Title
Solid organ transplants in HIV-infected patients.

Authors
Harbell, Jack
Terrault, Norah A
Stock, Peter

Solid Organ Transplants in HIV-infected Patients

Jack Harbell, M.D.[1], **Norah A. Terrault, M.D., M.P.H.**[1,2], and **Peter Stock, M.D., Ph.D.**[1]

[1]Department of Surgery, University of California San Francisco, San Francisco, CA

[2]Department of Medicine, University of California San Francisco, San Francisco, CA

Abstract

There is a growing need for kidney and liver transplants in persons living with HIV. Fortunately, with the significant advances in antiretroviral therapy and management of opportunistic infections, HIV infection is no longer an absolute contraindication for solid organ transplantation. Data from several large prospective multi-center cohort studies have shown that solid organ transplantation in carefully selected HIV-infected individuals is safe. However, significant challenges have been identified including prevention of acute rejection, management of drug-drug interactions and treatment of recurrent viral hepatitis. This article reviews the selection criteria, outcomes, and special management considerations for HIV-infected patients undergoing liver or kidney transplantation.

Keywords

Liver transplantation; kidney transplantation; HIV; AIDS; liver failure; renal failure; hepatitis B; hepatitis C; immune suppression; opportunistic infection; graft survival; patient survival; selection criteria; antiretroviral therapy; CD4+ T-cell count

Introduction

With advances in therapy for HIV infection, survival of HIV-infected patients has increased substantially. This increased survival has led to a greater need for treating chronic conditions such as liver and kidney failure. Historically, fears that the chronic immunosuppressed state of patients suffering from HIV/AIDS would lead to increased morbidity and mortality following solid organ transplantation resulted in HIV-infection being considered a contraindication for organ transplantation [1]. Recently, advances in knowledge of outcomes

Address correspondence to: Peter G. Stock, M.D., Ph.D., University of California San Francisco, Department of Surgery, 505 Parnassus Avenue, M884, San Francisco, CA 94143, (415) 353-8617, peter.stock@ucsfmedctr.org.
Jack Harbell, M.D., University of California San Francisco, Department of Surgery, 513 Parnassus Ave., Room S321, San Francisco, CA 94143, 415-476-1239, jack.harbell@ucsfmedctr.org
Norah Terrault, M.D., M.P.H., University of California San Francisco, Division of Gastroenterology, 513 Parnassus Avenue, Room S-357, San Francisco, CA 94143-0358, Phone: (415) 476-2227, 415-476-0659, norah.terrault@ucsf.edu

associated with this patient population have changed this philosophy, and HIV-infection is now no longer considered a contraindication for liver or kidney transplantation.

This changed view of the transplant community was precipitated by several factors. The dramatic advancements in the treatment of HIV infection over the past 3 decades resulted in improved survival of patients with HIV infection [2], which has made HIV infection a manageable chronic disease rather than frequently fatal condition. Because patients with HIV are living longer, there is now an increasing proportion of HIV-infected patients with advanced liver and kidney disease that could benefit from transplantation [2–4]. The etiology of liver disease among HIV-infected individuals is mainly due to complications related to hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, which have similar modes of transmission as HIV, and has led to the emergence of liver disease as a major cause of mortality among HIV-infected patients [5–7]. An increase in the demand for kidney transplantation has also occurred among HIV-infected individuals due to the emergence of renal failure from complications associated with HIV infection, such as HIV-associated nephropathy (HIVAN), immunoglobulin (Ig) A nephropathy, and glomerulonephritis as a result of HIV co-infection with HBV and HCV [8–11].

Data supporting acceptable outcomes among HIV-infected solid organ transplant recipients initially came from single patient experiences or case series at single institutions [12, 13]. Subsequently, retrospective and prospective studies involving multiple centers provided more robust data [14–17], and led to improvements in the way HIV-infected patients are selected for and treated after transplantation. These studies also provided key insights into the management of antiretroviral agents, immunosuppressive regimens, and surgical complications in these patients post-transplant.

This review will summarize the eligibility criteria for HIV-infected liver or kidney transplant candidates, as well as the latest outcomes in liver and kidney transplantation in the era of highly active antiretroviral therapy (HAART). We will then focus in greater detail on the medical management of the HIV-infected patient post transplantation.

Selection Criteria

Due to the accumulation of data supporting the safety and efficacy of solid organ transplantation in HIV-infected patients, the eligibility criteria have continued to evolve (Table 1). Current selection criteria include minimum CD4+ T-cell counts (>200 cells/mm^3 for kidney, >100 cells/mm^3 for liver), suppressed or expected suppression of HIV RNA, stable antiretroviral regimen, no active opportunistic infections or neoplasms, and no history of chronic cryptosporidiosis, primary CNS neoplasm or progressive multifocal leukoencephalopathy [15–19]. The criteria regarding opportunitic infections have been liberalized over time as more data have become available regarding outcomes in HIV-infected transplant recipients. For example, a history of any opportunistic infection is no longer an absolute contraindication to transplantation [19]. However, a history of infection for which there is no definitive post-transplantation therapy, such as multifocal leukoencephalopathy, chronic cryptosporidiosis, primary central nervous system lymphoma, and drug resistant fungal infections remain a contraindication to transplantation.

