

HIV RNA Suppression Following Liver and Kidney Transplantation

Michelle Roland¹, Burc Barin², Michael Wong³, Marla Keller⁴, Margaret Ragni⁵, David Hardy⁶, Emily Blumberg⁷, Judith Feinberg⁸, Don Stablein², and Peter Stock¹

¹University of California, San Francisco, CA ²The EMMES Corporation, Rockville, MD, ³Beth Israel Deaconess, Boston, MA, ⁴Mt. Sinai Medical Center, New York, NY,

⁵University of Pittsburgh, Pittsburgh, PA, ⁶Cedars-Sinai, Los Angeles, CA, ⁷University of Pennsylvania, Pennsylvania, PA and ⁸University of Cincinnati, Cincinnati, OH

Background

- Solid organ transplantation is increasingly available to HIV-infected patients.
- HIV-related complications appear rare.
 - Overall, CD4+ T-cell counts have been stable.
 - Few opportunistic infections have been reported, even in patients with low CD4+ T-cell counts following the use of thymoglobulin to treat rejection or delayed graft function.
- Patterns of post-transplant plasma HIV RNA have not been described in this population.
 - Immunosuppression and/or drug interactions may make durable HIV RNA control difficult.
 - Conversely, antiviral and/or immune modulating effects of immunosuppression may enhance virologic control.

Methods

Prospective, multi-site cohort study of HIV-infected liver and kidney recipients

Subject selection criteria: Pre-transplant HIV RNA

- Pre-transplant HIV RNA was undetectable, or
- Complete suppression was predicted in liver transplant candidates who could not tolerate antiretroviral therapy and thus had detectable HIV RNA

Interventions: Antiretroviral and immunosuppression medication protocols

- Antiretroviral and immunosuppression choices were individualized.

Measurements

- Ultrasensitive assays were used most commonly, but standard assays were acceptable.
- Incidence (95% CI) of any detectable HIV RNA
- Median [IQR], (range) peak HIV RNA
- Duration of detectability in subjects with more than a single detectable HIV RNA measurement that resolved
- Episodes were classified as
 - 1) any single detectable RNA value that resolved
 - 2) occurring off ARVs
 - 3) resulting in ARV change

Statistical analysis

- Predictors of first detectable RNA were evaluated in univariate and multivariate Cox proportional hazards models. Covariates were analyzed as time-dependant covariates as appropriate.

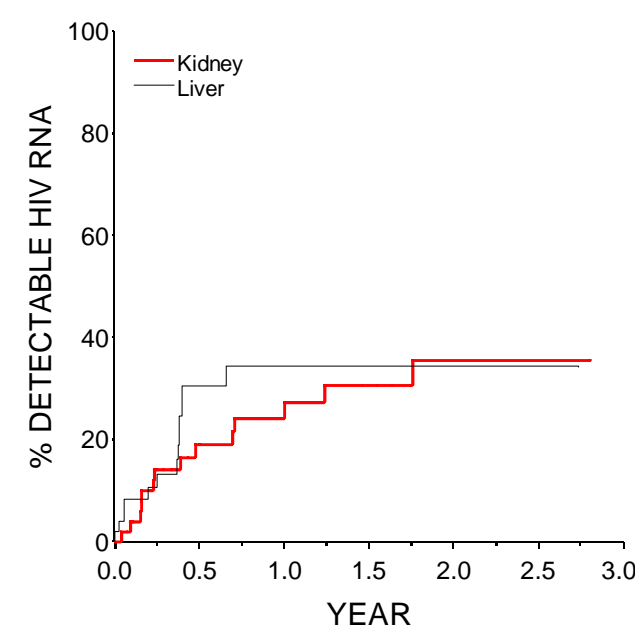
Results

Subjects

- 104 subjects were transplanted between 11/03 and 9/06.
 - 52 kidney and 52 liver recipients

Incidence of detectable HIV RNA

- 38 episodes of detectable HIV RNA occurred in 27 (26%) of the 104 subjects.
 - 8 (8%) subjects had >1 episode of detectable HIV RNA
- The 1- and 2-year cumulative incidence (95% CI) of any detectable HIV RNA was as follows:
 - Kidney recipients: 27% (14%, 41%) & 36% (19%, 52%)
 - Liver recipients: 34% (19%, 50%)



- The proportion of subjects with undetectable HIV RNA at 6, 12, and 18 months post-transplant was 88%, 89%, and 91%, respectively.

