1- to 3-Year Outcomes in HIV-Infected Liver and Kidney Transplant Recipients

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Background

- Liver and kidney failure are growing problems in the HAART era.
- Solid organ transplantation may be a safe and effective option given:
  - improvements in HIV-associated morbidity and mortality
  - improvements in post-transplant immunosuppressive strategies and opportunistic infection prophylaxis
  - hypothetical benefit of immunosuppressives in HIV-infected patients.
- Data from the pre-HAART era show inconsistent but relatively poor outcomes.
- Case series and small prospective studies in the HAART era suggest that patient and graft outcomes may be similar to those seen in HIV-uninfected patients.
- We describe the largest cohort of HIV-infected transplant recipients in the HAART-era with the longest follow-up to date.

Methods

Study design

- Prospective observational study of HIV-infected kidney and liver transplant recipients followed for up to 5 years for:
  - patient and graft survival
  - HIV-related complications and changes in CD4+ T-cell counts and HIV RNA
  - rejection and graft function, including HCV and HBV progression
  - other complications

Subject selection criteria

- CD4+ T-cell count ≥ 200 for kidney recipients and ≥ 100 for liver recipients
- HIV RNA undetectable. Liver recipients who are unable to tolerate ARVs but in whom full post-transplant virologic suppression is predicted are included.
- Opportunistic complication history excluded until protocol revision in April 2002 to allow most OIs with continued exclusion of PML, cryptosporidiosis and visceral KS. (One subject with a history of pulmonary KS is included.)

Interventions

- Donors: Deceased and living donors were used.
  - Deceased organs were considered to be at "high infectious risk" if they were serologically negative for HIV and hepatitis B and C but the donor may have engaged in behavior putting them at risk for recent acquisition.
- Immunosuppression and rejection management: initial immunosuppression included either cyclosporine or tacrolimus with or without mycophenolate mofetil (MMF), in combination with steroids. Daclizumab use was allowed. Rejections were managed with a steroid pulse, changing calcineurin inhibitors or doses, and/or adding sirolimus and/or thymoglobulin.
- Antiretroviral management: all ARVs were allowed. AZT and D4T use was minimized due to in vitro data showing antiretroviral antagonism with MMF.
- HIV and transplant prophylaxis: standard prophylaxis was employed for PCP, CMV, MAC and candida.

Results

29 subjects were enrolled between March 2000 and September 2003.

Table 1. Baseline Characteristics of HIV-Infected Transplant Recipients

Characteristic	Liver Recipients (N = 11)	Kidney Recipients (N = 18)
Age - yr	46±12	44±6
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 (subjects)	1 (9)	4 (22)
Pneumocystis carinii pneumonia	1	1
*Cytomegalovirus**	0	2
Cryptococcal Meningitis	1	0
Mycobacterium avium complex	0	1
Tuberculosis	0	1
Kaposi's Sarcoma	0	1
CD4+ T-cell Count (cells/mm³)†	279 (104 - 450)	439 (293-613)
HIV RNA †		
Any detectable - no. (%)	2 (18)	0
Copies/mL – median (range)	Undetectable (<50 – 23,247)	Undetectable (all <50)
Viral Hepatitis - no. (%)		
Hepatitis C	6 (55)	5 (28)
Hepatitis B Surface Antigen Positive	5 (45)	0
Hepatitis B Core Antibody Positive	2 (18)	2 (11)

* Cytomegalovirus associated lymphadenitis and enteritis

† Most recent pre-transplant 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

Table 2. Past Medical History of HIV-Infected Transplant Recipients

Diagnosis	Liver Recipients (N = 11)	Kidney Recipients (N = 18)
Hemophilia	3	—
Diabetes mellitus	1	2
Hypertension	3	14
Congestive heart failure/ Cardiomyopathy	—	3
Atrial fibrillation	—	1
Pericarditis/pericardial effusion	—	3
Hyperlipidemia	—	4
COPD/asthma/other respiratory	—	3
Pancreatitis	—	1
GERD/peptic ulcer disease/ gastritis	2	1
Ulcerative colitis	1	—
Endocarditis	—	1
Septic arthritis	2	—
Bacteremia	1	1
Catheter infection	—	1
Pneumonia	1	5
Soft tissue infection	—	1
Sinusitis	1	—
Infectious diarrhea	1	3
Herpes zoster	4	7
Herpes simplex	5	5
Genital warts	4	5
Thrush	4	1
Avascular necrosis of the hip DJD/arthritis	—	1
Peripheral neuropathy	2	—
Seizure disorder	1	3
Leukemia	—	1
Skin cancer	1	—

