

# HIV-Infected Liver and Kidney Transplant Recipients: 1- and 3-Year Outcomes

M. E. Roland<sup>a,\*</sup>, B. Barin<sup>b</sup>, L. Carlson<sup>a</sup>,  
L. A. Frassetto<sup>a</sup>, N. A. Terrault<sup>a</sup>, R. Hirose<sup>a</sup>,  
C. E. Freise<sup>a</sup>, L. Z. Benet<sup>a</sup>, N. L. Ascher<sup>a</sup>,  
J. P. Roberts<sup>a</sup>, B. Murphy<sup>c</sup>, M. J. Keller<sup>c</sup>,  
K. M. Olthoff<sup>d</sup>, E. A. Blumberg<sup>d</sup>,  
K. L. Brayman<sup>e</sup>, S. T. Bartlett<sup>f</sup>, C. E. Davis<sup>f</sup>,  
J. M. McCune<sup>a</sup>, B. M. Bredt<sup>a</sup>, D. M. Stablein<sup>b</sup>  
and P. G. Stock<sup>a</sup>

<sup>a</sup>University of California, San Francisco, CA

<sup>b</sup>EMMES Corporation, Rockville, MD

<sup>c</sup>Mount Sinai School of Medicine, New York, NY

<sup>d</sup>University of Pennsylvania, Philadelphia, PA

<sup>e</sup>University of Virginia, Charlottesville, VA

<sup>f</sup>University of Maryland, Baltimore, MD

\*Corresponding author: Michelle E. Roland,  
Michelle.Roland@cDpH.CA.gov

**Improvements in human immunodeficiency virus (HIV)-associated mortality make it difficult to deny transplantation based upon futility. Outcomes in the current management era are unknown. This is a prospective series of liver or kidney transplant recipients with stable HIV disease. Eleven liver and 18 kidney transplant recipients were followed for a median of 3.4 years (IQR [interquartile range] 2.9–4.9). One- and 3-year liver recipients' survival was 91% and 64%, respectively; kidney recipients' survival was 94%. One- and 3-year liver graft survival was 82% and 64%, respectively; kidney graft survival was 83%. Kidney patient and graft survival were similar to the general transplant population, while liver survival was similar to the older population, based on 1999–2004 transplants in the national database. CD4+ T-cell counts and HIV RNA levels were stable; and there were two opportunistic infections (OI). The 1- and 3-year cumulative incidence (95% confidence intervals [CI]) of rejection episodes for kidney recipients was 52% (28–75%) and 70% (48–92%), respectively. Two-thirds of hepatitis C virus (HCV)-infected patients, but no patient with hepatitis B virus (HBV) infection, recurred. Good transplant and HIV-related outcomes among kidney transplant recipients, and reasonable outcomes among liver recipients suggest that transplantation is an option for selected HIV-infected patients cared for at centers with adequate expertise.**

**Key words:** Hepatitis B virus (HBV), hepatitis C virus, HIV, end-stage liver disease, end-stage renal disease, transplantation

Received 24 May 2007, revised 27 September 2007 and  
accepted for publication 15 October 2007

## Introduction

Organ failure is a significant problem for patients with human immunodeficiency virus (HIV) infection in the current era of effective highly active antiretroviral therapy (HAART) (1–3). Improvements in HIV-associated morbidity and mortality have made it difficult to deny solid organ transplantation to this population based upon futility arguments alone (4). However, concerns that posttransplant immunosuppression may result in accelerated HIV disease progression have limited the availability to a small number of transplant centers. Despite the need for transplantation, the safety and efficacy of this intervention in HIV-infected recipients is unknown.

Transplantation outcomes in the pre-HAART era were generally poor (5–9). More contemporary retrospective analyses, case reports and small prospective studies suggest that patient and graft survival in selected HIV-infected patients may be similar to those seen in HIV-uninfected patients (10–16). While there are no reports of significant HIV disease progression, allograft rejection rates have been unexpectedly high (14,17). In this study, we describe the patient, graft and HIV-related outcomes of a prospective cohort of both kidney and liver recipients followed for over 3 years in the HAART era.

## Methods

HIV-infected kidney and liver transplant recipients were followed prospectively at four transplant centers in the United States in a nonrandomized trial. The research protocol was approved by the institutional review boards (IRB) at the University of California, San Francisco (UCSF), the University of Maryland, The Mount Sinai School of Medicine and the University of Pennsylvania. Each subject provided written informed consent and indicated understanding of the study.

## Subjects

Subjects met center-specific standard transplant criteria and provided written informed consent. They had CD4+ T-cell counts of more than 200 (kidney recipients) or 100 (liver recipients) cells per cubic millimeter for 6 months, and undetectable plasma HIV RNA on a stable HAART regimen for 3 months, prior to transplantation. For liver recipients who were unable to tolerate HAART, HIV study specialists predicted complete suppression

of HIV viremia following transplantation, based on medication and HIV RNA history and antiretroviral resistance test results. Prior to April 2002, patients with a history of any AIDS-defining opportunistic infection (OI) except *Candida* esophagitis were excluded from the study. Subsequently, patients with previously treated opportunistic complications (except progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, lymphoma and visceral Kaposi's sarcoma [KS]) were eligible. A kidney transplant recipient with an HLA identical donor and a history of resolved pulmonary KS was enrolled with an exemption from the UCSF IRB.

### Interventions

Deceased and living donor organs were used for both liver and kidney transplants. For both organs, initial immunosuppression included corticosteroids and the calcineurin inhibitors (CNI), cyclosporine or tacrolimus, with or without mycophenolate mofetil. Sirolimus was used to minimize CNI use in subjects with renal insufficiency. Prophylactic antibody induction with an interleukin-2 receptor inhibitor was permitted for kidney transplant recipients. Thymoglobulin induction therapy was not used in this cohort. Rejection therapy included changing the CNI and/or the use of steroids or sirolimus. Except for one liver subject who received a dual organ transplant and experienced a kidney rejection, antilymphocyte preparations (thymoglobulin) were only used in kidney transplant recipients.