Quantity of HIV RNA when detectable

Median [IQR], (range) peak HIV RNA cps/mL

- All kidney recipients: **286** [76, 2700], (52–500000)
- All liver recipients: **1367** [161, 14500], (61–47600)
- Subjects with single detectable measure followed by undetectable: **121** [65, 326], (53–1800)

Total duration of detectability

Median [IQR], (range) days of detection:

- All kidney recipients: **208** [99, 294], (28–577)
- All liver recipients: **217** [42, 462], (12–547)
- Subjects with single detectable measure followed by undetectable: 9 (33%) subjects (7 kidney and 2 liver)

Antiretroviral use

- Median (range) total number of lifetime pre-transplant ARVs = 5 (0–14)
- Median (range) number of ARVs post-transplant = 3 (0–6)
- 8 (21%) episodes detectable HIV RNA occurred while not on ARVs:
 - 1 kidney and 7 liver recipients
 - 3 cases occurred shortly after transplant, before ARVs had been reinitiated
 - 1 experienced early acute rejection and was off ARVs for re-transplantation
 - Of the remaining 4 cases
 - 3 had hospitalizations and/or infections (cellulitis, CMV antigenemia), allograft rejection, recurrent HCV while off ARVs
 - 1 had no adverse events reported, but had 2 ARV regimen changes prior to being off ARVs for approx. 1 month
- 5 (13%) resulted in ARV change with subsequent suppression of HIV RNA
 - 2 kidney recipients
 - 3 liver recipients

Predictors of first detectable HIV RNA (Table 1)

In univariate models

- **Increased risk of detectable HIV RNA:** Not being on ARVs prior to measurement (hazard ratio [HR] 4.2; CI 1.7, 10.7)
- **Protective factors:** Increasing # of ARVs (HR 0.6; CI 0.5, 0.8) and NNRTI-based regimens (HR 0.36; CI 0.14, 0.96)
- Covariates with HR p-value of <0.1, included in initial multivariate models: hepatitis C, total # lifetime pre-transplant ARVs, prednisone use
- No association with age, race, nadir and most recent CD4+ T cell count, transplanted organ, pre-transplant HIV RNA, time to ARV initiation post-transplant, ZDV or D4T use with mycophenolate mofetil, ddI or abacavir use with mycophenolate mofetil, total # of medications, immunosuppression type, organ function and hospitalization, rejection or infection in prior 30 days

In the *final multivariate model*, the **number of ARVs** (HR 0.43; CI 0.21, 0.87) and the **total number of lifetime pre-transplant ARVs** (HR 1.20; CI 1.04, 1.38) were significant after being adjusted for being off ARVs, NNRTI-based regimens, HCV status, and prednisone use.

Table 1. Univariate and Multivariate Analyses of Predictors of First Detectable HIV RNA

Univariate Predictor	Hazard Ratio (95% CI)	P-Value	Multivariate Predictors	Hazard Ratio (95% CI)	P-Value
Race (white vs. others)	0.9 (0.4, 2.0)	0.88	Number ARVs (count)*	0.43 (0.21, 0.87)	0.02
Age (continuous)	1.0 (0.97, 1.04)	0.79	NNRTI-based ARV (Yes/No)*	0.61 (0.21, 1.79)	0.37
Organ (kidney vs. liver)	1.3 (0.6, 2.7)	0.52	Off-ARV (Yes/No)*	0.28 (0.03, 2.62)	0.26
Hepatitis C (Yes/No)	2.1 (0.9, 4.5)	0.07	Hepatitis C (Yes/No)	1.42 (0.60, 3.38)	0.43
Total # lifetime pre-transplant ARVs	1.1 (0.99, 1.3)	0.07	Total # lifetime pre-transplant ARVs	1.20 (1.04, 1.38)	0.01
Time to ARV initiation post-transplant	1.00 (0.98, 1.01)	0.61	Prednisone (Yes/No)*	0.53 (0.24, 1.20)	0.13
Detectable HIV RNA pre-transplant (Yes/No)	2.6 (0.6, 11.4)	0.20			
Off ARV (Yes/No)*	4.2 (1.7, 10.7)	0.002			
Number ARVs (count)*	0.6 (0.5, 0.8)	0.0003			
Creatinine (most recent, kidney only)	1.1 (0.8, 1.3)	0.65			
Total bilirubin (most recent, liver only)	1.03 (0.96, 1.11)	0.38			
CD4+ T-cell count					
Nadir Pre-Tx (Per 50 cells/milliliter)	1.01 (0.94, 1.09)	0.83			
Most recent (Per 50 cells/milliliter)*	0.95 (0.87, 1.04)	0.25			
Infection in the last 30 days (Yes/No)*	0.9 (0.3, 2.7)	0.87			
Rejection in the last 30 days (Yes/No)*	1.4 (0.3, 6.1)	0.68			
Hospitalization in the last 30 days(Yes/No)*	0.3 (0.1, 1.3)	0.11			
ARV medication					
PI-based (Yes/No)*	1.0 (0.4, 2.2)	0.96			
NNRTI-based (Yes/No)*	0.36 (0.14, 0.96)	0.04			
PI+NNRTI-based (Yes/No)*	0.0 (0.0, N/A)	1.00			
Immunosuppression medication					
Cyclosporine (Yes/No)*	1.4 (0.6, 3.1)	0.38			
Tacrolimus (Yes/No)*	0.9 (0.4, 2.0)	0.87			
MMF/Cellcept (Yes/No)*	1.4 (0.6, 3.1)	0.46			
Prednisone (Yes/No)*	0.5 (0.2, 1.1)	0.08			
MMF/Cellcept + AZT/D4T (Yes/No)*	0.5 (0.2, 1.5)	0.21			
MMF/Cellcept + ddI/ABC (Yes/No)*	0.9 (0.4, 2.2)	0.88			
Total # medications (count)*	0.94 (0.86, 1.01)	0.10			