There have been additional refinements in the criteria for selecting HCV/HIV co-infected patients for liver transplantation that have come from observations in long-term outcomes in this population. Lower patient and graft survival was observed in patients with a BMI less than 21 kg/m^2, and who needed a concomitant kidney transplant [15], suggesting that patients who are more debilitated and who have concomitant renal failure requiring combined liver-kidney transplant may be less ideal candidates.

Another selection criterion that continues to evolve is the absolute CD4+ T-cell count prior to transplantation. Most centers now require a CD4+ T-cell count of >200 cells/mm^3 in HIV-infected kidney transplant recipients any time in the 16 weeks prior to transplantation [19]. For liver transplantation, a CD4+ T-cell count of >100 cells/mm^3 is required, except in patients with a history of opportunistic infection or malignancy where >200 cells/mm^3 is required. The lower number of CD4+ T-cells acceptable in liver transplant recipients is to account for presumed splenic sequestration due to portal hypertension. In children, the percentage of CD4+ T-cells is more important than the absolute number, and should be >30% in patients 1–2 years of age and >20% in patients 2–10 years of age [19].

Finally, HIV RNA levels remain an important consideration in HIV-infected solid organ transplant recipients. Most centers require HIV RNA levels to be undetectable based on the level checked in the 16 weeks prior to transplant [19]. One exception to this is in liver transplant candidates who are not able to tolerate HAART because of drug-associated hepatotoxicity. In this case, HIV-infected patients can be considered for transplantation if viral suppression could be confidently predicted to occur post-transplantation with available antiretroviral therapies.

Outcomes

Kidney Transplantation

Several studies demonstrate excellent outcomes among HIV-infected kidney transplant recipients [16–18, 20–23]. The largest series, published in 2010, was a prospective, non-randomized trial that reported outcomes in 150 HIV-infected kidney transplant recipients [17]. In this study with a median follow-up of 1.7 years, 1 and 3 year patient survival was 95% and 88%, and allograft survival 90% and 74% respectively. The patient survival of HIV-infected recipients in this study was similar to that observed in HIV-uninfected recipients older than 65 years of age during the same time period, as reported by the US Scientific Registry of Transplant Recipients (SRTR). Selection criteria for patients in this trial included pre-transplant CD4+ T-cell counts of at least 200 per cubic millimeter and undetectable plasma HIV type 1 (HIV-1) RNA levels while being treated with a stable antiretroviral regimen.

Rejection rates have been observed to be 2–3 times higher in HIV-infected kidney transplant recipients than HIV-uninfected recipients. The early experience with renal transplantation in HIV-infected patients included no induction immune suppression, and maintenance therapy with cyclosporine and mycophenolate mofetil (MMF). More than half of these patients developed acute rejection requiring therapy with antilymphocyte globulin [18, 24]. In the US multicenter trial of HIV-infected kidney transplant recipients, the 1 and 3 year rejection rates

were 31% and 41%, compared to a rate of 12% in kidney transplant recipients without HIV infection [17]. However, the higher observed rejection rates did not have a significant impact on overall short-term graft survival as mentioned above.

Liver Transplantation

Survival and Graft Function—in a report from the US Scientific Registry of Transplant Recipients (SRTR) summarizing early experiences with transplantation in HIV-infected recipients since 1996 (i.e. in the era of widespread use of HAART), the 1 year survival for HIV-infected liver transplant recipients varied from 60–100% [18, 25–27]. The series published by Ragni et al. in 2003 [27] included data from investigators at several centers including Pittsburgh, Miami, San Francisco, Minneapolis, and London. The authors compared outcomes in 24 HIV-infected transplant recipients to a cohort of 5225 age and race matched HIV-uninfected recipients from the United Network for Organ Sharing (UNOS), and found there was no significant difference in cumulative survival at 1, 2, and 3 years in the HIV-infected patients (87%, 73%, and 73%) compared to the matched controls (87%, 82%, and 78%). They also found that among the HIV-infected recipients, decreased survival was associated with HCV infection, inability to tolerate HIV medications post-transplant, and CD4+ T cell counts <200 post-transplant. Compared to HIV-uninfected HCV-positive controls, HCV infection was also associated with a higher mortality in HIV-infected patients, but this finding did not reach statistical significance.

In a recent review and meta-analysis of liver transplant outcomes in HIV-infected patients, Cooper et al. [28] analyzed 15 cohort studies and 49 case series with individual patient data. These authors reported 1, 3 and 5 year survival of 85%, 66%, and 64%, respectively. Improved survival was identified in HIV-HBV co-infected recipients compared to HBV uninfected patients. Decreased survival was found in patients with detectable HIV viral load at the time of transplant. Also, HCV infection resulted in worse survival in unadjusted analysis, but did not predict worse survival when adjusted for other confounding variables.

Hepatitis B—Several reports have demonstrated excellent outcomes in HIV-HBV co-infected patients following liver transplantation [14, 29]. The largest series included a prospective cohort of 22 HIV-HBV co-infected patients transplanted between 2001–2007 [14]. The authors compared the outcomes in the 22 HIV-HBV co-infected patients with 20 HBV mono-infected patients on similar HBV prophylaxis, and found that patient and graft survival was similar: 100% versus 85% in HBV mono- versus co-infected patients. In this series, all patients received anti-HBV nucleoside or nucleotide analogues, and hepatitis B immune globulin (HBIG) indefinitely following transplantation with a decrease in dose frequency after 12 months. All patients remained Hepatitis B surface antigen (HBsAg) negative with no clinical evidence of hepatitis B recurrence, with a median follow up of 3.5 years. Low-level HBV viremia was intermittently detected in 7/13 patients, but not associated with HBsAg detection or ALT elevation.

