Kidney and Liver Transplantation and HIV Infection

U.S. Multi-Site Studies

Update as of January 2010

Acknowledgments

We'd like to acknowledge the participating transplant centers and their study investigators and study coordinators, too many to name.

University of California, SF
Peter Stock (PI)
Michelle Roland (Co-PI)

Cedars-Sinai, LA
Fred Poordad (PI)
Nicholas Nissen (Co-PI)

University of Maryland
Robert Redfield (PI)
Stephen Bartlett (Co-PI)

Drexel
Anil Kumar (PI – Kidney)
Burkhardt Ringe (PI – Liver)
Jeffrey Jacobson (Co-PI)

University of Virginia
Kenneth Brayman (PI)

University of Pennsylvania
Kim Olthoff (PI)
Emily Blumberg (Co-PI)

University of Pittsburgh
Margaret Ragni (PI)
Ron Shapiro (Co-PI)

Washington Hospital Center
Jimmy Light (PI)

Mt. Sinai
Barbara Murphy (PI)
Thomas Schiano (Co-PI)

Columbia University
Lorna Dove (PI)
Jean Emond (Co-PI)

Georgetown University
Lynt Johnson (PI)

University of Chicago
J. Michael Millis (PI)

University of Cincinnati
Kenneth Sherman (PI)
Rita Alloway (Co-PI)

University of Miami
Jorge Diego (PI - Kidney)
Andreas Tzakis (PI – Liver)
David Roth (Co-PI – Kidney)

Beth Israel Deaconess
Douglas Hanto (PI)
Michael Wong (Co-PI)

Emory University
Tom Pearson (PI)

Rush University
David Simon (PI)

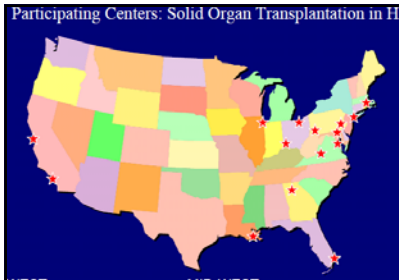
Tulane University
Douglas Slakey (PI)

Cleveland Clinic
John Fung (PI)

Johns Hopkins
Aruna Subramanian (PI)

Northwestern
Tina Stosor (PI)
Richard Green (Co-PI)

Participating Centers: Solid Organ Transplantation in HIV: Multi-Site Study



NORTHEAST

Baltimore, MD
Johns Hopkins (K,L)
University of Maryland (K)
Boston, MA
Beth Israel Deaconess (K, L)
New York, NY
Mt. Sinai (K, L, Peds K)
Columbia University (L, Peds L)
Philadelphia, PA
Drexel University (L)
University of Pennsylvania (K, L)
Pittsburgh, PA
University of Pittsburgh (K, L)
Washington, D.C.
Washington Hospital Center (K)
Georgetown Medical Center (K, L)

SOUTHEAST

Atlanta, GA
Emory University (K)
Charlottesville, VA
University of Virginia (K,L)
Miami, FL
University of Miami (K, L)
New Orleans, LA
Tulane (K, L, Peds K, Peds L)

WEST

San Francisco, CA
UCSF (K, L, Peds K, Peds L)
Los Angeles, CA
Cedars-Sinai (L)

MID-WEST

Chicago, IL
University of Chicago (K, L, Peds K, Peds L)
Rush University (K, L)
Northwestern (K,L)
Cincinnati, OH
University of Cincinnati (K, L)
Cleveland, OH
Cleveland Clinic (K, L)

Support

- Supported by the Solid Organ Transplantation in HIV: Multi-Site Study (AI052748) funded by the National Institute of Allergy and infectious Diseases.

