Renal Transplantation in People Infected with HIV

Stephen Tomlanovich M.D.
University of California, San Francisco
Do not follow where the path may lead. Go instead where there is no path and leave a trail.

*Ralph Waldo Emerson*
Questions to be Answered

Is renal transplant in HIV-infected patients safe and effective?

Does HIV disease progress after transplant?

What are the problem areas?

What is the future for transplantation in HIV-infected patients?
Introduction

• 1. **NIH sponsored study.** 148 patients transplanted, 353 in the referral/evaluation process

• 2. A New Conversation occurring around transplantation and HIV

• 3. Insurers authorizing Transplants in persons with HIV

• 4. **It’s a Law:** *California Law Prohibits Insurance Coverage Denials Based Solely on HIV Status*

  - AB 228, authored by Assemblyman Paul Koretz (D-West Hollywood), has been signed by Governor Arnold Schwarzenegger. The bill was passed by the Legislature with bipartisan support and is the first in the nation to prohibit insurers from denying coverage for organ transplants based solely on a patient’s HIV status
HIV and Transplant: The Past

• HIV+ transplants in the 80’s had discouraging results

• Factors limiting those initial experiences included:
  – Occurred prior to the advent of HAART therapy and routine prophylaxis against opportunistic infections
  – Limited information on pre transplant HIV status and post transplant management of HIV
  – Predated the newer immunosuppressive medications
HIV and Transplant: The Present

- HAART-associated improvements:
  - decreased mortality
  - decreased incidence of opportunistic infections
  - decreased hospitalization rates
Immunosuppressive may have anti-HIV effects

Sirolimus  CellCept  Cyclosporine
Need for Transplantation

- 750,000-1.5 million people infected with HIV with 40,000 new cases added each year
- Life expectancy is high
Need for Transplant in HIV + CKD Patients

- Between 1995 – 2002 approx 800 new patients a year report HIVAN as the cause of CKD to the USRDS. 90% of those cases were reported by people of African descent.
- Currently in the US, HIVAN is the most common cause of renal failure among people with HIV and is the 3rd most common cause of ESRD in African Americans between the age of 20-60 years. (Cosgrove et al, 2000).
Should All HIV + Patients With ESRD from Be Excluded Transplantation? 1998 and 2004 Survey Results

Transplant Center Response Rate: 149/248 (60%)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>UN SURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Would a patient who refuses HIV testing be considered for transplantation? 1998</td>
<td></td>
<td>84%</td>
<td>16%</td>
</tr>
<tr>
<td>Would an HIV-infected ESRD pt be considered for cadaveric transplantation? 1998</td>
<td>9%</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>Would an HIV-infected ESRD pt be considered for cadaveric transplantation? 2004</td>
<td>29%</td>
<td>68%</td>
<td>3%</td>
</tr>
<tr>
<td>Would an HIV-infected ESRD pt be considered for living donor transplantation? 2004</td>
<td>5%</td>
<td>91%</td>
<td>4%</td>
</tr>
</tbody>
</table>
EARLY AND UNEXPECTED RESULTS IN A MULTICENTER STUDY OF KIDNEY TRANSPLANTATION IN HIV-INFECTED RECIPIENTS

Peter Stock, MD, PhD, Michelle Roland, MD
University of California, San Francisco

Douglas Hanto, MD, Scott Johnson, MD, Martha Pavlakis, MD
Beth Israel Deaconess Medical Center

Jimmy Light, MD
Washington Hospital Center

Burc Barin, MS
The EMMES Corporation

Dushyantha Jayaweera, MD
The University of Miami

Barbara Murphy, MD
Mt. Sinai School of Medicine

On behalf of HIVTR: Solid Organ Transplantation in HIV Multisite Study: NIH Grant U01 AI052748
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
- Washington, D.C.
  - Washington Hospital Center (K)
  - Georgetown Medical Center (K, 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)

**SOUTHEAST**
- Atlanta, GA
  - Emory University (K)
  - Charleston, SC
  - University of Virginia (K, L)
  - Miami, FL
  - University of Miami (K, L)
  - New Orleans, LA
  - Tulane (K, L, Peds K, Peds L)
Specific Aims

• To evaluate the impact of kidney transplantation and post-transplant immunosuppression on HIV disease progression

• To evaluate the impact of HIV disease on kidney function in addition to patient and allograft survival
Subject Selection Criteria
HIV+ Kidney Transplant Recipients

- CD4+ T-cell count > 200 for kidney recipients
- HIV RNA undetectable.
- Opportunistic infection history acceptable for most OIs with continued exclusion of PML, chronic cryptosporidiosis and visceral KS.
- Otherwise usual selection criteria for non-HIV-infected transplant candidates
Immunosuppression and Rejection Management

• Initial immunosuppression included cyclosporine or tacrolimus +/- mycophenolate mofetil (MMF), in combination with steroids.
  – IL2R antagonist use was allowed.
• Rejections managed with a steroid pulse, changing calcineurin inhibitors or doses, and/or thymoglobulin, and/or adding sirolimus
Study Accrual
(as of May 20, 2009)

148 transplants (150 target)

Average follow-up time: 1.8 years (max = 5.0)