Table 3. Indications for Transplantation and Donor Characteristics

Liver Transplant Recipients		Kidney Transplant Recipients	
Indications for Transplantation	**Number (%)**	**Indications for Transplantation**	**Number (%)**
HCV without HCC	3 (27)	HIVAN[1]	8 (44)
HCV with HCC	2 (18)	Hypertension	10 (56)
HBV	4 (36)	Diabetes	2 (11)
HCV and HBV	1 (9)	Other[2]	3 (17)
Other	1 (9)	**Donor Characteristics**	
Donor Characteristics		Living (related)	5 (28)
Living	3 (27)	Living (unrelated)	3 (17)
Deceased	6 (55)	Deceased	6 (33)
Deceased/high Infectious Risk[1]	1 (9)	Deceased/High Infectious Risk[3]	4 (23)
Deceased/Other High Risk[2]	1 (9)		

[1] Recent incarceration. In addition, 1 HBV+ recipient received a hepatitis B Surface Ag+ donor organ.

[2] Liver hematoma

[1] HIV-Associated Nephropathy, only 1 case biopsy documented, thus this number likely over-represents the true number of cases with HIVAN

[2] MGPN, IgA nephropathy, chronic pyelonephritis/interstitial nephritis

[3] Recent incarceration in 3 cases; recent injection drug use. In addition, 2 HCV+ recipients received HCV+ donor organs.

Patient and Graft Survival

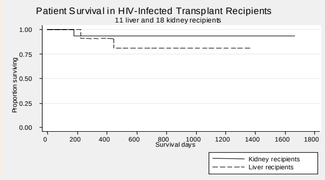


Figure 1. Kaplan–Meier Estimates of Death from Any Cause among Patients Who Received Liver or Kidney Transplants

- There were 2 deaths due to recurrent HCV among 11 liver transplant recipients followed for 701 (218-1364) days after transplantation.
- There was 1 death due to congestive heart failure among 18 kidney transplant recipients followed for a median of 869 (12-1664) days after transplantation. The subject followed for only 12 days experienced graft failure and was terminated from the study.
- The 1 and 3 year patient survival rates for liver transplant recipients were 91% and 81% respectively.
- The 1 and 3 year patient survival rate for kidney transplant recipients was 94%.

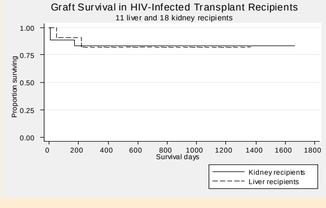


Figure 2. Kaplan–Meier Estimates of Graft Failure, without Censoring Death with Function, from Any Cause among Patients Who Received Liver or Kidney Transplants

- There was 1 graft loss among 11 liver transplant recipients (small for size graft lesion in living liver recipient) and 2 graft losses among 18 kidney transplant recipients (rupture due to severe acute rejection; chronic allograft nephropathy).
- The 1 and 3 year graft survival rate for liver transplant recipients was 91% with censoring death with function and 82% without censoring death with function.
- The 1 and 3 year graft survival rate for kidney transplant recipients was 89% with censoring death with function and 83% without censoring death with function.

