



Liver and Kidney Transplantation in HIV-Infected Patients: A Preliminary Multi-Site Experience

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BACKGROUND

- HIV-infected patients have often been excluded from consideration for transplantation for two reasons:
 - First*, concerns that HIV-associated morbidity and mortality were too high to justify the use of a scarce resource
 - Second*, concerns that post-transplant immunosuppression might accelerate HIV disease progression
- HAART-associated improvements in morbidity and mortality have eliminated the first justification for withholding this intervention
- The second concern is being evaluated in a prospective, multi-center study with the following aims:
 - Evaluate the impact of immunosuppression on survival and HIV disease progression
 - Evaluate the impact of HIV infection on graft function
 - Describe the important pharmacokinetic interactions between the PI s/NNRTIs and immunosuppressants
- Many participating centers have transplanted patients prior to the initiation of the study, using similar selection criteria

METHODS

- Combined prospective analysis of enrolled subjects and retrospective review of HIV-infected transplant recipients at centers participating in the multi-site clinical trial in the HAART-era
- "Eligible" Subjects*: at the time of transplant, met or would have met selection criteria
- "Ineligible" Subjects*: at the time of transplant, did not meet selection criteria

	Inclusion Criteria	Exclusion Criteria
CD4+ T-cell count	Kidney: > 200 cells/μl Liver: > 100 cells/μl	—
HIV-1 RNA*	Kidney: < 50 copies/ml Liver: < 50 copies/ml or Unable to tolerate ARVs with prediction of full suppression post-transplant	—
Opportunistic Complications	—	Any AIDS-defining except candida esophagitis**
Mental Status	—	Unable to evaluate fully to exclude HIV-associated complications

* Under regular review for possible future revision
** Currently under revision

RESULTS:

Demographics (N = 49)

- 41 *"Eligible" Subjects*: 22 kidney + 19 liver recipients
- 8 *"Ineligible" Subjects*: 6 kidney + 2 liver recipients
 - Undiagnosed HIV (advanced): 1 kidney recipient (post-transplant CD4 count = 5, HIV-1 RNA = 187,000)
 - CD4+ T Cell Count < 100: 1 liver recipient (76 cells/μl)
 - HIV-1 RNA > 50: 3 kidney recipients (median = 580 copies/ml; range = 84 – 2000 copies/ml)
 - History of Opportunistic Complications: 2 kidney recipients (PCP + CMV, KS + CMV)
 - Mental Status: 1 liver recipient without full evaluation of baseline altered mental status

	Kidney	Liver
Gender:		
Male	20 (91%)	18 (95%)
Female	2 (9%)	1 (5%)
Age: Median years (range)	45 (33–64)	44 (15–67)
Ethnicity:		
Caucasian	9 (41%)	15 (79%)
African American	12 (54%)	1 (5%)
Latino	0	2 (11%)
Asian	1 (5%)	1 (5%)

Baseline Data ("Eligible Subjects")

Indications for Transplant: Kidney	
Hypertension	5 (23%)
Hypertension + HIVAN	5 (23%)
Diabetes Mellitus	4 (18%)
Hypertension + Diabetes	1 (4%)
Other	7 (32%) (IgA nephropathy, FPGN, lupus, polycystic kidney disease [2], unknown)
Indications for Transplant: Liver	
Hepatitis C	11 (58%)
Hepatitis B	3 (16%)
Hepatitis C + B	2 (11%)
Fulminant Hepatitis A	1 (5%)
Primary sclerosing cholangitis	1 (5%)
Nevirapine hepatotoxicity	1 (5%)
Hepatitis C co-infection: Kidney	8 (36%)
CD4+ T-cell count: median (range)	
Kidney	455 cells/μl (200–1054)
Liver	321 cells/μl (103–973)
HIV-1 RNA: median (range)	
Liver	<50 copies/ml (<50–115,776)

Table 3: Organ Donor Source

	Kidney	Liver
Living	7 (32%)	4 (21%)
Cadaveric	11 (50%)	14 (74%)
"High Risk" Cadaveric	4 (18%)	1 (5%)

Outcomes ("Eligible Subjects")

A. GENERAL OUTCOMES

Median follow-up (1/22/02)	279 days (3–1567)
Deaths (1 kidney + 3 liver)	4
HIV-associated	0
Transplant-associated (post-op pancreatitis, ischemic bowel)	2
Recurrent Hepatitis C	1
Rejection	1
(due to discontinuation of PI and resulting low immunosuppression levels)	

B. HIV-RELATED OUTCOMES

Opportunistic Complications	1 CMV esophagitis 1 candida esophagitis
CD4+ T-cell count: median (range)	
Kidney	460 cells/μl (76–1300)
Liver	296 cells/μl (89–590)
HIV-1 RNA: median (range)	
Kidney	< 50 copies/ml (<50–11,343)
Liver	< 50 copies/ml (<50–80)

Table 4: Antiretroviral Use

No Change	36 (88%)
PI	20 (49%)
NNRTI	8 (20%)
Both	5 (12%)
Neither	3 (7%)
Changed	5 (12%)
PI to NNRTI	3 (7%)
PI to neither	1 (2.5%)
Neither to NNRTI	1 (2.5%)

