucleoside reverse transcriptase inhibitors, although these are less profound.⁹⁰ Efavirenz is a P4503A inducer; thus, immunosuppressant dosages must be increased when used with efavirenz. When both a protease inhibitor and a nonnucleoside reverse transcriptase inhibitor are used, immunosuppressant dosages are similar to those used with protease inhibitors alone. Typical initial and maintenance immunosuppressant dosing guidelines are available.⁹⁰ Care must be taken when considering antibiotics, antifungals, and other agents that are metabolized by the hepatic P450 system.

There are no reports describing the impact of immunosuppressants on antiretroviral drug levels. Fortunately, the cohort and retrospective studies described earlier report continued HIV RNA suppression despite immunosuppression, implying that adequate HAART drug levels are maintained after transplantation. Some centers try to use specific antiretroviral regimens, for example, avoiding protease inhibitors or using nucleoside-only regimens. However, it is often best to continue the antiretroviral regimen that makes most sense from an HIV suppression perspective with the following caveats: (1) atazanavir should be avoided when proton pump inhibitors will be used and it should be used with caution in combination with other antacids and (2) the additive myelotoxicity of zidovudine and the post-transplantation 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.^{52,54,55,57,59,61}

HBV Management

Lamivudine and emtricitabine are cytosine analogues with activity against HIV and HBV. In HIV-negative patients, lamivudine-resistant HBV can develop within 6 months and is seen in 50% of patients after 3 years of therapy. Fortunately, lamivudine-resistant HBV is sensitive to other nucleotide analogues, including adefovir dipivoxil and tenofovir.⁹²⁻⁹⁴ Lamivudine has been used in the treatment of HIV infection since the early 1990s; emtricitabine was introduced more recently. Liver and kidney transplant recipients coinfecting with HIV and HBV may be at increased risk for recurrent or progressive HBV infection after transplantation because of preexisting lamivudine-resistant HBV.⁹⁵⁻⁹⁷ Fortunately, all published reports describing HBV-HIV-coinfecting patients report ongoing suppression of HBV in the post-transplantation period.⁹⁸

The peritransplantation management of HBV in the HIV-coinfecting patient is complicated by the need to manage both infections effectively with antiviral agents while avoiding the development of HIV resistance by using incompletely suppressive anti-HIV regimens. It is preferable to defer the reinitiation of

HAART until the patient is able to take orals reliably and is unlikely to be fasting for procedures. The development of HIV resistance is most likely when antiretroviral doses are missed or delayed; thus, it is essential to avoid missed doses. Deferring HAART for days to weeks does not appear to have any adverse consequences. In the context of HBV coinfection, however, it is also critical to start HBV antiviral therapy as soon as possible. Thus, in the peritransplantation and early post-transplantation period, lamivudine, adefovir, or tenofovir or a combination should be continued if prescribed before transplantation, with appropriate dose adjustments for renal insufficiency. If the patient is unable to start HAART after transplantation because of an inability to take oral medications consistently, HBV antiviral medications should be held until the patient is able to start HAART. If the pre-transplantation HBV DNA titer was greater than 10,000, adefovir or entecavir or both may be started without HAART. The risk of developing HIV resistance associated with adefovir is very low and is warranted in this situation with a high likelihood of HBV recurrence in the absence of therapy. Likewise, entecavir does not have anti-HIV properties. Lamivudine and tenofovir should not be used without the entire HAART regimen.

Hepatitis B immune globulin (HBIG) remains critical to control viral recurrence after transplantation and is used as follows: (1) 10,000 IU during the anhepatic phase and on admission to the intensive care unit; (2) 5000 IU every 6 hours on days 1 and 2 after transplantation (if the hepatitis B surface antigen [HBsAg] is positive on day 2, use 10,000 IU every 12 hours until it becomes negative); (3) 10,000 IU daily for days 3 to 7 after transplantation; (4) 10,000 IU monthly for first 3 months; (5) 5000 IU for the next 3 months; and (6) 2500 IU (intramuscularly or IV) monthly thereafter, indefinitely. If the patient had detectable HBV DNA before liver transplantation and HBV antivirals are being held, HBsAg should be checked daily, and HBIG 5000 IU every 6 hours should be continued until HBsAg is negative. Once the HBsAg is negative, the dose is decreased to 10,000 IU daily for 7 more days of treatment.