There were no HAART restrictions. In most cases, subjects continued their pre-transplant regimen in the posttransplant period. Referring health care providers were advised of the unknown implications of *in vitro* antiretroviral antagonism between mycophenolate mofetil and the thymidine analog nucleoside reverse transcriptase inhibitors, zidovudine and stavudine (18). In three cases, the provider modified the HAART regimen prior to transplant to replace these agents. HAART was reinitiated once the subject was stable and able to consistently take pills by mouth following transplantation.

OI prophylaxis included life-long trimethoprim-sulfamethoxazole, dapsone or atovaquone to prevent *Pneumocystis carinii* pneumonia (PCP), brief antifungal prophylaxis using fluconazole, and *Cytomegalovirus* (CMV) prophylaxis with either acyclovir or valcyte, depending upon the recipient and donor CMV status. We initiated macrolide prophylaxis against *Mycobacterium avium* complex (MAC) when the CD4+ T-cell count dropped below 75 cells per cubic millimeter. Subjects with an OI history were maintained on secondary prophylaxis for 1 month posttransplant, 1 month postrejection therapy and whenever the CD4+ T-cell count dropped below a specified level consistent with national guidelines for the treatment of OI (19).

Hepatitis B virus (HBV)-coinfected liver transplant recipients received high-dose hepatitis B immune globulin (HBIG) in addition to single or combination nucleoside analog therapy (lamivudine, tenofovir and adefovir) post-transplantation. Those with hepatitis C virus (HCV) coinfection were treated for recurrent disease with interferon and ribavirin when they developed cholestatic hepatitis or evidence of fibrosis progression on liver biopsy.

### Measurements

Subjects were evaluated prior to transplant and then 13 times in the first year, every 3 months in years 2 and 3, and every 6 months in years 4 and 5 posttransplant. At baseline, demographic, medical history, donor type and donor-recipient immunologic variables were collected. Immunosuppressant and antiretroviral medication use, trough immunosuppressant levels, plasma HIV RNA levels, CD4+ T-cell counts and flow cytometric analysis of the activation markers HLA-DR, CD38 and CD69 on CD4+ and CD8+ T-lymphocytes were collected longitudinally. Patient and graft survival were the primary outcomes. Secondary outcomes related to HIV disease progression included the incidence of opportunistic complications, changes in CD4+ T-cell counts and incidence of detectable plasma HIV RNA levels.

We described the incidence and predictors of allograft rejection. Allograft biopsies were performed based upon clinical indications and rejection was defined using standard histologic criteria. The last follow-up date for each outcome was the last date prior to October 6, 2006 that the measurement was available in the study database. For subject and graft survival, we used the date of death or last contact, return to dialysis in the case of kidney recipients or retransplant in the case of liver recipients.

### Statistical analysis

Patient survival, graft survival and allograft rejection estimates were calculated using the Kaplan–Meier method and associated 95% confidence intervals (CI) with Greenwood's formula. Survival estimates were compared with national Organ Procurement and Transplantation Network (OPTN) survival estimates available on November 29, 2006 for all patients and for patients of 65 years or older. An OPTN STAR file with a data cutoff date of April 24, 2005 was used to obtain the OPTN survival estimates and for HCV-infected liver recipients.

Quantitative CD4+ T-cell changes from baseline at years 1, 2 and 3 post-transplant and annual changes in serum creatinine were compared with the Wilcoxon signed-rank test.

The rank-sum test was used to compare annual serum creatinine in subjects who had and had not experienced rejection.

In kidney recipients, the following potential predictors of first allograft rejection were evaluated in univariate proportional hazard models: race, age at transplant, use of antibody induction therapy, opportunistic complication history, hepatitis C infection status, donor type, number of mismatched donor-recipient antigens, panel reactive antibody (PRA) at transplant, delayed cyclosporine initiation beyond the second posttransplant day and CD4+ T-cell count at baseline. Posttransplant CD4+ T-cell counts, HIV RNA levels, protease inhibitor use, cyclosporine trough level, mycophenolate mofetil use and the immune activation markers (CD38+, HLA-DR+ CD4+ and CD8+ cells and CD69-CD25+ CD4+ and CD8+ cells) were analyzed as time-dependent covariates. Given the small number of events and subjects, multivariate models were not constructed.

A two-sided p-value of less than 0.05 was considered to be statistically significant. Statistical analyses were performed using SAS version 8.2, Cary, NC.

## Results

### Subject and transplant characteristics

We enrolled 11 liver and 18 kidney recipients between March 2000 and September 2003 and followed them for a median of 3.4 years (interquartile range [IQR] 2.9–4.9, Table 1). Pretransplant median CD4+ T-cell counts were 279 and 439 cells per cubic millimeter in liver and kidney recipients, respectively. Six (55%) liver recipients were coinfecting with HCV and five (45%) with HBV. Two HCV-infected liver recipients had hepatocellular carcinoma at the time of transplant. Eight (73%) liver recipients received a deceased donor liver. No liver was from a HCV-infected donor. Ten (56%) kidney recipients had hypertension and two (11%) had diabetes. Although seven (39%) were diagnosed with HIV-associated nephropathy (HIVAN), only one had biopsy-documented HIVAN. Deceased donor organs were used in 10 (56%) kidney recipients.