* As a time-dependent covariate.

† CI calculated using likelihood ratio based 95% confidence interval; p-value refers to likelihood ratio test.

Limitations/Future Analytic Plans

- No data are currently collected directly on medication adherence, reasons for not being on ARVs, pre-transplant ARV resistance test results.
- ARV resistance testing is driven by clinical considerations, and thus, results are not routinely available.
- HIV RNA assays are not standardized (used standard and ultrasensitive assays).
- The study is ongoing and still enrolling.
 - We anticipate having 5-year follow-up data on up to 150 kidney and 125 liver recipients.

Contact:

Michelle Roland, MD
UCSF Positive Health Program at
San Francisco General Hospital
Ward 84, Building 80
995 Potrero Avenue
San Francisco, CA 94110
Tel: (415)476-4082 x432
Fax: (415)476-6953
E-mail: mroland@php.ucsf.edu

University of California
San Francisco
AIDS Research Institute

Conclusions

- **HIV RNA is very well-controlled in liver and kidney transplant recipients despite complex drug interactions and multiple medications and co-morbidities.**

- Few subjects had persistent detectable levels.
- Even in subjects with detectable HIV RNA, the levels were generally low.

- **No unusual predictors of virologic breakthrough were identified.**

- Increased total lifetime pre-transplant ARVs used was associated with detectable HIV RNA post-transplant.
 - Hypothesis: Marker for ARV resistance
- Decreased post-transplant ARVs used was associated with detectable HIV RNA post-transplant.
 - Hypothesis: Regimens with more agents are more potent.

Transplant Study For People with HIV

A study to evaluate the safety and effectiveness of kidney and liver transplants in a select population of HIV infected individuals is currently in progress at 20 transplant centers across the country.

- Must meet criteria for transplantation
- Must have a T-cell count >200 (kidney) or >100 (liver)
- Must meet HIV viral load criteria depending on which organ is needed
- Patients with certain Opportunistic Infections in the past will be considered
- Pediatric patients are being enrolled at several participating centers (see below)

Specific Site & Study Information can be found at:
www.HIVtransplant.com

Study Related Presentations & Published Literature can be found at:
www.HIVtransplant.com

An Internet Support Group for persons with HIV interested in transplantation or persons with HIV who have received a transplant can be accessed at: http://groups.yahoo.com/group/HIV_Support_Group/

PARTICIPATING CENTERS (Visit the study website for updated list of centers and contact information)

Baltimore • Johns Hopkins (D)	Miami • University of Miami (D, L, Pre-K)
Boston • Beth Israel Deaconess (D)	Minneapolis • University of Minnesota (D)
Butte • Montana State (D)	New York • Mount Sinai School of Medicine (D, L, Pre-K)
Chapel Hill • University of North Carolina (D)	Philadelphia • University of Pennsylvania (D, L, Pre-K)
Chicago • Northwestern (D, L)	Pittsburgh • University of Pittsburgh (D, L)
Denver • University of Colorado (D, L)	San Francisco • University of California, L, Pre-K, Pre-L
Detroit • Wayne State (D)	Seattle • University of Washington (D, L)
Los Angeles • Cedars-Sinai (D, L)	Washington, D.C. • Georgetown (D, L, Pre-K, Pre-L)