Hepatitis C—In contrast to the data supporting control of the co-pathogen in HIV-HBV infected liver transplant recipients, the outcomes in HIV-HCV infected patients are more variable. In a Spanish prospective multicenter study that included 84 HIV-HCV co-infected

liver transplant recipients that were compared to 252 matched HCV mono-infected recipients, the authors reported survival rates at 5 years of 54% and 71%, respectively (p=0.008) [30]. HIV infection was found to be an independent predictor of mortality with 2.20 higher risk of death than HCV mono-infected recipients. Also, among HIV-HCV co-infected recipients, HCV genotype 1, donor risk index, and positive plasma HCV RNA were associated with mortality in multivariate analyses. In another prospective, multicenter cohort study from the U.S., patient and graft survival in 89 HIV-HCV co-infected patients was compared to 2 control groups: 235 HCV-monoinfected liver transplant recipients, and all transplant recipients who were 65 years old or older [15]. In this study, 3-year patient and graft survival rates were 60% and 53% for the HIV/HCV patients and 79% and 74% for the HCV-infected recipients (p<0.001). HIV infection was the only factor associated with decreased patient and graft survival (HR=1.9, 95% CI: 1.2–3.1, p=0.01). Treated acute rejection, which occurred significantly more often in coinfected patients compared to mono-infected controls was of borderline significance as a predictor of graft and patient mortality (HR=2.0, p=0.06). Among co-infected patients, older donor age, combined kidney-liver transplantation, an anti-HCV-positive donor, and body mass index (BMI) <21 kg/m^2 were independent predictors of graft loss. If only HIV-HCV co-infected recipients without these risk factors were considered, then patient and graft survival rates were similar to those of control HCV mono-infected liver transplant recipients, demonstrating that recipient and donor selection may significantly influence the outcomes in this patient population.

Medication Management

Immunosuppression and Drug Interactions

Based on the currently available data, it is not clear whether any particular immunosuppressive regimen is more effective in HIV-infected transplant recipients. Most centers avoid lymphocyte depleting agents for induction, such as thymoglobulin, as these agents can have a profound effect on CD4+ T-cells [19]. However, based on higher than expected rates of rejection in HIV-infected liver and kidney recipients [18, 24], most centers use interleukin-2 receptor inhibitors (Basiliximab) for induction therapy in kidney transplant recipients. Immunosuppressive regimens in HIV-infected liver transplant recipients have avoided induction therapy, as episodes of rejection in these patients have been controlled with steroid therapy and adjustments in maintenance immunosuppression.

At most centers, maintenance immunosuppression for HIV-infected liver and kidney transplant recipients consists of a regimen of steroids, a calcineurin inhibitor (tacrolimus or cyclosporine A), and the anti-proliferative agent mycophenolate mofetil (MMF) [14, 15, 18, 19, 30]. Both cyclosporine A and MMF have well described antiretroviral qualities [31–37], but many centers utilize cyclosporine A as the preferred calcineurin inhibitor because of the decreased propensity for inducing glucose intolerance compared to tacrolimus [19]. This consideration is important in the HIV-infected recipient because many protease inhibitors used in antiretroviral regimens may also be diabetogenic. In one study, cyclosporine A use was associated with increased risk of kidney graft rejection but did not impact graft survival [17]. Additionally, because there is often some degree of renal insufficiency present in many HIV-infected recipients, the mTOR inhibitor sirolimus may be a useful alternative to

calcineurin inhibitors. Sirolimus has important properties that make it beneficial in the HIV-infected recipient. It is a potent immunosuppressive agent that is less nephrotoxic and beta cell toxic than calcineurin inhibitors, and it is an effective anti-proliferative agent against Kaposi's Sarcoma [38]. Additionally, sirolimus has the hypothetical potential to enhance antiretroviral therapies by downregulating the expression of CCR5 receptors on CD4+ T-cells and acting synergistically with the antiretroviral agents enfuviride and maraviroc, which inhibit viral entry or CCR5 chemokine coreceptor-facilitated attachment [39, 40].

Antiretroviral Therapy

Post-operative antiretroviral regimens in HIV-infected liver and kidney transplant recipients are similar to other HIV-infected patients. These include a combination of drugs which include the nucleoside analog reverse transcriptase inhibitors (NRTIs), the non-nucleoside analog reverse transcriptase inhibitors (NNRTIs), HIV-protease inhibitors, entry inhibitors or integrase inhibitors. The goals with respect to antiretroviral regimens in the HIV-infected transplant recipient are to provide continuous suppression of HIV, ensure adequate therapeutic levels of the immunosuppressive medications, and minimize additive drug toxicities with other medications. The unique challenge in the post-transplant HIV patient is the management of drug-drug interactions with the need for potent antiretroviral regimen in combination with immunosuppression and prophylaxis for opportunistic infections.