**Table 1:** Baseline characteristics of HIV-infected transplant recipients

Characteristic	Liver recipients (N = 11)	Kidney recipients (N = 18)
Age, year (median [IQR])	46 [41–49]	44 [40–49]
Male sex, no. (%)	11 (100)	17 (94)
Race/ethnicity, no. (%)		
White	6 (55)	10 (56)
African American	2 (18)	8 (44)
Hispanic	1 (9)	0
Asian	2 (18)	0
Prior opportunistic complications, no. (%)		
Any opportunistic complication	1 (9)	4 (22)
<i>Pneumocystis carinii</i> pneumonia	1	1
Cytomegalovirus <sup>1</sup>	0	2
Cryptococcal meningitis	1	0
<i>Mycobacterium avium</i> complex	0	1
Tuberculosis	0	1
Kaposi's sarcoma	0	1
CD4+ T-Cell (cells/mm <sup>3</sup> ), median (range) <sup>2</sup>	279 (104–450)	439 (293–613)
HIV RNA <sup>2</sup>		
Any detectable, no. (%)	2 (18)	0
Copies/mL, median (range)	Undetectable (<50–12 128)	Undetectable (all < 50)
Viral hepatitis, no. (%)		
Hepatitis C	6 (55)	5 (28)
Hepatitis B surface antigen positive	5 (45)	0

<sup>1</sup>Cytomegalovirus-associated lymphadenitis and enteritis.  
<sup>2</sup>Most recent pretransplant value, within 2 months of transplant. Lower limit of detection 50 or 75 copies/mL for all subjects except one and less than 400 copies/mL for that one subject. IQR, interquartile range.

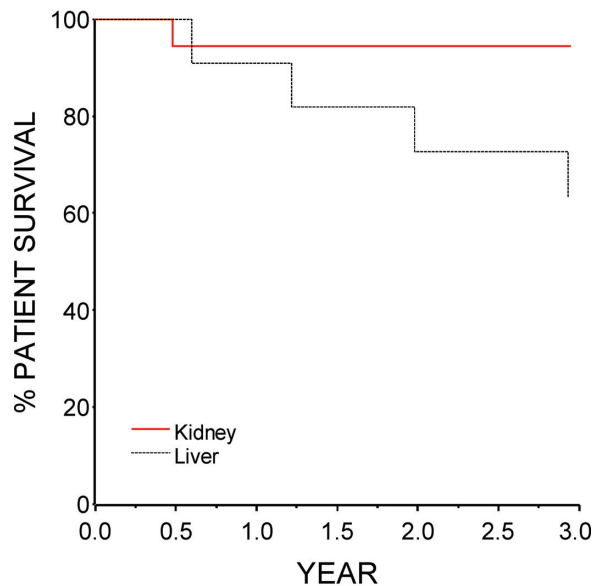
Cyclosporine was used as an initial CNI therapy in 12 (67%) of the kidney transplant recipients and 9 (82%) of the liver transplant recipients. Five (28%) kidney and two (18%) liver transplant recipients initially received sirolimus. Mycophenolate mofetil was provided initially to 16 (89%) of the kidney transplant recipients and 11 (100%) of the liver transplant recipients. Seven (39%) of the kidney transplant recipients received antibody induction therapy. Among initial posttransplant HAART regimens, 12 (41%) included a protease inhibitor, 10 (34%) included a nonnucleoside reverse transcriptase inhibitor and 6 (21%) included both.

**Patient and graft survival**

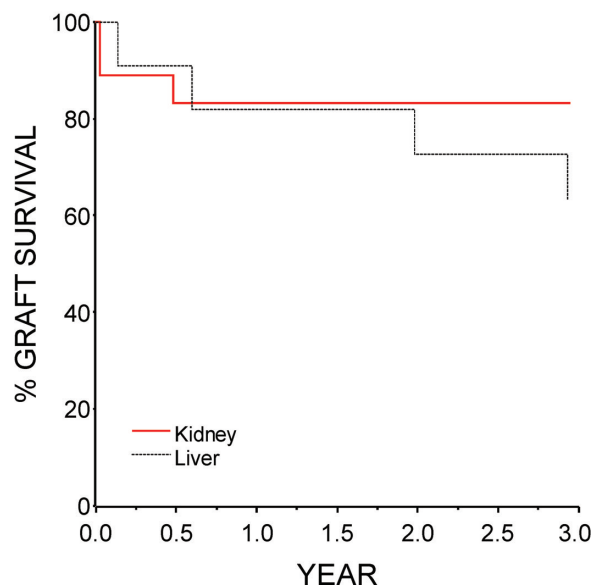
The median (IQR) follow-up duration was 3.0 (2.0–4.4) years after liver transplantation and 4.0 (3.0–5.7) years after kidney transplantation. No subject was lost to follow-up. One- and 3-year liver recipient survival was approximately 91% and 64%, respectively (Figure 1 and Table 2). Two liver transplant recipients died from complications of recurrent HCV infection (posttransplant days 218 and 445),

the third subject died of *Stenotrophomonas maltophilia* sepsis in the setting of recurrent HCV-associated cirrhosis (day 724) and the fourth subject died due to disseminated recurrent hepatocellular carcinoma (day 1071). One- and 3-year kidney recipient survival was approximately 94%. One kidney transplant recipient died from congestive heart failure at day 175 posttransplant, one from pulmonary fibrosis (day 1452), one from complications of a myocardial