HCV Management

There are no data available to suggest that HCV RNA clearance rates are higher when antiviral therapy is started preemptively after transplantation as opposed to waiting until recurrent HCV disease is documented. In addition, reserving HCV therapy for those with documented recurrence avoids drug interactions and additive toxicity with HAART and immunosuppression, especially in the early post-transplantation period. Thus, as with the strategy used in HIV-negative, HCV-positive recipients, the current recommendations are that HCV treatment not be initiated preemptively after transplantation. Rather, HCV treatment should be

Table 2 HIV-Specific Opportunistic Infection Prophylaxis

Condition	Primary Prophylaxis*	Secondary Prophylaxis [†]
<i>Pneumocystis carinii</i> pneumonia (PCP)	Indicated for life; initiate immediately after transplantation	Indicated for life; initiate immediately after transplantation
Toxoplasmosis	Toxoplasmosis IgG-positive patients with CD4 + T cell count \leq 200	CD4 cell count below 200 cells/mL; discontinue when CD4 + T cell count is above 200 cells/mL for 3–6 months [‡]
<i>Mycobacterium avium</i> complex (MAC)	Indicated when CD4 + T cell count \leq 50–75; discontinue when the CD4 count is above 100 cells/mL for 3–6 months	CD4 cell count below 50–75 cells/mL; discontinue when CD4 + T cell count is above 100 cells/mL for 3–6 months [‡]
Cytomegalovirus (CMV)	No HIV-specific indication	CD4 cell count below 75–100 cells/mL; discontinue when CD4 + T cell count is above 100–200 cells/mL for 3–6 months [‡]
Cryptococcosis, extrapulmonary	No HIV-specific indication	CD4 cell count below 200 cells/mL; discontinued when CD4 + T cell count is above 200 cells/mL for 3–6 months [‡]
Histoplasmosis	No HIV-specific indication	Continue regardless of CD4 + T cell count (this criterion should be modified if/when the DHHS guidelines are modified)

*No history of the infection.

[†]Prior history of the infection.

[‡]Secondary prophylaxis should also be reinstated immediately after transplantation for 1 month and during the treatment of acute rejection for 1 month following completion of acute rejection therapy. If the CD4 + T cell count is suppressed, continuation should be guided by the CD4 + T cell count.

DHHS, Department of Health and Human Services.

initiated after transplantation when there is liver biopsy documentation of recurrent HCV infection and disease is severe or progressive. A histologic activity index score greater than 8 or fibrosis stage higher than 2 or both are considered indications for treatment by most transplant physicians.⁹⁹ The use of interferon and ribavirin adds another level of complexity, and adjunctive therapy with growth factors and antidepressants are usually required.

HIV-Specific Opportunistic Infection Prophylaxis

In addition to standard post-transplantation prophylaxis, the following HIV-specific prophylactic strategies are recommended (Table 2). First, *Pneumocystis carinii* pneumonia (PCP) prophylaxis should continue for life regardless of CD4 + T cell count. A glucose-6-phosphate dehydrogenase (G6PD) level should be documented prior to transplantation in case the patient is intolerant of trimethoprim-sulfamethoxazole. Dapsone is contraindicated in G6PD-deficient individuals. Atovaquone is another option for PCP prophylaxis.

HIV-infected patients with a CD4 + T cell count below 50 to 75 cells/mL are at risk for developing disseminated *Mycobacterium avium* complex.¹⁰⁰ They should receive macrolide prophylaxis with weekly azithromycin, which has less potent drug interaction potential than daily clarithromycin. Patients with CD4 + T cell counts below 50 cells/mL are also at risk for cytomegalovirus retinitis and should have biannual ophthalmologic examinations; in the case of new visual

changes, such patients should have an urgent dilated funduscopic examination within 1 to 2 days.

The risk of developing active tuberculosis in the context of HIV infection is about 10% per year in those with a positive purified protein derivative (PPD). HIV-infected patients should have PPD screening every 6 months; those with a positive PPD should receive 9 months of treatment. Treatment can be initiated before transplantation and completed after transplantation. Patients should also be screened for syphilis. Central nervous system syphilis should be considered in patients with a positive untreated syphilis test of unknown duration.