There are multiple bidirectional drug interactions between antiretroviral and immunosuppressive regimens [41], and necessary adjustments to the doses of immunosuppressive agents will depend on which antiretroviral drug is used. Because of the perturbations of the cytochrome P450 3A4 system by different classes of antiretroviral drugs, the doses of calcineurin inhibitors and sirolimus often require dramatic adjustments. Protease inhibitors inhibit the cytochrome P450 3A4 system, which results in decreased doses necessary to maintain similar trough levels of these drugs [42–44]. The NNRTI efavirenz is a potent inducer of the P450 system, and has the opposite effect on dosing of calcineurin inhibitors and sirolimus [45]. However, the induction of the P450 system by efavirenz is less profound than the inhibition by protease inhibitors, and when used together the doses of immunosuppressive agents used should be similar to those when protease inhibitors are used in the absence of NNRTIs. In addition to interactions between antiretroviral agents and immunosuppression regimens, several antibiotics and antifungal agents used for prophylaxis and treatment in immunosuppressed patients can inhibit the cytochrome P450 system. One example is fluconazole, and further reduction in the doses of calcineurin inhibitors and sirolimus may be necessary when this agent is used in combination with protease inhibitors [19].

Management of HIV-infected Patients with Viral Hepatitis

HBV—Recommended post-transplantation guidelines for the management of HBV infection in the HIV-coinfected patient are similar to those for HIV-uninfected patients. Recommendations differ for liver versus kidney transplant recipients.

For liver transplant recipients, the goal is prevention of recurrent infection, and treatment includes the use of hepatitis B immune globulin (HBIG), as well as antiretrovirals that have

activity against HBV [14, 19, 29]. Typically HBIG is given intravenously during the anhepatic phase and daily for the first 5–7 days post-transplant, then continued indefinitely to maintain protective anti-HBs titers [19]. The antiretroviral agents of choice for the treatment of HBV are lamivudine or emtricitabine with tenofovir [29]. Since many patients have HBV resistance to lamivudine, combination antiviral therapy is recommended to prevent virologic breakthrough. In cases where HAART therapy must be held post-transplant, lamivudine and tenofovir should also be held to minimize the risk of creating resistance to these agents if they are given alone. In this situation, adefovir can be used in combination with HBIG therapy to control HBV infection, as adefovir at HBV treatment doses does not have anti-HIV effects and therefore does not present a risk for HIV resistance [19]. Entecavir has also recently been identified to have anti-HIV effects, and therefore should not be utilized in HIV/HBV patients until HAART therapy can be restarted post-transplant [46]. Whether HBIG can be discontinued in some patients at low risk for recurrent HBV infection, as is being done in HBV monoinfected patients [47], is unknown. In the absence of more definitive data, long term management should include HBIG maintenance therapy in combination with lamivudine or emtricitabine and tenofovir, with doses adjusted to renal function.

For kidney transplant recipients with chronic HBV infection, long-term suppression of HBV replication is necessary to prevent progressive disease. HBIG has no role in this patient population. Antiretrovirals with activity against HBV are the best options for management of HBV post-kidney transplantation. Similar to liver transplant patients, the combination of lamivudine or emtricitabine with tenofovir offers an HBV-combination therapy with a high barrier to resistance. Again, if there is a need to interrupt antiretroviral therapy post-transplant, an alternative antiviral for HBV that does not have anti-HIV activity should be used, such as adefovir, in order to prevent a flare of the hepatitis B. Monitoring of treatment efficacy is performed using HBV DNA levels every 3–6 months.

HCV—Unlike HBV, there are no prophylactic therapies for HCV and all patients who are viremic at the time of liver transplantation will develop graft reinfection. Disease progression is more rapid post-transplant than pre-transplant and some studies report accelerated progression to cirrhosis among coinfected compared to monoinfected HCV transplant patients[30, 48]. Thus, monitoring of disease progression with serial biopsies is important and HCV treatment is typically recommended if there is severe necroinflammation or moderate fibrosis. This is similar to recommendations for treatment initiation for non-HIV-infected patients [15]. There are no data supporting preemptive therapy with ribavirin and peginterferon after transplantation in HIV-HCV co-infected recipients. Antiviral therapy with peginterferon and ribavirin has been the mainstay of treating recurrent HCV for the past decade. Among HCV-monoinfected transplant recipients, the rates of sustained virologic response (SVR) with peginterferon and ribavirin are ~30%, with higher rates achievable in patients with non-1 genotypes [49, 50]. Estimates of SVR among HCV-HIV confected patients treated with interferon and ribavirin are poorly characterized, but appear to be <20% [27, 48, 51]. Poor tolerability of therapy is a major obstacle with many patients stopping treatment early due to significant adverse events. More recently, protease inhibitor (PI) triple therapy has been considered for treatment of transplant

recipients with recurrent HCV, though such use is off-label. Preliminary results suggest higher rates of early virologic response but SVR rates are unknown. However, HCV PI-triple therapy is associated with greater toxicity than peginterferon and ribavirin dual therapy and the challenges in managing drug-drug interactions are significant. Thus, any HCV therapy that utilizes a peginterferon and ribavirin "backbone" will have significant limitations in coinfected transplant recipients and the need for alternative, interferon-free treatment options is high [52–55].