**A Patient Survival**

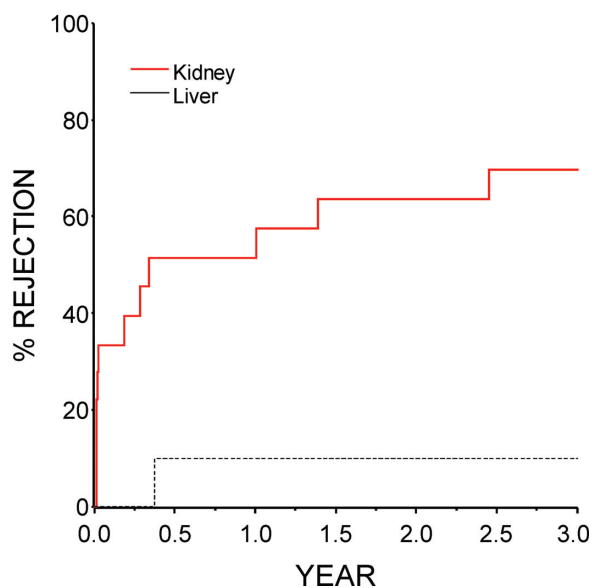


**B Graft Survival**



**Figure 1: Kaplan–Meier estimates of patient and graft survival and first allograft rejection.** The solid lines represent kidney transplant recipient and the dashed lines represent liver transplant recipients. In panel B, graft failure from any cause is plotted without censoring death with function.

**C Time to First Acute Allograft Rejection**



**Figure 1:** Continued.

infarction in the setting of respiratory failure of undetermined etiology (day 2095) and one from an unknown cause 51 days following an uncomplicated aortic valve replacement (day 1452).

Without censoring death with function, 1- and 3-year liver graft survival was approximately 82% and 64%, respectively. One liver graft failed due to a ‘small-for-size syndrome’ in a living donor’s right-lobe recipient (day 49) and one failed due to recurrent HCV infection (day 218). The living liver recipient received a second transplant from a deceased donor and subsequently died from HCV-associated cirrhosis 396 days after retransplantation (445 days after the initial transplant). Without censoring death with function, 1- and 3-year kidney graft survival was approximately 83%. Severe acute rejection (day 8), chronic rejection (days 1174 and 1773) and vascular thrombosis (day 8) resulted in four kidney graft losses. Patient and graft survival at 1 and 3 years were similar to those reported in the national database for older (greater than or equal to 65 years) transplant recipients in the United States during a similar time frame (Table 2).

**HIV disease progression**

Two (7%) subjects developed an OI, including one case each of CMV and *Candida* esophagitis. The CD4+ T-cell count at the time of diagnosis in the liver transplant recipient was approximately 200 cells per cubic millimeter. His clinical status was poor due to the rapid progression of end-stage liver disease, and he subsequently died of liver failure. The *Candida* esophagitis occurred in a diabetic kidney recipient who had previously been treated with

**Table 2:** Patient and graft survival in HIV-infected study subjects and in the Organ Procurement and Transplantation Network (OPTN) database<sup>1</sup>

	One-year patient survival		Three-year patient survival	
	Liver	Kidney	Liver	Kidney
Study subjects <sup>2</sup>	90.9 (73.9–100)	94.4 (83.9–100)	63.6 (35.2–92.1)	94.4 (83.9–100)
OPTN (≥65 years) <sup>1</sup>	81.5 (79.4–83.6)	91.5 (90.7–92.3)	68.8 (66.2–71.3)	80.1 (78.9–81.2)
OPTN (HCV-infected) <sup>1</sup>	85.8 (84.5–87.1)	NA	75.6 (73.9–77.3)	NA
OPTN (general) <sup>1</sup>	87.7 (87.2–88.3)	95.9 (95.8–96.1)	79.9 (79.3–80.5)	90.8 (90.5–91.1)
	One-year graft survival		Three-year graft survival	
Study subjects <sup>3</sup>	81.8 (59.0–100)	83.3 (66.1–100)	63.6 (35.2–92.1)	83.3 (66.1–100)
OPTN (≥65 years) <sup>1</sup>	78.6 (76.4–80.8)	87.9 (87.0–88.8)	65.4 (62.8–68.0)	74.4 (73.2–75.7)
OPTN (HCV-infected) <sup>1</sup>	83.1 (81.7–84.5)	NA	71.9 (70.1–73.6)	NA
OPTN (general) <sup>1</sup>	83.4 (82.8–84.0)	91.9 (91.6–92.1)	73.7 (73.1–74.4)	82.4 (82.0–82.7)

All numbers represent the median and 95% confidence interval.

<sup>1</sup>Kidney patient and graft survival were similar to the general transplant population (log-rank test; p = 0.34 and 0.18, respectively), while liver patient and graft survival were similar to the older population (log-rank test; p = 0.99 and 0.91, respectively), based on 1999–2004 transplants in the Organ Procurement and Transplantation Network (OPTN) database.

<sup>2</sup>One-year survival is based on 2002–2004 transplants and 3-year survival is based on 1999–2002 transplants in the OPTN database.

<sup>3</sup>Without censoring death with function. When death with function is censored, 1- and 3-year graft survival rates are equal, since there were no new events in the period. These graft survival percentages were 81.8 (59.0–100) and 88.9 (74.4–100) for liver and kidney transplants, respectively.

NA, not available.

thymoglobulin for acute rejection and responded promptly to topical antifungal treatment (20).

The median (IQR) change in CD4+ T-cells per cubic millimeter at 1, 2 and 3 years posttransplant compared to baseline was 18.0 (−275, 95,  $p = 0.52$ ), 53.5 (−128.5, 176.5,  $p = 0.55$ ) and 109.0 (−75, 228,  $p = 0.17$ ), respectively. Two liver recipients had detectable plasma HIV RNA levels at transplant and were rapidly suppressed to undetectable levels posttransplantation. Following transplantation, five (45%) liver and seven (39%) kidney recipients had detectable plasma HIV RNA levels. Two subjects were not taking HAART at the time of the detectable measurements (63–45 741 copies per milliliter). The range of detectable viremia was 52–44000 copies per milliliter in the 10 subjects on HAART. Five of these subjects had single detectable RNA values (blips) (55–6490 copies per milliliter) that resolved. Among the other five, there were nine episodes of transient viremia (56–44000 copies per milliliter). Among the 21 surviving subjects, only one had detectable plasma HIV RNA (52 copies) levels at their last study visit, 3.4 years posttransplant.