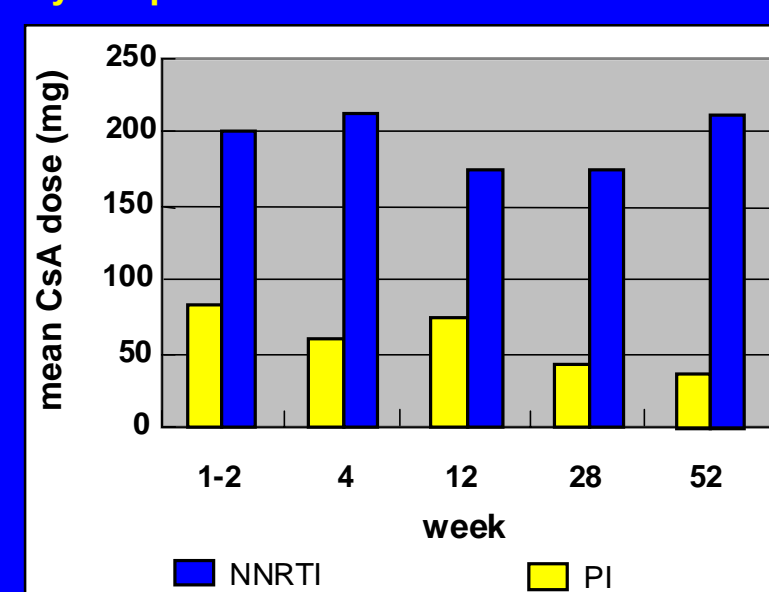
C. TRANSPLANT RELATED OUTCOMES

Re-transplantation (Living donor small for size graft failure)	1 liver
Graft loss (Unable to achieve adequate immunosuppression levels)	1 kidney
Additional subjects experiencing rejection	8 (36%) kidney 2 (11%) liver

Table 5: Immunosuppressant Use

Calcineurin Inhibitor: No Change	38 (93%)
Cyclosporine	21 (51%)
Tacrolimus	18 (44%)
Calcineurin Inhibitor: Changed	3 (7%)
Cyclosporine to tacrolimus, then to cyclosporine + sirolimus	2 (5%)
Tacrolimus to tacrolimus + sirolimus	1 (2%)
Other Agents	
Mycophenolic Acid	14 (34%)
IL-2 receptor inhibitors	10 (24%)
Anti T-cell agents	2 (5%)

Figure 1. Impact of PI and NNRTI on Cyclosporine Levels



*PI use increases cyclosporine levels, requiring dose reduction.

D. OTHER COMPLICATIONS

- Endocrine: diabetes, hyperlipidemia
- Infection: Recurrent hepatitis C infection (4 – includes 2 deaths), genital herpes, endocarditis (2), cholangitis with candida sepsis, influenza, bacterial pneumonia, epididymitis, CMV viremia (2)
- Neoplasia: squamous cell carcinoma/skin, bowen's disease
- Medication related: peripheral neuropathy (2), pancreatitis (mild), lactic acidosis with hepatic steatosis (mild)
- Other: post-op myocardial infarction, post-surgical infections (2), ATN (3)

Outcomes ("Ineligible Subjects")

- 2 Deaths: kidney recipient with undiagnosed advanced HIV (PML, MAC at 2.5 months)+ liver recipient without full evaluation of baseline mental status abnormality (PML at 4 months)
 - CD4+ T Cell Count < 100: 1 liver recipient (102 cells/μl at 5 weeks)
 - HIV-1 RNA > 50: 3 kidney recipients < 50 or < 400
 - History of Opportunistic Complications: 2 kidney recipients without recurrence at 15 months and 5 weeks
- There is *no evidence of significant HIV disease progression* in the "eligible subjects," those without a history of opportunistic complications and with relatively preserved CD4 counts and suppressed or suppressible HIV viremia
 - Both of the opportunistic complications in this group, CMV and candida esophagitis, could have resulted from the effects of immunosuppression alone. The role of HIV is unclear.
 - CD4+ T-cell counts have remained stable in kidney and liver recipients
 - Most subjects continue to have fully suppressed plasma HIV on HAART
 - There is *evidence of HIV disease progression* in a sub-set of the "ineligible subjects," those with unrecognized advanced (untreated) HIV infection and altered mental status not fully evaluated, both of whom developed PML
 - As with any co-morbidity, the stage and severity of HIV infection should be considered in the evaluation for transplantation
 - Graft survival* is good in HIV-infected transplant recipients in the HAART-era, similar to all recipients in the UNOS database.
 - 36/41 (88%) of carefully selected subjects have functioning grafts
 - 89% of kidney grafts are functioning
 - UNOS 1997-98 one year graft function data: cadaveric kidney recipients = 89.4%; living kidney recipients is 94.5%
 - 84% of liver grafts are functioning
 - UNOS 1997-98 one year graft function data: liver recipients = 81.4%
 - The evaluation and management of HIV-infected transplant recipients is complex and requires a well-coordinated multi-disciplinary team. These preliminary data are very promising.
 - For more information about the multi-site study, see www.emmes.com