- 250 Transplanted Recipients:
  - 150 KT (median follow up 1.8 yrs, range 3 mo- 5 years)
  - 125 LT which includes 8 KT/LT pairs (median follow up 1.5 years, range 4 weeks to 2.5 years)

Overview: Kidney Transplantation and HIV

1) 2 prospective, multisite studies (N = 18, Pilot + 150, U01)
   - **Patient & graft survival**
   - **HIV disease progression**
   - **Rejection**
   - **Drug interactions**
2) Potential HCV, HHV8, HPV complications
3) Cardiovascular, metabolic, malignant complications
4) Donors
5) Successful clinical management

Subject Selection Criteria

- CD4+ T-cell count > 200 cells/mm^3
- HIV RNA undetectable on ARV therapy
- Opportunistic complication history
  - all excluded from 3/00 - 4/02
  - After 4/02 OI restrictions changed to only:

    PML, cryptosporidiosis and visceral KS excluded

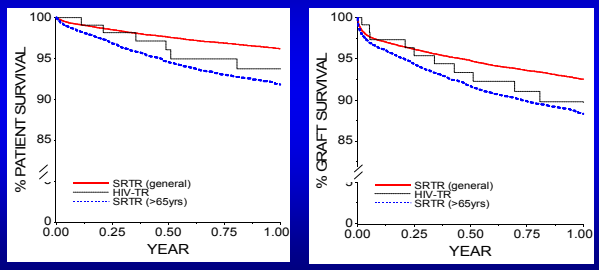
Study #2: Baseline Characteristics

- N = 150
- 80% male
- 28% white, 68% black
- Average age = 46 (range: 9-72)
- 24% with history of AIDS-related OIs
- 19% HCV+
- Average follow-up 5/09: 1.8 years (max = 5.0)
- Comparison group: SRTR data on KT >65 yrs old

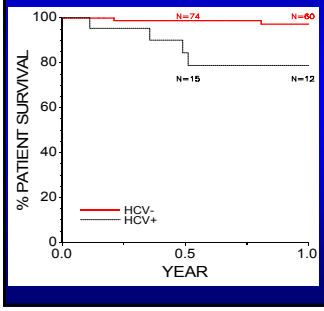
Abstract only; preliminary results 2009

www.HIVtransplant.com

Study 2: 1-Year Patient and Graft Survival and Comparison to HIV neg.



Study 2: 1-Year Patient Survival by HCV Status



- 1-year survival rates

HCV- : 97% (CI 89,99)

HCV+: 79% (CI 53,92)

Log-rank test; p=.002

Study 2:
Regression Models - Kidney Failure in 1st Year

Univariate Predictor	Hazard Ratio (95% CI)	P Value
Recipient Characteristics		
Black Race	1.6 (0.6, 4.5)	0.33
Hepatitis C	1.6 (0.6, 4.5)	0.34
Cyclosporine as Initial IS Med (vs.Tac)	0.6 (0.2, 1.7)	0.36
Delayed Graft Function	2.4 (1.0, 5.7)	0.05
Rejection*	5.9 (2.2, 16.2)	0.001
Donor Characteristics		
Age? 50	1.3 (0.6, 3.2)	0.53
Live Donor	0.3 (0.1, 0.9)	0.04
>4 Mismatched Donor-Recipient Antigens	1.5 (0.6, 3.5)	0.37
High-infectious Risk Donor	0.8 (0.2, 2.7)	0.71
Extended Criteria Donor	0.8 (0.2, 2.8)	0.73

Multivariate Predictors	Hazard Ratio (95% CI)	P Value
Delayed Graft Function	1.3 (0.5, 3.3)	0.56
Rejection*	5.0 (1.8, 13.9)	0.002
Live Donor	0.4 (0.1, 1.3)	0.12

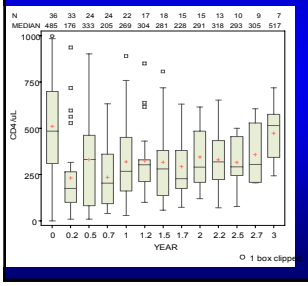
*As a time-dependent covariate.