### **Allograft rejection**

Twelve (67%) kidney and one (9%) liver recipient experienced a total of 20 rejection episodes (Figure 1). The 1- and 3-year cumulative incidence of rejection (95% CI) for liver transplant recipients was 10% (0–29%). The 1-, 2- and 3-year cumulative incidence of rejection for kidney transplant recipients was 52% (28–75%), 64% (41–87%) and 73% (50–96%), respectively. Among kidney rejection episodes, 14 (78%) were acute cellular, 1 (6%) was acute vascular and 2 (11%) were acute cellular and vascular. There was one presumptive diagnosis of recurrent rejection without biopsy.

Only age (hazard ratio [HR] 6.33,  $p = 0.005$ ) and PRA at transplant (HR 0.84,  $p = 0.05$ ) were associated with first kidney rejection episode at  $p$  less than 0.05 level in unadjusted univariate analyses. Use of antibody induction therapy (HR 3.23,  $p = 0.06$ ), most recent CD4+ T-cell count (HR 0.89,  $p = 0.12$ ), delayed initiation of cyclosporine (HR 3.27,  $p = 0.17$ ), cyclosporine trough level adjusted for delayed initiation (HR = 0.99,  $p = 0.12$ ) and antigen mismatch (HR 1.54,  $p = 0.19$ ) may be associated with kidney rejection. While the other variables examined, including immune activation markers, were not associated with kidney rejection, there may be an inadequate power to detect these associations.

### **Additional observations**

Despite frequent kidney rejection and a 50% incidence of delayed graft function, the median (IQR) change in creatinine in kidney recipients at years 1,2 and 3 compared to 3 months posttransplant was 0.0 (−0.1, 0.2), 0.1 (0.0, 0.5) and 0.2 (−0.1, 0.7) mg/dL, respectively. Kidney recipients with rejection episodes had a higher median creatinine

than those who did not reject (year 1: 1.95 mg/dL versus 1.10 mg/dL,  $p = 0.008$ ; year 2: 2.30 mg/dL versus 1.20 mg/dL,  $p = 0.002$ ; year 3: 2.20 mg/dL versus 1.10 mg/dL,  $p = 0.0009$ ).

There was no evidence of HBV recurrence detected by serologic or virologic monitoring among the five HBV-coinfected liver recipients (21). All HBV-coinfected subjects were treated with a combination of lamivudine and either adefovir or tenofovir plus HBIG. Three (60%) subjects had clinical evidence of lamivudine resistance prior to transplant. The median aspartate aminotransferase (AST) in this group at years 1,2 and 3 posttransplant was 25, 29 and 40 U/L, respectively.

Among six recipients with HCV coinfection, four had histologic evidence of disease recurrence. All these subjects received interferon and ribavirin therapy, initiated at a median (range) of 109 (15–339) days posttransplantation. The other two recipients did not have any clinical evidence of HCV recurrence and thus did not undergo liver biopsy. Thus, they may also have had histologic evidence of recurrent disease, but this was not examined.

Serum potassium level  $>5.6$  mEq/L (grade 1 on the National Institute of Allergy and Infectious Diseases [NIAID] Division of Acquired Immunodeficiency Syndrome [DAIDS] toxicity scale) was common (52%), but did not occur more frequently in Septra users or those with elevated CNI levels. Leukopenia below  $1 \times 10^9/L$  occurred infrequently (3/29 [10%]), and only in liver transplant recipients, one of whom received thymoglobulin.

## **Discussion**

Although important patient selection and management questions remain, particularly with respect to HCV-infected liver transplant candidates and kidney allograft rejection, this study suggests that transplantation is a reasonable option for selected HIV-infected patients. One- and 3-year kidney patient and graft survival are comparable to the general kidney recipient population. Liver survival rates are similar to those in older, HIV-uninfected transplant recipients. HIV-specific outcomes are excellent.

We believe the most important question is not if HIV-infected transplant recipients do as well as age-matched controls, but rather if they do as well as other relatively poor prognosis groups that are considered appropriate transplant candidates. Older and HCV-infected recipients are considered acceptable for transplantation, yet have comorbid conditions associated with the potential for shortened survival compared to the general transplant population. This study is not adequately powered to formally compare our survival estimates with a control group derived from the OPTN database. Our patient and graft survival estimates are consistent with the hypothesis that the HIV-infected