Survival Comparison with National Transplant Data

Table 4. Patient and Graft Survival in Organ Procurement and Transplantation Network (OPTN) Database and in HIV-Infected Study Subjects

	One Year Patient Survival Liver	One Year Patient Survival Kidney	Three Year Patient Survival Liver	Three Year Patient Survival Kidney
All OPTN	87.6 (87.0, 88.2)	95.6 (95.4, 95.8)	79.9 (79.3, 80.5)	90.8 (90.5, 91.1)
65 years+ OPTN	80.5 (77.9, 83.0)	90.4 (89.4, 91.3)	69.6 (66.9, 72.2)	78.0 (76.6, 79.4)
HIV-infected study subjects	90.9 (73.9, 100)	93.8 (81.9, 100)	80.8 (56.8, 100)	93.8 (81.9, 100)
	One Year Graft Survival		**Three Year Graft Survival**	
All OPTN	82.4 (81.8, 83.1)	91.3 (91.0, 91.5)	73.5 (72.8, 74.2)	81.8 (81.4, 82.2)
65 years+ OPTN	76.5 (73.9, 79.1)	86.2 (85.1, 87.3)	66.6 (63.9, 69.2)	72.3 (70.9, 73.8)
HIV-infected study subjects*	81.8 (59.0, 100)	83.3 (66.1, 100)	81.8 (59.0, 100)	83.3 (66.1, 100)

Based on OPTN data as of February 4, 2005. One year survival is based on 1999 - 2001 transplants, and 3 year survival is based on 1996 - 1999 transplants. http://www.optn.org/latestData/step2.asp

* 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 90.9 (73.9, 100) and 88.9 (73.9, 100) for liver and kidney transplants, respectively.

Table 5. HIV Disease Progression Post-Transplant

Characteristic	Liver Transplant Recipients	Kidney Transplant Recipients
Opportunistic Infections, No. (%)		
CMV esophagitis[1]	1 (9)	—
Candida esophagitis[2]	—	1 (6)
CD4+ T-cell Count (cells/mL), Mean (95% CI)		
Change from baseline	72 (-75, 219)	-27 (-180, 127)
HIV RNA, No. (%)		
Detectable at most recent visit[3]	1 (9)	0
Ever detectable[4]	6 (55)	6 (33)

[1] In a subject with CD4 count of approximately 200 who died of recurrent HCV

[2] Discovered incidentally in a subject with diabetes; resolved with clotrimoxazole.

[3] No subjects currently being followed in the study have detectable HIV RNA. The liver recipient with detectable HIV RNA at the last visit has expired.

[4] 2 liver recipients had detectable HIV RNA at transplant and were rapidly suppressed. There was transient viremia in 3 additional liver recipients (67 – 1330 copies) and 6 kidney recipients (63 – 44,000).

Rejection

- 12 (67%) kidney and 1 (9%) liver recipients had a total of 20 rejection episodes
  - 16 (80%) acute cellular
  - 1 (5%) acute vascular
  - 2 (10%) acute cellular and vascular
  - 1 (5%) presumptive diagnosis of recurrent rejection without biopsy
- 5 were taking cyclosporine and 8 had not yet initiated calcineurin inhibitor therapy at the time of the first rejection diagnosis in accordance with the general UCSF transplant protocol of not starting calcineurin inhibitors until the serum creatinine is below 3 mg/dL.
- Among subjects taking cyclosporine, mean plasma levels were not different in those who did and did not have rejection episodes.
- Overall, cyclosporine was being taken at the time of 10 rejection diagnoses and tacrolimus at the time of 2 diagnoses.
- 7 subjects received thymoglobulin in response to 8 rejection episodes

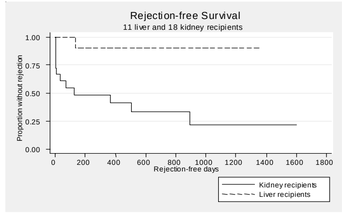


Figure 3. Kaplan–Meier Estimates of Rejection-Free Survival among Patients Who Received Liver or Kidney Transplants

- The 1 and 3 year cumulative rejection estimate (SE) for liver transplant recipients is 10% (9%).
- The 1, 2 and 3 year cumulative rejection estimates (SE) for kidney transplant recipients are 52% (12%), 66% (12%) and 77% (12%).

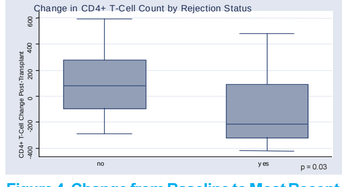


Figure 4. Change from Baseline to Most Recent CD4+ T-Cell Counts in Subjects with and without Rejection

- Subjects who had one or more rejection episodes had a mean decrease in CD4+ T-cell counts (-111; 95% CI -281, 58) while those without any rejection episodes had a mean increase in CD4+ T-cell counts (110; 95% CI -18, 238) (p = 0.03, two-sample t test with unequal variances).