Kidney transplant recipients with coinfection need to be monitored for disease progression post-transplantation. Since treatment with peginterferon and ribavirin is generally not recommended post-kidney transplant due to concerns regarding interferon-induced kidney rejection [56], treatment is reserved for those that showed rapidly progressive disease or with advanced fibrosis (bridging fibrosis or cirrhosis) on post-transplant biopsies. The frequency of liver biopsies post-kidney transplant is not established and should be guided by the stage of fibrosis present.

HIV-specific Health Care Issues

HIV-specific Outcomes

While most studies have not shown HIV-disease progression to AIDS or an increase in HIV-associated opportunistic infections following transplant, some studies have shown that CD4+ cell counts can be affected depending on the type of immunosuppressive agents used [17]. In one study, the use of thymoglobulin was associated with a greater decline in CD4+ T-cells in the first year after transplant when compared to kidney recipients who did not receive thymoglobulin induction (−238 vs. −135 cells per cubic millimeter). However, at 3 years post-transplant there was no significant difference between the two groups (−57 vs. −52 cells per cubic millimeter).

Prophylaxis for Opportunistic Infections

There are relatively few reports of HIV-associated opportunistic infections post-transplantation. In the U.S. multicenter prospective study of 150 HIV-infected kidney transplant recipients, there were 2 cases of newly diagnosed cutaneous Kaposi's Sarcoma and one case each of candida esophagitis, presumptive *P. jiroveci* pneumonia, and cryptosporidiosis [17].

In addition to what is standard prophylaxis for low CD4+ T-cell counts, transplant specific prophylaxis includes lifelong prophylaxis for *Pneumosystis jiroveci* pneumonia (PCP) with trimethoprim/sulfamethoxazole (TMP/SMX), prophylaxis for *Mycobacterium avium* complex (MAC) with azithromycin in patients with CD4+ T-cell counts <50 cells/mm^3, and for toxoplasmosis with TMP/SMX in toxoplasmosis IgG positive recipients (or donor), or CD4+ T-cells <200 cells/mm^3 [19]. Additionally, any patients with a history of opportunistic infection should receive prophylaxis for cryptococcosis and toxoplasmosis when CD4+ T-cells <200, and cytomegalovirus (CMV) infection when CD4+ T-cells <75–100 (Table 2). Tuberculosis screening and treatment are the same for HIV-infected transplant recipients as

for all HIV-infected patients, and immunizations for HIV infected patients are the same as recommended for transplant patients who are not HIV-infected [19].

HIV-associated Malignancies

HIV-infected transplant recipients are at increased risk for cancers associated with chronic immune suppression related to prevention of rejection as well as the immunosuppressed state due to HIV infection. These malignancies include Kaposi's sarcoma (KS), non-Hodgkin lymphoma (NHL), hepatocellular carcinoma (HCC), anal and cervical cancers associated with human papilloma virus (HPV), melanoma, and non-melanoma skin cancers such as basal cell and squamous cell carcinoma [57–62]. Routine screening for these malignancies is recommended, although no specific guidelines exist for the HIV-infected transplant recipient. There are data to suggest that there may be a greater impact of immunosuppression on the progression of HPV associated cervical and anal neoplasias [63–65], and routine PAP smears as well as colposcopy should be performed for patients with these lesions [19, 65].

Conclusion

HIV infection is no longer a contraindication to solid organ transplantation, and excellent results have been reported for HIV-infected patients undergoing liver and kidney transplantation. Careful selection of HIV-infected patients with well controlled HIV infection is essential to ensure the best outcomes in this patient population. As this population ages, the need for kidney and liver transplantation will only increase due to the co-morbidities associated with HIV that lead to end stage liver and renal disease, as well as co-morbidities affecting all patients such as hypertension, diabetes mellitus and chronic hepatitis.

Large cohort studies have shown patient and graft survival in carefully selected HIV-infected liver and kidney transplant recipients are similar to HIV-uninfected patients. However, HIV-infected recipients appear to experience higher rates of rejection, and HCV-HIV co-infected patients are at higher risk of graft loss following transplantation.

Despite the challenges presented by drug interactions between HAART regimens, antimicrobial prophylaxis and immune suppression, there has not been significant progression of HIV disease following transplantation in HIV-infected individuals studied to date. Reports of opportunistic infections following transplantation are rare, and do not appear to be significantly higher than in non-HIV infected transplant recipients.

Recently, proposals to use organs from donors with HIV in HIV-infected recipients have gained acceptance. In a report of four successful kidney transplants between HIV infected brain dead donors and HIV-infected recipients, Muller et al. showed that with careful donor selection this can be carried out safely [66]. These authors advocate selecting donors based on the absence of proteinuria, and normal post hoc kidney biopsy. The four recipients in this report all were receiving antiretroviral therapy, had stable disease (defined as an HIV viral load of <50 copies per milliliter for >6 months), and had no previous opportunistic infections other than fully treated pulmonary tuberculosis. All four transplants were from

deceased donors who had not received antiretroviral therapy. The authors note that there may be a risk of accelerating HIV disease progression by superinfecting the recipient with a different HIV clade or recombinant virus, and prospective studies are needed to assess viral characteristics in donor–recipient pairs as factors for graft failure and disease progression.