**Table 3:** Immunosuppression, antiretroviral therapy, rejection and HIV viremia

Subject #	Organ: deceased or living	Induction and initial immunosuppression*	Immunosuppression changes* (day #)	Rejection (day #)	Initial antiretroviral regimen*	Antiretroviral changes* (day #)	Detectable HIV viral load (day # and copies/mL)	Patient and graft status (day #)
Liver recipients								
001	Deceased	CsA MMF MP	D6: MP-> prednisone, D535: prednisone stopped, D733: MMF stopped D53: MMF stopped, D73: CsA->sirolimus	N/A	3TC DDI EFV	D145: EFV->NVP		D1618: Alive, functioning
002	Deceased	CsA MMF prednisone		N/A	3TC EFV TDF 3TC	D67: TDF-> DDI, EFV-> LPV/RTV, D186: DDI->ABC No changes		D724: Expired
003	Deceased	CsA MMF prednisone	D34: +sirolimus, D124: CsA stopped	N/A	DDI EFV TDF			D1077: Alive, functioning
004	Living	CsA MMF prednisone	No changes	N/A	3TC DDI NFV	D144: DDI-> D4T, D239: all stopped, D426: 3TC, D4T started	D35: 23247, D42: 45741, D57: 230, D307: 101, D379: 1669, D418: 9600 D852: 144	D49: Graft failure, D445: Expired
005	Deceased	CsA MMF MP	D9: MP-> prednisone, D31: CsA-> Tac, D58: Tac-> CsA, D689: CsA-> Tac, D698: Tac->CsA	D137, D689	3TC ABC NFV TDF	D117:NFU stopped, D243: TDF-> LPV/RTV No changes		D1116: Alive functioning
006	Deceased	CsA MMF MP	D12: MP stopped, D12-18: thymo, D18: CsA-> Tac, D19: +prednisone	N/A	3TC ABC APV EFV			D1071: Expired
007	Deceased	CsA MMF prednisone	D625: prednisone stopped	N/A	3TC ABC IDV NVP	D250: + TDF, D709: IDV -> LPV/RTV, D1032: 3TC, ABC stopped, Trizivir started	D248: 525, D361: 67, D976: 1330	D1726: Alive, functioning
008	Living	MMF MP Tac	D14: MP-> prednisone, D58: MMF stopped, D138: Tac-> CsA, D719: prednisone stopped	N/A	3TC ABC NFV TDF	D252: ARVs stopped, D267: +3TC, TDF, EFV, LPV/RTV, D645: EFV stopped	D140: 586	D1209: Alive, functioning
009	Living	CsA MMF prednisone	D895: prednisone stopped	N/A	3TC D4T DDI DLV SOV	D180: DDI, D4T, DLV, SOV stopped, AZT, NVP, NFV started		D1870: Alive, functioning

Continued.

**Table 3:** Continued

Subject #	Organ: deceased or living	Induction and initial immunosuppression*	Immunosuppression changes* (day #)	Rejection (day #)	Initial antiretroviral regimen*	Antiretroviral changes* (day #)	Detectable HIV viral load (day # and copies/mL)	Patient and graft status (day #)
010	Deceased	CsA MMF prednisone sirolimus	D4: CsA stopped, D208: sirolimus stopped	N/A	3TC ABC TDF	D88: ABC-> LPV/RTV & EFV, D113: ARVs stopped, D119: ARVs re-started, D146: EFV -> D4T, D188: EFV re-started, D189: +NFV	D17: 401, D32: 1116, D56: 813	D1096: Alive, functioning
011	Deceased	MMF MP Tac	D6: MP-> prednisone, D122: prednisone stopped	N/A	3TC D4T LPV/RTV	No changes	D218: Expired	
Kidney Recipients								
012	Living	Basiliximab CsA prednisone sirolimus	No changes	D507	3TC D4T EFV	No changes	D53: 44000, D112: 74	D878: Alive, functioning
013	Living	CsA prednisone sirolimus	D12: sirolimus->MMF	D105, D216, D250	3TC ABC LPV/RTV SQV	No changes	D544: 6490, D819: 59	D1100: Alive, functioning
014	Deceased	Basiliximab CsA MMF	D36: + prednisone, D61: + sirolimus, D256: CsA stopped	N/A	3TC ABC EFV	No changes	D1074: Alive, functioning	
015	Living	CsA MMF prednisone	D111: CsA -> Tac, D134: Tac -> CsA, D289: +sirolimus	D124, D292	3TC ABC DDI IDV	D29: DDI stopped, IDV -> NFV	D2267: Alive, functioning	
016	Living	CsA MMF prednisone	D371: CsA->Tac, D369-375: thymo, D494-594: sirolimus	D368, D493	3TC ABC NVP	No changes	D1174: Graft failure, D1791: Alive	
017	Deceased	MMF sirolimus	D10: +CsA, D1815: sirolimus stopped	D5	3TC ABC NVP	No changes	D13: 55	D2095: Expired

Continued.

Table 3: Continued

Subject #	Organ: deceased or living	Induction and initial immunosuppression*	Immunosuppression changes* (day #)	Rejection (day #)	Initial antiretroviral regimen*	Antiretroviral changes* (day #)	Detectable HIV viral load (day # and copies/mL)	Patient and graft status (day #)
018	Deceased	Basiliximab MMF prednisone	D7-14: thymo, D16-47: sirolimus, D36-50: CsA, D50-91: Tac, D94: MIMF stopped	D6, D48	3TC, D4T, NFV	No changes	D175: Expired	D175: Expired
019	Living	basiliximab CsA MMF prednisone	D4-10: thymo, D7: CsA-> Tac, D123: MMF stopped, D167-173: thymo, D172-220: sirolimus, D220: +azathioprine	D4, D166	3TC DDI NFV NVP	D872: 3TC, NFV stopped, RTV, FTC, ATV started, D1578: ATV stopped, FPV started, D1654: FPV stopped	D157: 440, D1243: 52	D1243: Alive, functioning
020	Living	CsA MMF prednisone	No changes	N/A	3TC ABC DDI NVP	No changes	D1293: Alive, functioning	D1293: Alive, functioning
021	Living	Daclizumab MMF prednisone sirolimus	D8-13: thymo, D14: +CsA, D118: sirolimus stopped, D155: MMF stopped	D8	3TC ABC NVP	D68: ARVs stopped, D71: ARVs re-started	D1883: Alive, functioning	D1883: Alive, functioning
022	Deceased	CsA MMF prednisone	D889: CsA-> Tac, D1905: Tac->sirolimus	D896	3TC ABC NFV	D473: NFV -> NVP	D2255: Alive, functioning	D2255: Alive, functioning
023	Deceased	CsA MMF prednisone	No changes	N/A	3TC DDI NVP	D27: +ABC, D1829: ARVs stopped, D2072: ARVs re-started	D2263: Alive, functioning	D2263: Alive, functioning
024	Deceased	Basiliximab MMF	D3: thymo	D5	3TC EFV NFV	No changes	D8: Graft failure, D1251: Alive	D8: Graft failure, D1251: Alive
025	Deceased	basiliximab MMF prednisone,	D3-14: thymo, D12: +CsA, D261: +sirolimus	D5	D4T LPV/RTV NVP	D11: ARVs stopped, D20: ARVs re-started, D293: D4T -> 3TC + TDF, D464: TDF-> ABC	D28: 258, D862: 56, D1287: 69	D1452: Expired
026	Deceased	MMF prednisone sirolimus	D10: sirolimus-> thymo, D13: thymo-> CsA	N/A	3TC D4T DDI LPV/RTV	D178: DDI-> TDF, LPV/RTV->EFV, D185: EFV stopped, D232: D4T-> NFV, D234: +SQV, D281: SQV stopped, D297: +APV	D14: 1726, D294: 67, D316: 68, D1064: 89	D1452: Expired