Minimal HIV disease progression

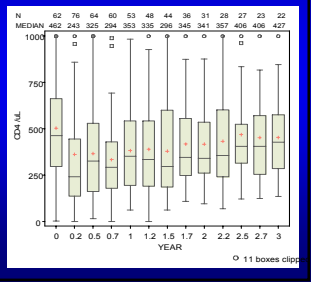
- Pilot Study:
  - 1 case of candida esophagitis
  - HIV RNA generally suppressed
  - CD4+ T-cell counts relatively stable
- Study 2:
  - 1 candida esophagitis
  - 1 presumptive PCP
  - HIV RNA generally suppressed
  - CD4+ T-cell initial decline

Study 2:
CD4 Cell Counts with induction.

Thymoglobulin (3 doses)



IL-2R inhibitor



Infections

- 1 Candida esophagitis in thymoglobulin user
- 10 serious infections in 6 thymoglobulin recipients
  - All bacterial
  - All but 1 when the CD4+ T-cell count was < 200 cells/µL.
- 2 serious infections in no thymoglobulin group
  - 1 bacterial, 1 influenza
  - 1 occurred when CD4+ T-cell count was 25 cells/µL while the recipient was receiving a high dose of sirolimus

Drug Interactions

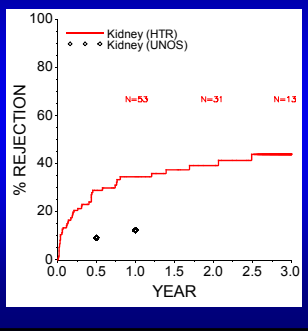
- Cyclosporine, tacrolimus & sirolimus *dosing*
  - low with PI and PI+NNRTI combinations due to the "boosting" effect of the PI (particularly RTV)
  - typical to high with NNRTI (specifically EFV)
- PI and NNRTI levels affected but remain within adequate treatment ranges

Cyclosporine Dosing

	Initial dose of CsA	Maintenance dose of CsA	Mean CsA trough (ng/mL) (Range)
PI			
Nelfinavir	50–75 mg bid	25 mg bid	112 (59–174)
Indinavir	75–100 mg bid	75 mg bid	125 (74–175)
NNRTI			
Nevirapine	200–250 mg bid	100–175 mg bid	122 (45–195)
Efavirenz	350–450 mg bid	250–400 mg bid	117 (84–182)
PI and NNRTI			
Nevirapine-nelfinavir	25 mg bid	25 mg bid or qd	169 (152–176)

Frassetto et al. Transplantation 80:13-17; 2005

Second Study: Time to First Rejection



Significant MV risk factors identified with AR were:

Cardiac deceased donor kidneys

Increased risk, HR 2.10 (1.04-4.21) p=0.04

Cyclosporin Use

increased risk, HR 2.10 (1.14-3.89) p=0.02

Tacrolimus trough

decreased risk, HR 0.89 (0.80-0.99) p=0.03

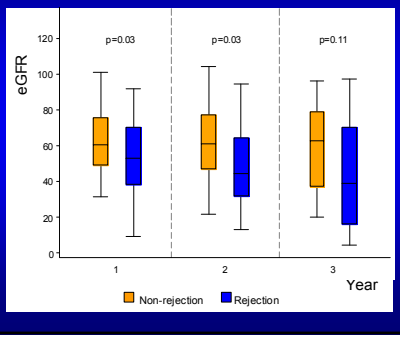
First Acute Rejection MV Models

Baseline Covariates	Hazard Ratio (95% CI)	P Value
Black Race	0.61 (0.31, 1.20)	0.15
Age	0.90 (0.51, 1.58)	0.70
Simulect/Daclizumab Induction	1.29 (0.73, 2.28)	0.37
Opportunistic infection history	0.97 (0.51, 1.87)	0.93
Hepatitis C infection	1.81 (0.77, 4.26)	0.17
Deceased Donor	2.10 (1.04, 4.21)	0.04
# Mismatched Antigens >4	1.68 (0.95, 2.97)	0.07
PRA at tx >0	1.18 (0.60, 2.33)	0.64
CD4+ T-cell count (Per 50 cells/ml)	0.99 (0.94, 1.04)	0.64