Kidney Function

- Median (IQR) creatinine in kidney recipients = 1.8 (1.3, 2.5)
- Kidney recipients with rejection episodes have a higher mean creatinine than those without (2.8 versus 2.4; p<0.05) (Two-sample Wilcoxon rank-sum [Mann-Whitney] test)

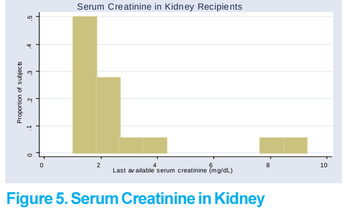


Figure 5. Serum Creatinine in Kidney Transplant Recipients

Liver Function

- There has been no HBV progression among 5 recipients with HBV infection
- Among 6 recipients with HCV infection, 4 have evidence of disease progression
- Median (IQR) AST in liver recipients = 36 (32, 194)
- Liver recipients with HCV co-infection have a higher mean AST than those without (202 versus 32; p=0.05)

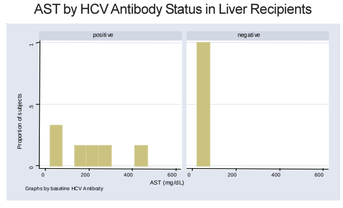


Figure 6. AST in Liver Transplant Recipients

Adverse Events

Table 6. Adverse Events Post-Transplant

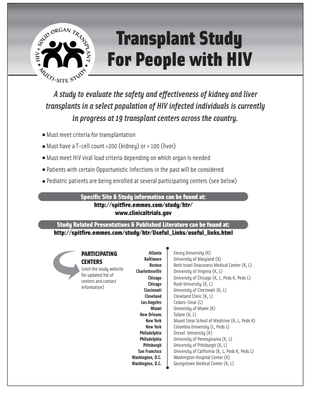
Complication	Liver Transplant Recipients No. Subjects	Liver Transplant Recipients No. Events	Kidney Transplant Recipients No. Subjects	Kidney Transplant Recipients No. Events
Total adverse events and severity[1]	11	141	17	165
Mild	11	32	13	26
Moderate	11	80	17	100
Severe	7	21	12	26
Life-threatening	4	8	4	11
Hospitalization required or prolonged	6	25	10	34
Resulted in change in immunosuppression				
Reduced	7	14	10	26
Held	3	5	6	8
Discontinued	2	4	3	4
Increased	1	1	3	3
Resulted in change in ARV				
Reduced	1	1	1	1
Held	1	2	3	7
Discontinued	3	4	3	3
Increased	1	1	0	0

[1] Main safety outcomes that are analyzed separately (death, graft failure, rejection, and HBV and HCV recurrence) are not included in the table. In liver transplant recipients, maximum severity per subject is 'life-threatening' for 4, 'severe' for 4, and 'moderate' for 3 subjects. In kidney transplant recipients, maximum severity per subject is 'life-threatening' for 4, 'severe' for 8, and 'moderate' for 5 subjects. No adverse events were reported for one of the kidney transplant recipients who was withdrawn from the study after very early graft failure.

- Adverse events are common in the context of transplantation and often results in hospitalization and medication changes.

Discussion

- Overall graft and patient survival outcomes are promising even when compared to outcomes in the general transplant population; the trends continue to hold up over longer periods of follow-up than previously reported.
- Areas of concern include potential high rates of HCV recurrence, also seen in HIV-negative transplant recipients, and high rates of rejection. Longer follow-up of more subjects will be required to determine if these trends are significant.
- Additional areas in an ongoing study enrolling patients at 19 US transplant centers include drug interactions, HPV-associated ano-rectal disease, HHV8-associated disease, clinical manifestations of other human herpes viruses, and outcomes in patients with lamivudine resistant HVB or HIVAN.
- At this stage of our research program, we believe it is reasonable to expect insurance reimbursement for liver and kidney transplants in people with HIV infection.



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