Continued.

**Table 3:** Continued

Subject #	Organ: deceased or living	Induction and initial immunosuppression*	Immunosuppression changes* (day #)	Rejection (day #)	Initial antiretroviral regimen*	Antiretroviral changes* (day #)	Detectable HIV viral load (day # and copies/mL)	Patient and graft status (day #)
027	Deceased	CsA MMF prednisone	D68: thymo, D71: CsA->Tac, D125: Tac->CsA & sirolimus, D145: MMF stopped, D1789: sirolimus stopped, D1816: CsA stopped, D1940: prednisone stopped	D68	3TC DDI IDV NFV	D157: DDI -> D4T, IDV -> EFV, D1855: 3TC, D4T & NFV stopped, LPV/RTV started	D1773: Graft failure, D2120: Alive	
028	Deceased	CsA MMF prednisone	D8: IS stopped	N/A	3TC D4T RTV SQV	No changes	D5: 63	D8: Graft failure, D1686: Alive
029	Living	CsA MMF prednisone	No changes	N/A	3TC AZT SQV	No changes		D1015: Alive, functioning

IS = immunosuppressant agents: MP = methylprednisolone, MMF = mycophenolate, CsA = cyclosporine, Tac = tacrolimus, thymo = thymoglobulin

ARVs = antiretrovirals: 3TC = lamivudine, ABC = abacavir, APV = amprenavir, ATV = atazanavir, AZT = zidovudine, D4T = stavudine, DDI = didanosine, DLV = delavirdine, EFV = efavirenz, FPV = fosamprenavir, FTC = emtricitabine, IDV = indinavir, NFV = nelfinavir, NVP = nevirapine, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, LPV/RTV = lopinavir/ritonavir.

Symbols

-> = replaced with.

+ = added.

D = day.

transplant recipients have outcomes similar to or better than the older, HIV-uninfected transplant population. However, the imprecision of these survival estimates is important, especially if the true estimates approached the lower bounds of the 95% CI. An ongoing study aims to enroll 275 liver and kidney recipients at 21 U.S. transplant centers and is powered to allow comparisons using both over 65-year-old and age-, organ type- and transplant indication-matched control groups ([www.hivtransplant.com](http://www.hivtransplant.com)).

The existing literature comparing recurrent HCV and survival outcomes in HCV/HIV-coinfected and HCV-monoinfected liver transplant recipients remains scant and contradictory (13,22,23). In our study, two liver transplant recipients died from complications of recurrent HCV infection, the third died of sepsis in the setting of recurrent HCV-associated cirrhosis and the retransplanted living liver recipient subsequently died from HCV-associated cirrhosis. Four of six HCV-infected liver recipients demonstrated histologic fibrosis progression, resulting in initiation of interferon and ribavirin therapy. Poorer results in the HCV- as compared to the HBV-coinfected liver recipients are of concern, and represent a key area of ongoing investigation.

Despite frequent rejection, the 3-year kidney allograft loss rate was similar to that seen among the general transplant population. Drug interactions resulting in alterations in the immunosuppressant exposure may be associated with rejection (24). Our analysis of the predictors of kidney rejection is limited by the small number of events and the large number of potential immunologic, pharmacologic and other factors contributing to this phenomenon. Although altered exposure to the immunosuppressive agents as a result of drug interactions may play a role in the increased rejection rates, some of the aggressive rejections occurred within the first week following the transplant. These rejections were consistent with a very accelerated course, and really could not be explained by an inadequate exposure to maintenance immunosuppressive agents. We have hypothesized that the patients with HIV infection have an altered immune system, which may have contributed to the aggressive, accelerated rejection observed in some subjects. Ongoing studies aim to delineate the mechanisms contributing to this aggressive alloimmune response.

Graft function in this study was better than that reported in a series of 40 HIV-infected kidney transplant recipients who had fewer rejection episodes (16). Thus, higher CNI levels may prevent rejection at the cost of nephrotoxicity. It is our current practice to allow thymoglobulin induction therapy in kidney recipients as a result of the aggressive alloimmune response seen in this pilot study. However, serious non-OIs resulting in hospitalization were more common among those who required thymoglobulin treatment, and CD4+ T-cell counts often remain suppressed for months (20). In addition, there was an early sepsis-related death in

a liver transplant recipient with hepatorenal syndrome who received thymoglobulin to facilitate renal recovery (unpublished data). As a result, we recommend minimizing thymoglobulin use in the early period following liver transplantation by as much as possible.