Time-Dependent Covariates	Hazard Ratio (95% CI)	P Value
Protease Inhibitor	1.13 (0.64, 1.99)	0.67
Mycophenolate Mofetil	0.60 (0.33, 1.10)	0.10
CD4+ Cell Count (Per 50 cells/ml)	0.95 (0.90, 1.00)	0.06
Detect. Viral Load	1.49 (0.46, 4.83)	0.50
CsA use	2.10 (1.14, 3.89)	0.02
CsA trough level	1.00 (0.99, 1.00)	0.21
Tac use	0.61 (0.33, 1.12)	0.61
Tac trough level	0.89 (0.80, 0.99)	0.03

Deceased donor and tacrolimus trough level remained significant in opposing effects in the multivariate model

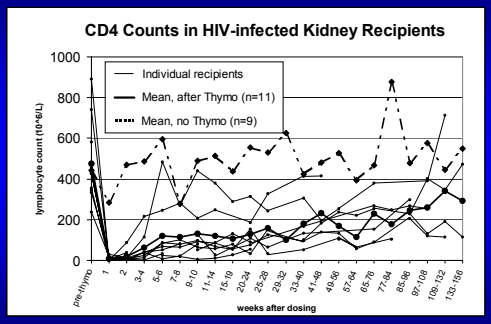
eGFR by Rejection Status



Infectious Consequences of Rejection (N=20 kidney)

- 11 received thymoglobulin
  - 7 for rejection
  - 4 for delayed/slow graft function
- Mean CD4+ T-cell counts
  - "second time" effect far more profound
  - thymo: 475±192 → 9±10 cells/μL
- Recovery time: 2 years

Carter et al, American Journal of Transplantation 2006



Liver Transplantation and HIV

2 prospective, multi-site studies

1) Very good HBV outcomes
2) Fair HCV outcomes
3) Complex drug interactions
   - No significant HIV disease progression
   - *May* contribute to rejection risk
4) No significant HHV8, HPV complications
5) MELD predicts pre-transplant outcome
6) Successful clinical management

Inclusion Criteria
(N=11 and N=125)

- CD4+ T-cell count ≥ 100 (≥ 200 if prior OI
- HIV RNA undetectable if on ARV therapy
  det. if intolerant but predict suppr.
- Opportunistic complication history
  - all excluded until 2002
  - After 4/2002, modified to only PML, cryptosporidiosis and visceral KS excluded

www.HIVtransplant.com

Overview: Liver Transplantation and HIV

1) 2 prospective, multisite studies (N = 11, Pilot + 125, U01)
   - **HBV and HCV outcomes**
   - **Patient & graft survival**
   - **HIV disease progression**
   - **Rejection**
   - **Drug interactions**
2) Potential HHV8, HPV complications
3) Cardiovascular, metabolic, malignant complications
4) Donors
5) Death on List
6) Successful clinical management

Hepatitis B

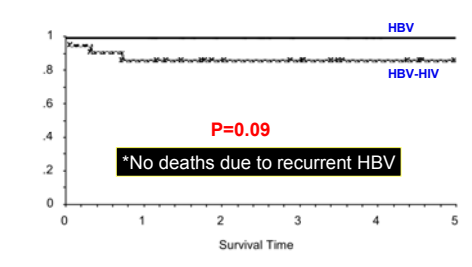
- Re-infection rapid and fatal without virologic control
- Lamivudine-resistant HBV common in HIV
- Entecavir selects HIV M184V mutation
- Tenofovir highly effective in suppressing HBV
- Pre-OLT HBV Suppression and Post-OLT passive Ig support with routinized HBIG to evidence based time specific titers
- **Management to reduce HIV & HBV resistance**

Preliminary HBV Analysis

- 22 HBV/HIV co-infected subjects
  - antivirals: tenofovir +lamivudine *or* emtricitabine
  - Hepatitis B Immune Globulin (HBIG)
    - 10,000 units anhepatic phase, daily x 6; monthly x 1 year; HBIG dose to maintain anti-HBs titers >200 IU/L
- 20 HBV mono-infected contemporaneous controls

