Poster #824

HIV RNA Suppression Following Liver and Kidney Transplantation

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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 immuno-suppression 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.

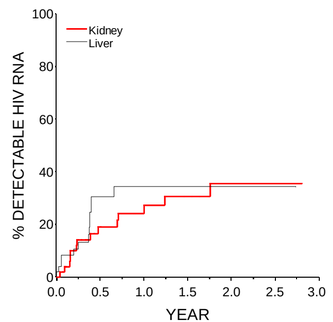
Results

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** (HR1.20; 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
Race (white vs. others)	0.9 (0.4, 2.0)	0.88
Age (continuous)	1.0 (0.97, 1.04)	0.79
Organ (kidney vs. liver)	1.3 (0.6, 2.7)	0.52
Hepatitis C (Yes/No)	2.1 (0.9, 4.5)	0.07
Total # lifetime pre-transplant ARVs	1.1 (0.99, 1.3)	0.07
Time to ARV initiation post-transplant	1.00 (0.98, 1.01)	0.61
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

Multivariate Predictors	Hazard Ratio (95% CI)	P-Value
Number ARVs (count)*	0.43 (0.21, 0.87)	0.02
NNRTI-based ARV (Yes/No)*	0.61 (0.21, 1.79)	0.37
Off-ARV (Yes/No)*	0.28 (0.03, 2.62)	0.26
Hepatitis C (Yes/No)	1.42 (0.60, 3.38)	0.43
Total # lifetime pre-transplant ARVs	1.20 (1.04, 1.38)	0.01
Prednisone (Yes/No)*	0.53 (0.24, 1.20)	0.13

** 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.

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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.