Continued advancement in the treatment of HCV infection, and more experience with the management of immune suppression in HIV-infected transplant recipients will likely lead to improved outcomes in this patient population. As more data is collected on the outcomes in HIV-infected recipients, further refinements in the selection criteria will likely lead to better treatment of end-stage kidney and liver disease among HIV-infected patients.

Acknowledgments

References

Papers of Particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Spital A. Should all human immunodeficiency virus-infected patients with end-stage renal disease be excluded from transplantation? The views of U.S. transplant centers. Transplantation. 1998; 65:1187–1191. [PubMed: 9603166]

2. 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. [PubMed: 9516219]

3. Feinberg MB. Changing the natural history of HIV disease. Lancet. 1996; 348:239–246. [PubMed: 8684203]

4. 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):S5–14. [PubMed: 10770911]

5. Ockenga J, Tillmann HL, Trautwein C, et al. Hepatitis B and C in HIV-infected patients. Prevalence and prognostic value. J Hepatol. 1997; 27:18–24. [PubMed: 9252068]

6. Staples CT Jr, Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. Clin Infect Dis. 1999; 29:150–154. [PubMed: 10433578]

7. Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol. 1997; 26:1–5.

8. Selik RM, Byers RH Jr, Dworkin MS. Trends in diseases reported on U.S. death certificates that mentioned HIV infection, 1987–1999. J Acquir Immune Defic Syndr. 2002; 29:378–387. [PubMed: 11917243]

9. USRDS: the United States Renal Data System. Am J Kidney Dis. 2003; 42:1–230.

10. Tokizawa S, Shimizu N, Hui-Yu L, et al. Infection of mesangial cells with HIV and SIV: identification of GPR1 as a coreceptor. Kidney Int. 2000; 58:607–617. [PubMed: 10916084]

11. Winston JA, Bruggeman LA, Ross MD, et al. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. N Engl J Med. 2001; 344:1979–1984. [PubMed: 11430327]

12. 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. [PubMed: 1822098]

13. Trullas JC, Cofan F, Tuset M, et al. Renal transplantation in HIV-infected patients: 2010 update. Kidney Int. 2011; 79:825–842. [PubMed: 21248716]

14•. Coffin CS, Stock PG, Dove LM, et al. Virologic and clinical outcomes of hepatitis B virus infection in HIV-HBV coinfected transplant recipients. Am J Transplant. 2010; 10:1268–1275. A prospective cohort study of HIV-hepatitis B virus (HBV) coinfected patients transplanted between 2001–2007. Compared with 20 HBV monoinfected patients on similar HBV, patient and graft survival were similar. [PubMed: 20346065]

15••. Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. Liver Transpl. 2012; 18:716–726. A prospective, multicenter US cohort study comparing patient and graft survival for 89 HCV/HIV-coinfected patients and 2 control groups 235 HCV-monoinfected liver transplant controls and all US transplant recipients who were 65 years old or older. Patient and graft survival rates were lower for HCV/HIV-coinfected liver transplant patients compared to HCV-monoinfected liver transplant patients, and rates of treated acute rejection (but not the rates of HCV disease severity) were significantly higher for HCV/HIV-coinfected recipients versus HCV-infected recipients. The authors concluded that HCV per se is not a contraindication to liver transplant in HIV-infected patients, but recipient and donor selection and the management of acute rejection strongly influence outcomes. [PubMed: 22328294]

16. Harbell J, Fung J, Nissen N, et al. Surgical complications in 275 HIV-infected liver and/or kidney transplantation recipients. Surgery. 2012; 152:376–381. [PubMed: 22938898]

17••. Stock PG, Barin B, Murphy B, et al. Outcomes of kidney transplantation in HIV-infected recipients. N Engl J Med. 2010; 363:2004–2014. A prospective, nonrandomized trial of kidney transplantation in 150 HIV-infected patients. The patient survival of HIV-infected recipients in this study was similar to that observed in HIV-uninfected recipients older than 65 years of age during the same time period. Rejection rates were higher in HIV-infected kidney recipients than what is observed in non-infected patients. However, the higher observed rejection rates did not have a significant impact on overall short-term graft survival. [PubMed: 21083386]

18. 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. [PubMed: 12883195]

19. Stock PG, Roland ME. Evolving clinical strategies for transplantation in the HIV-positive recipient. Transplantation. 2007; 84:563–571. [PubMed: 17876267]

20. 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. [PubMed: 15153575]

21. 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. [PubMed: 15780120]

22. Qiu J, Terasaki PI, Waki K, et al. HIV-positive renal recipients can achieve survival rates similar to those of HIV-negative patients. Transplantation. 2006; 81:1658–1661. [PubMed: 16794531]

23. Pelletier SJ, Norman SP, Christensen LL, et al. Review of transplantation in HIV patients during the HAART era. Clin Transpl. 2004:63–82. [PubMed: 16704139]

24. 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. [PubMed: 16539632]

25. Neff GW, Bonham A, Tzakis AG, et al. Orthotopic liver transplantation in patients with human immunodeficiency virus and end-stage liver disease. Liver Transpl. 2003; 9:239–247. [PubMed: 12619020]

26. Prachalias AA, Pozniak A, Taylor C, et al. Liver transplantation in adults coinfected with HIV. Transplantation. 2001; 72:1684–1688. [PubMed: 11726833]