Coffin et al
AJT 2010, in press

Patient Survival: HBV



Median follow-up 3.5 years

HBV Recurrence & Viremia

- No recurrent HBsAg in the HIV/HBV recipients
- No histologic recurrence by protocol biopsies
- 53% detectable HBV DNA post-transplant
  - Mean HBV DNA 108 IU/ml (range 20-790 IU/ml)
  - More frequent in patients with detectable HBV DNA pre-transplant and those with prior treated acute rejection
- No *persistently* detectable HBV DNA

HBV Conclusions

- Short-term patient and graft survival in HBV/HIV co-infected recipients similar to HBV mono-infected
- Recurrent HBV prevented with HBIG and antivirals
  - Low level viremia in ~ half supports the long-term use of combined HBIG plus antivirals
  - HBIG may be particularly important to prevent virologic breakthrough due to antiviral drug resistance

Hepatitis C

- Common in liver and kidney candidates in the U-01 (30% KT and 78% OLT recipients)
- Relatively poor outcomes in HIV negative recipients
- Accelerated natural history in context of HIV
- Variable post-transplant experience

Preliminary HCV Analysis

- HCV-HIV co-infected vs HCV mono-infected
  - Controls: 3:1 HCV mono-infected recipients: HIV/HCV
    - contemporaneously matched on study site
    - single vs dual organ transplant
    - HCC
- Predictors of patient and graft survival

Terrault et al, 2009 ATC

Subject Characteristics

Characteristic	HCV-HIV N=81	HCV N=213	P value
Recipient Age, median (IQR)	**50 (44-53)**	**54 (50-59)**	**<0.0001**
Male gender (%)	77	71	0.38
Caucasian Race (%)	**67**	**53**	**0.04**
BMI at Listing, *median (IQR)*	***25 (23-28)***	***28 (25-32)***	***<0.0001***
MELD at LT median (IQR)	20 (15-25)	20 (14-27)	0.82
HCC (%)	32	31	1.00
HCV genotype 1/4/other (%)	80	80	0.97
HBV co-infection (%)	4	1	0.13

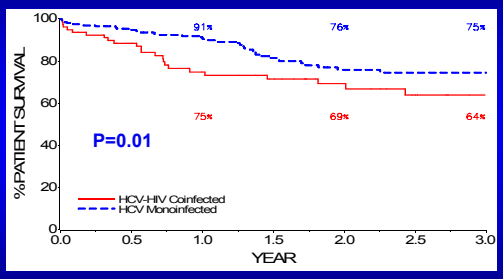
Donor and Transplant Characteristics

Variable	HCV-HIV N=81	HCV N=213	P Value
Donor Age, median (IQR)	**37 (24-48)**	**42 (30-52)**	**0.05**
Living Donor LT (%)	1	6	0.12
Donor Anti-HCV + (%)	12	11	0.84
Dual Organ (%)	9	8	0.82
Treated Acute Rejection (%)	***35***	***18***	***0.001***
HCV Treatment (%)	**38**	**16**	**<0.0001**
Follow-up Post-LT, median (IQR)	1.5 (0.5-2.5)	1.4 (0.7-2.3)	0.95

HIV-Infected Subjects
N=81

Characteristic	Value
CD4 count at LT, median (IQR)	284 (179-416)
HIV RNA undetectable at LT	89%
On HAART within 1st week post-LT	78%
Initial immunosuppression	
Tacrolimus	60%
Cyclosporine	38%

Patient Survival: HCV



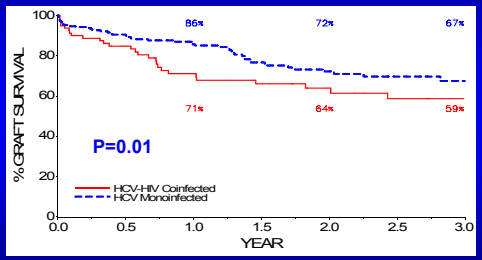
HCV mono-infected	N=135	N=67	N=22
HCV-HIV co-infected	N=46	N=28	N=14