Patients with a prior history of opportunistic infection need to receive secondary prophylaxis in certain circumstances. With HAART-induced immune restoration it is safe to discontinue secondary prophylaxis (also known as chronic maintenance therapy) when the CD4 + T cell count shows a sustained increase above the level at which people are at risk for developing the infection.¹⁰⁰ Such secondary prophylaxis must be reinitiated when the CD4 + T cell count drops below the specific level and continued for several months after increasing above that level. Secondary prophylaxis should be reinitiated in the immediate post-transplantation period and in the case of treatment for acute rejection.

HIV-Specific Health Care Maintenance

Women with HIV are at elevated risk for developing cervical cancer and should receive cervical Pap smear or colposcopy screening at least every 6 to 12 months. Men

and women are at risk for HPV-associated anal cancers; the impact of post-transplantation immunosuppression on these lesions is unknown and is currently under investigation.¹⁰¹⁻¹⁰³ Anal Pap smears and colposcopy examinations with biopsies should be performed when available.

Prior to transplantation, patients should be vaccinated with polyvalent pneumococcal vaccine (Pneumovax) and hepatitis A and B vaccines (if not immune). There is no consensus about influenza vaccination in the context of transplantation, although it is recommended in HIV-infected patients. Adult patients should *not* be vaccinated against varicella, but patients exposed who are immunoglobulin G (IgG) (–) should receive varicella-zoster immune globulin. Household contacts should not receive oral polio vaccine and, in most cases, should not receive smallpox inoculation.

Children should be vaccinated with all vaccines, except some live vaccines, as early in life as possible following the routine schedule. Vaccines that can be used include diphtheria, tetanus toxoids, and pertussis (DTP); *Haemophilus influenzae* type B (HiB); hepatitis A and B; inactivated polio vaccine; pneumococcal vaccine; and influenza. Live vaccines (measles-mumps-rubella [MMR], varicella) should be administered only before transplantation and should not be administered 6 weeks or less before transplantation. HIV-infected children who are eligible for transplantation can be immunized with MMR and live varicella vaccine (Varivax).

ETHICS AND POLICY

Several authors have outlined the ethical arguments for providing the opportunity to be considered for transplantation to patients with HIV infection.^{22-24,104} Absent poor outcome data, it is difficult to rationalize denying transplantation to selected individuals based upon HIV infection status alone. Third-party payers are increasingly developing internal reimbursement criteria or being compelled by legislation or administrative law decisions to provide reimbursement for this evaluation, care, and treatment.

UNOS policy does not consider HIV infection to be a contraindication for transplantation. The United States Veterans Affairs Administration has recently revised its policy to allow transplantation for HIV-infected patients.¹⁰⁵ Both Spain and the United Kingdom have published policies and guidelines for liver transplantation in HIV-infected patients.^{106,107}

CONCLUSIONS

The need for liver transplantation in HIV-infected individuals is significant and is likely to grow with ongoing improvements in HIV management and the aging of the HIV-infected population. Rapidly evolving

preliminary data in the HAART era suggest that transplantation is safe from the perspective of HIV disease progression, with few opportunistic infections, stable CD4 + T cell counts, and ongoing suppression of HIV RNA with antiretroviral therapy. Patient and graft survival rates similar to those of the general transplant population suggest that this intervention is also effective. Patients with lamivudine-resistant hepatitis B infection are reported to be doing well with the use of newer antivirals and HBIg. As in the HIV-uninfected population, hepatitis C-coinfected patients appear to have variable outcomes. Ongoing studies are aimed at identifying factors associated with both good and poor outcomes in this important population. International guidelines and policies, as well as third-party payer policies in the United States, are increasingly supporting solid organ transplantation in this population. The evaluation and management of HIV-infected transplant candidates and recipients require excellent communication among a multidisciplinary team of health care providers, the primary HIV care provider, and the patients. It is critical that HIV clinicians, hepatologists, and patients are aware that liver transplantation is an option for HIV-infected patients at many transplant centers, as delays in referral result in unnecessary mortality during the pretransplantation evaluation process.^{6,16}

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ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
dGTP	deoxyguanosine triphosphate
G6PD	glucose-6-phosphate dehydrogenase
HAART	highly active antiretroviral therapy
HBIg	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IgG	immunoglobulin G
IL-2	interleukin 2
KS	Kaposi's sarcoma
MMR	measles-mumps-rubella
NIH	National Institutes of Health
PCP	<i>Pneumocystis carinii</i> pneumonia
PPD	purified protein derivative
TOR	target of rapamycin
UCSF	University of California, San Francisco
UNOS	United Network for Organ Sharing

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