We have shown that posttransplant immunosuppression does not cause rapid HIV disease progression in the context of an aggressive OI prophylaxis. Stability in CD4+ T-cell counts and the ability to successfully suppress plasma HIV RNA levels suggest minimal HIV disease progression. Of note, half of the subjects with a detectable HIV RNA level had single, relatively low RNA values without clinical significance. In the others, there were nine episodes of transient viremia, and only one of 21 subjects had a detectable HIV RNA level at the last study visit. Antiretroviral and immunosuppressant medication adjustments were required frequently (Table 3) in order to manage complex drug interactions and side effects (24–27). There were no OIs or poorer outcomes among the five subjects with an OI history who were included later in the study, suggesting that this strategy is safe, even among those with a history of KS. Concerns about potential KS recurrence remain, given the serious implications of posttransplant KS. A patient in another cohort developed *de novo* KS and Castleman's disease postliver transplant and was reported to have his disease controlled and to be doing well (28). Considering transplant and HIV-related OIs with regard to prophylaxis, differential diagnosis and therapy requires coordination of a multidisciplinary team of transplant, HIV and pharmacology experts.

In conclusion, promising early patient and graft survival rates in HIV-infected liver and kidney transplant recipients continue with longer follow-up (14,17). The relatively high death rate in the HCV-coinfected liver recipients and the frequent allograft rejection among the kidney transplant recipients are the focus of the ongoing investigation. Larger studies will facilitate identification of potential predictors of poor outcomes that may be used to modify patient selection criteria or to target specific therapeutic approaches. Basic science laboratory studies focusing on host immunologic and viral characteristics may elucidate the pathogenesis of these complications and promote modifications in clinical management.

## Acknowledgments

This study was conducted with proper institutional review board approval from each participating center, as well as annual safety review by the University of California, Office of the President, University AIDS Research Program (UARP) Medical Monitoring Committee.

## References

1. Rodriguez RA, Mendelson M, O'Hare AM, Hsu LC, Schoenfeld P. Determinants of survival among HIV-infected chronic dialysis patients. *J Am Soc Nephrol* 2003; 14: 1307–1313.

2. Martin-Carbonero L, Soriano V, Valencia E, Garcia-Samaniego J, Lopez M, Gonzalez-Lahoz J. Increasing impact of chronic viral hepatitis on hospital admissions and mortality among HIV-infected patients. *AIDS Res Hum Retroviruses* 2001; 17: 1467–1471.
3. 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.
4. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med* 2002; 347: 284–287.
5. 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.
6. Poli F, Scalapogna M, Pizzi C, Mozzi F, Sirchia G. HIV infection in cadaveric renal allograft recipients in the North Italy Transplant Program. *Transplantation* 1989; 47: 724–725.
7. Tzakis AG, Cooper MH, Dummer JS, Ragni M, Ward JW, Starzl TE. Transplantation in HIV+ patients. *Transplantation* 1990; 49: 354–358.
8. Erice A, Rhame FS, Heussner RC, Dunn DL, Balfour HH, Jr. Human immunodeficiency virus infection in patients with solid-organ transplants: Report of five cases and review. *Rev Infect Dis* 1991; 13: 537–547.
9. Bouscarat F, Samuel D, Simon F, Debat P, Bismuth H, Saimot AG. An observational study of 11 French liver transplant recipients infected with human immunodeficiency virus type 1. *Clin Infect Dis* 1994; 19: 854–859.
10. Ragni MV, Dodson SF, Hunt SC, Bontempo FA, Fung JJ. Liver transplantation in a hemophilia patient with acquired immunodeficiency syndrome. *Blood* 1999; 93: 1113–1114.
11. 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.
12. 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.
13. Ragni MV, Belle SH, Im K et al. Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis* 2003; 188: 1412–1420.
14. 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.
15. 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.
16. 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.
17. Roland ME, Stock PG. Review of solid-organ transplantation in HIV-infected patients. *Transplantation* 2003; 75: 425–429.
18. Margolis D, Heredia A, Gaywee J, Oldach D, Drusano G, Redfield R. 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.
19. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). *MMWR Recomm Rep* 1999; 48: 1–59, 61–56.
20. Carter JT, Melcher ML, Carlson LL, Roland ME, Stock PG. Thymoglobulin-associated CD4+ T-cell depletion and infection risk in HIV-infected renal transplant recipients. *Am J Transplant* 2006; 6: 753–760.
21. Terrault NA, Carter JT, Carlson L, Roland ME, Stock PG. Outcome of patients with hepatitis B virus and human immunodeficiency virus infections referred for liver transplantation. *Liver Transpl* 2006; 12: 801–807.
22. Norris S, Taylor C, Muesan P et al. Outcomes of liver transplantation in HIV-infected individuals: The impact of HCV and HBV infection. *Liver Transpl* 2004; 10: 1271–1278.
23. de Vera ME, Dvorchik I, Tom K et al. Survival of liver transplant patients coinfecting with HIV and HCV is adversely impacted by recurrent hepatitis C. *Am J Transplant* 2006; 6: 2983–2993.
24. 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.
25. Frassetto L TT, Aggarwal AM, Bucher P et al. Pharmacokinetic interactions between cyclosporine and protease inhibitors in HIV+ subjects. *Drug Metab Pharmacokin* 2003; 18: 114–120.
26. Frassetto LA, Baluom M, Roland ME, Carlson L, Stock P, Benet LZ. Two-year evaluation of the interactions between antiretroviral medication and cyclosporine in HIV+ liver and kidney transplant recipients. In: 10th Conference on Retroviruses and Opportunistic Infections; 2003 February 10–14, 2003; Boston, MA; 2003.
27. Frassetto LA, Chen W, Kansal N, Levi M et al. Immunosuppressant adjustments of doses and dosing intervals in HIV-infected kidney and liver transplant patients. In: *TransplantAsia* 2004; 2004 December 1–4, 2004; Singapore; 2004.
28. 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.