Predictors of Mortality

Predictor	HR (95% CI)	P Value	HR (95% CI)	P Value
	Univariate		Multivariate	
HIV co-infection	**2.0 (1.1, 3.5)**	**0.02**	**1.7 (1.0, 3.1)**	**0.06**
BMI <21	3.3 (1.0, 10.7)	0.04	2.7 (0.8, 9.1)	0.10
HCV+ donor	2.4 (0.8, 7.1)	0.13	- -	
Treated AR	1.8 (0.8, 3.9)	0.14	- -	

Other non-significant factors:
living donor, donor age, HCV genotype, recipient age, MELD at LT, HCV therapy

Graft Survival: HCV



HCV mono-infected	N=128	N=67	N=21
HCV-HIV co-infected	N=43	N=26	N=13

Predictors of Graft Failure

Predictor	HR (95% CI)	P Value	HR (95% CI)	P Value
	Univariate*		Multivariate	
HIV co-infection-	1.9 (1.1, 3.1)	0.02	1.4 (0.8, 2.5)	0.21
BMI <21	2.6 (0.9, 7.2)	0.07	2.4 (0.8, 7.2)	0.12
Treated Acute Rejection	**2.5 (1.2, 5.0)**	**0.01**	**2.5 (1.2, 5.3)**	**0.02**
HCV Therapy	2.2 (0.9, 5.8)	0.10	- -	-

Other non-significant factors:

deceased donor, HCV+ donor, donor age, HCV genotype, recipient age, MELD at LT

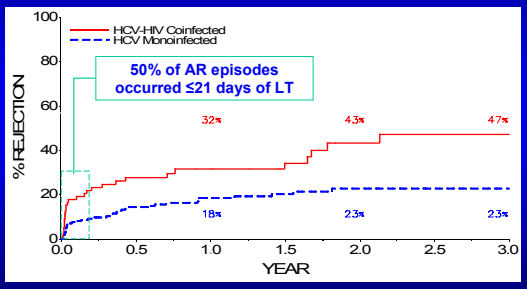
Graft Failure: HCV-HIV co-infected

Predictor Multivariate Analysis	Hazard Ratio (95% CI)	P value
Dual Kidney-Liver	5.5 (1.8, 16.9)	0.003
HCV+ Donor	4.5 (1.8,11.2)	0.001
BMI at Listing <21	2.7 (1.0, 7.3)	0.05
Treated Acute Rejection	2.9 (1.2, 7.0)	0.02

HCV outcomes and implications for patient selection

- Patient and graft survival in HCV-HIV co-infected transplant recipients are lower but acceptable
  - *Not* due to HIV-related complications
- Outcomes may be improved by:
  - Restricting to BMI >21; no dual kidney transplant
  - Avoiding use of livers from anti-HCV+ donors
  - Better management of acute rejection

Time to First Acute Rejection



Acute Rejection

- Acute rejection rates 2-fold higher in co-infected
- Treated acute rejection independent predictor of:
  - Graft loss in all recipients/co-infected patients
  - Severe HCV recurrence

Conclusions

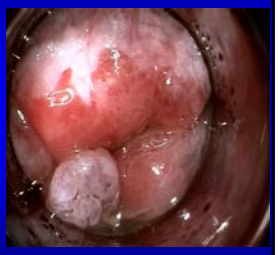
- *HIV RNA is very well-controlled in liver and kidney transplant recipients despite complex drug interactions and multiple medications and co-morbidities.*
  - Few subjects had persistent detectable levels.
  - Even in subjects with detectable HIV RNA, the levels were generally low.

Most liver transplant cases with detectable HIV RNA at transplant are successfully suppressed within 3 months

- *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.

HPV

- Will HVP-related cervical and anorectal disease, accelerated in people with HIV infection, be exacerbated by immunosuppression?
- Preliminary experience at UCSF: common, with progression, but not obviously more aggressive than in non-transplant population



This anal cancer was detected by Digital rectal examination

BK Infection

- Nephropathy (6), viremia (8)
- Cases of BK Nephropathy
  - Onset Day Post-Tx
    Median (IQR): 100 (61-271)
  - Rejection pre/post BK: 3 cases
  - Outcome
    1 graft loss due to rejection/compliance
    2 resolved; 1 case with a lot of scarring
    3 persistent