27. Ragni MV, Belle SH, Im K, et al. Survival of human immunodeficiency virus-infected liver transplant recipients. J Infect Dis. 2003; 188:1412–1420. [PubMed: 14624365]

28•. Cooper C, Kanters S, Klein M, et al. Liver transplant outcomes in HIV-infected patients: a systematic review and meta-analysis with synthetic cohort. Aids. 2011; 25:777–786. A meta-analysis to evaluate the effectiveness of liver transplantation in HIV-hepatitis co-infected patients. Within the HIV-infected population evaluated, HIV-hepatitis B virus (HBV) co-infection was associated with optimal survival. Individuals with an undetectable HIV viral load at the time of transplantation were more likely to survive when compared to those with detectable HIV viremia. [PubMed: 21412058]

29. 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. [PubMed: 16628690]

30••. Miro JM, Montejo M, Castells L, et al. Outcome of HCV/HIV-coinfected liver transplant recipients: a prospective and multicenter cohort study. Am J Transplant. 2012; 12:1866–1876. A prospective multicenter study evaluating eighty-four HCV/HIV-coinfected and 252-matched HCV-monoinfected liver transplant recipients. 5-year survival in HCV/HIV-coinfected liver recipients was lower than in HCV-monoinfected recipients, although an important subset with a favorable prognosis was identified in the HCV/HIV-coinfected group. [PubMed: 22471341]

31. 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. [PubMed: 10634204]

32. 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. [PubMed: 10458616]

33. Andrieu JM, Even P, Venet A, et al. Effects of cyclosporin on T-cell subsets in human immunodeficiency virus disease. Clin Immunol Immunopathol. 1988; 47:181–198. [PubMed: 3258211]

34. Groux H, Torpier G, Monte D, et al. Activation-induced death by apoptosis in CD4+ T cells from human immunodeficiency virus-infected asymptomatic individuals. J Exp Med. 1992; 175:331–340. [PubMed: 1346269]

35. 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. [PubMed: 8420072]

36. Streblow DN, Kitabwalla M, Malkovsky M, Pauza CD. Cyclophilin a modulates processing of human immunodeficiency virus type 1 p55Gag: mechanism for antiviral effects of cyclosporin A. Virology. 1998; 245:197–202. [PubMed: 9636359]

37. Rizzardi GP, Harari A, Capiluppi B, et al. Treatment of primary HIV-1 infection with cyclosporin A coupled with highly active antiretroviral therapy. J Clin Invest. 2002; 109:681–688. [PubMed: 11877476]

38. Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med. 2005; 352:1317–1323. [PubMed: 15800227]

39. Heredia A, Amoroso A, Davis C, et al. Rapamycin causes down-regulation of CCR5 and accumulation of anti-HIV beta-chemokines: an approach to suppress R5 strains of HIV-1. Proc Natl Acad Sci U S A. 2003; 100:10411–10416. [PubMed: 12915736]

40. Gilliam BL, Heredia A, Devico A, et al. Rapamycin reduces CCR5 mRNA levels in macaques: potential applications in HIV-1 prevention and treatment. Aids. 2007; 21:2108–2110. [PubMed: 17885304]

41. Izzedine H, Launay-Vacher V, Baumelou A, Deray G. Antiretroviral and immunosuppressive drug-drug interactions: an update. Kidney Int. 2004; 66:532–541. [PubMed: 15253704]

42. 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. [PubMed: 16003227]

43. Frassetto L, Thai T, Aggarwal AM, et al. Pharmacokinetic interactions between cyclosporine and protease inhibitors in HIV+ subjects. Drug Metab Pharmacokinet. 2003; 18:114–120. [PubMed: 15618725]

44. 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. [PubMed: 15237382]

45. Frassetto LA, Browne M, Cheng A, et al. Immunosuppressant pharmacokinetics and dosing modifications in HIV-1 infected liver and kidney transplant recipients. Am J Transplant. 2007; 7:2816–2820. [PubMed: 17949460]

46. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir - effects on HIV-1 replication and resistance. N Engl J Med. 2007; 356:2614–2621. [PubMed: 17582071]

47. Fox AN, Terrault NA. Individualizing hepatitis B infection prophylaxis in liver transplant recipients. J Hepatol. 2011; 55:507–509. [PubMed: 21601598]

48. Duclos-Vallee JC, Feray C, Sebagh M, et al. Survival and recurrence of hepatitis C after liver transplantation in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology. 2008; 47:407–417. [PubMed: 18098295]

49. Berenguer M, Palau A, Aguilera V, et al. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. Am J Transplant. 2008; 8:679–687. [PubMed: 18294165]

50. Xirouchakis E, Triantos C, Manousou P, et al. Pegylated-interferon and ribavirin in liver transplant candidates and recipients with HCV cirrhosis: systematic review and meta-analysis of prospective controlled studies. J Viral Hepat. 2008; 15:699–709. [PubMed: 18673428]

51. Terrault N, Barin B, Schiano T, et al. Safety and Efficacy of Antiviral Therapy in Hepatitis C Virus (HCV)-Human Immunodeficiency Virus (HIV) Coinfected Liver Transplant (LT) Recipients. Am J Transplant. 2012; 12LS3 Abs.196.

52. Lok AS, Gardiner DF, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med. 2012; 366:216–224. [PubMed: 22256805]

53. Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011; 54:1433–1444. [PubMed: 21898493]

54. Lawitz E, Poordad F, Kowdley KV, et al. A phase 2a trial of 12-week interferon-free therapy with two direct-acting antivirals (ABT-450/r, ABT-072) and ribavirin in IL28B C/C patients with chronic hepatitis C genotype 1. J Hepatol. 2013

55. Poordad F, Lawitz E, Kowdley KV, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med. 2013; 368:45–53. [PubMed: 23281975]

56. Baid S, Tolkoff-Rubin N, Saidman S, et al. Acute humoral rejection in hepatitis C-infected renal transplant recipients receiving antiviral therapy. Am J Transplant. 2003; 3:74–78. [PubMed: 12492714]

57. Goedert JJ, Cote TR, Virgo P, et al. Spectrum of AIDS-associated malignant disorders. Lancet. 1998; 351:1833–1839. [PubMed: 9652666]

58. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. Jama. 2001; 285:1736–1745. [PubMed: 11277828]

59. Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst. 2005; 97:425–432. [PubMed: 15770006]

60. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer. 2008; 123:187–194. [PubMed: 18435450]

61. MacDonald DC, Nelson M, Bower M, Powles T. Hepatocellular carcinoma, human immunodeficiency virus and viral hepatitis in the HAART era. World J Gastroenterol. 2008; 14:1657–1663. [PubMed: 18350596]

62. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007; 370:59–67. [PubMed: 17617273]

63. Holly EA, Ralston ML, Darragh TM, et al. Prevalence and risk factors for anal squamous intraepithelial lesions in women. J Natl Cancer Inst. 2001; 93:843–849. [PubMed: 11390533]

64. Palefsky JM, Holly EA, Ralston ML, et al. Effect of highly active antiretroviral therapy on the natural history of anal squamous intraepithelial lesions and anal human papillomavirus infection. J Acquir Immune Defic Syndr. 2001; 28:422–428. [PubMed: 11744829]

65. Nissen NN, Barin B, Stock PG. Malignancy in the HIV-infected patients undergoing liver and kidney transplantation. Curr Opin Oncol. 2012; 24:517–521. [PubMed: 22759736]

66•. Muller E, Kahn D, Mendelson M. Renal transplantation between HIV-positive donors and recipients. N Engl J Med. 2010; 362:2336–2337. A report of four successful kidney transplants between HIV infected brain dead donors and HIV-infected recipients showed that with careful donor selection this can be carried out safely. [PubMed: 20554994]

Table 1

Eligibility criteria for HIV-infected transplant candidates

Meet center-specific criteria for specific organ transplant
<u>HIV-related criteria</u>
• Kidney: CD4+ T-cell count >200 cells/mm^3
• Liver: CD4+ T-cell count >100 cells/mm^3 (CD4+ T cell count >200 cells/mm^3 if history of opportunistic infection or malignancy)
• HIV RNA suppressed (or expected suppression post-transplantation)
• Stable antiretroviral regimen
• No active opportunistic infection or neoplasm
• No history of chronic cryptosporidiosis, primary CNS lymphoma or progressive multifocal leukoencephalopathy
<u>Other</u>
• Liver (HCV): BMI >21 kg/m^2, no need for combined kidney transplant, no HCV+ donor

Table 2

Opportunistic infection prophylaxis for HIV-infected transplant recipients

Opportunistic infection	Preferred agent	Primary prophylaxis [*]	Secondary prophylaxis [**]
Pneumocystis jiroveci	Trimethoprim-Sulfamethoxazole Alternatives: dapsone if not G6PD deficient, atovaquone	Indicated for life; initiate immediately post-transplant	Indicated for life; initiate immediately post-transplant
Toxoplasmosis	Trimethoprim-Sulfamethoxazole Alternatives: atovaquine, sufadiazine + pyrimethamine + leucovorin	Toxoplasmosis IgG-positive patients with CD4 T-cell count 200 cells/mm^3	CD4 T-cell count <200 cells/mm^3 Discontinue when CD4+ T-cell count is >200 cells/mm^3 for 3–6 months [†]
Mycobacterium avium **complex**	Azithromycin Alternatives: clarithromycin	CD4+ T-cell count 50 cells/mm^3 Discontinue when CD4+ T-cell count >100 cells/mm^3 for 3–6 months	CD4+ T-cell count <50 cells/mm^3 Discontinue when CD4+ T-cell count is >100 cells/mm^3 for 3–6 months [†]
Cytomegalovirus	Valganciclovir Alternatives: foscarnet, cidofovir	No HIV specific indication	CD4 T-cell count <75–100 cells/mm^3 Discontinue when CD4+ T-cell count is >100–200 cells/mm^3 for 3–6 months [†]
Cryptococcosis, extrapulmonary	Fluconazole	No HIV specific indication	CD4 T-cell count <200 cells/mm^3 Discontinue when CD4+ T-cell count is >200 cells/mm^3 for 3–6 months [†]

[*] No history of infection

[**] Prior history of the infection

[†] Secondary prophylaxis should also be reinstituted immediately post-transplant 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.