116 eligible candidates in pre-transplant phase

237 active candidates in screening phase
Demographics

- 20% female
- 28% white, 68% black
- Average age = 46 (range: 9-72)
- 67% Medicare/Medicaid, 30% private insurance
Indications for Transplant
(Not all biopsy confirmed)

- Hypertension/nephrosclerosis (25%)
- HIV nephropathy (23%)
- Diabetic nephropathy/glomerulosclerosis (8%)
- Focal glomerulosclerosis (6%)
- Other (38%)
## Donor Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Donor</td>
<td>29</td>
</tr>
<tr>
<td>Donor Age &gt; 60 years</td>
<td>5</td>
</tr>
<tr>
<td>African-American Donor</td>
<td>20</td>
</tr>
<tr>
<td>HBV+ Donor</td>
<td>0</td>
</tr>
<tr>
<td>HCV+ Donor</td>
<td>5</td>
</tr>
<tr>
<td>Non-heart beating donor</td>
<td>8</td>
</tr>
<tr>
<td>High infectious risk donor</td>
<td>19</td>
</tr>
<tr>
<td>Extended Criteria Donor (ECD)</td>
<td>18</td>
</tr>
<tr>
<td># HLA Mismatch Antigens &gt; 4</td>
<td>41</td>
</tr>
</tbody>
</table>
1-Year Patient and Graft Survival

Graph showing the survival rates for different groups:
- SRTR (general)
- HIV-TR
- SRTR (>65yrs)

Patient and Graft Survival:
- Patient survival: 100% at 1 year, decreasing over time.
- Graft survival: 95% at 1 year, decreasing over time.

YEAR:
- 0.00
- 0.25
- 0.50
- 0.75
- 1.00

% PATIENT SURVIVAL:
- 100
- 95
- 90
- 85
- 5
- 0

% GRAFT SURVIVAL:
- 100
- 95
- 90
- 85
- 5
- 0
Time to First Rejection

% REJECTION

YEAR

N=53  N=31  N=13

Kidney (HTR)
Kidney (UNOS)
## Risk Factors for First Acute Rejection

### Univariate Models

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

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

Deceased donor and Tacrolimus trough level remained significant in the multivariate model.
Time to First Rejection by Initial Immunosuppression

- **Immunosuppression**
  - CsA (21%)
  - Tac (72%)
  - None reported (7%)
- **1-year rejection rates**
  - CsA: 52% (CI 35,72)
  - Tac: 29% (CI 20,40)
  - Log-rank test; p=.02
1-Year Patient Survival by HCV Status

- 19% of kidney recipients HCV+

- 1-year survival rates
  - HCV-: 97% (CI 89,99)
  - HCV+: 79% (CI 53,92)

Log-rank test; p=.002
PH Regression Models for Kidney Failure in 1st Year

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

<table>
<thead>
<tr>
<th>Multivariate Predictors</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed Graft Function</td>
<td>1.3 (0.5, 3.3)</td>
<td>0.56</td>
</tr>
<tr>
<td>Rejection*</td>
<td>5.0 (1.8, 13.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Live Donor</td>
<td>0.4 (0.1, 1.3)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*As a time-dependent covariate.
eGFR by Rejection Status

![Box plot showing eGFR by rejection status over three years.](image)
CD4 Cell Counts

Thymoglobulin

No Thymoglobulin

YEAR

CD4/uL
BK Polyomavirus Infection

Nephropathy (6), viremia (8)

Cases of BK Nephropathy
- Onset Day Post-Tx
  Median: 100 days (range 61-271 days)
- Rejection pre/post BK: 3 cases
- Outcome
  1 graft loss due to rejection/compliance
  2 resolved; 1 case with significant fibrosis
  3 persistent
Opportunistic Infections and Malignancies

24% with History of AIDS-related OIs pre-transplant

2 AIDS-defining OIs post-transplant
  1 candida esophagitis, 1 presumptive PCP
  No de novo KS
  No LPD
  HPV mediated dysplasia

6 non-AIDS malignancies
  Recurrent metastatic renal cell carcinoma
  Metastatic renal cell carcinoma
  2 oral squamous cell cancers
  1 basal cell skin cancer
  Thyroid gland cancer
Summary

In this study population:
– No significant HIV clinical, virologic nor immunologic disease progression in these immunosuppressed patients.
– No evidence of impaired graft function due to HIV.
– Rejection rates unexpectedly high.
– Treatment with anti-T-cell depleting agents results in prolonged depletion of CD4 positive cells.
– Co-infection with HCV associated with decreased patient and graft survival.
Conclusions from this Study

– One year graft and patient survival was acceptable with limited HIV/transplant complications
– Unexpectedly high rejection rates suggest the presence of a dysregulated rather than an absent immune system
– Improvements in immunotherapy are needed to decrease rejection and maximize long term graft function
## 2008 UCSF Demographics

<table>
<thead>
<tr>
<th></th>
<th>K</th>
<th>K/P</th>
<th>L</th>
<th>L/K</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Transplants</strong></td>
<td>85</td>
<td>41</td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>78</td>
<td>37</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td>26</td>
<td>20</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td>47</td>
<td>18</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td><strong>Asian</strong></td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Philipino</strong></td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>LR Donor</strong></td>
<td>14</td>
<td>11</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Deceased Donor</strong></td>
<td>71</td>
<td>30</td>
<td>37</td>
<td>2</td>
</tr>
</tbody>
</table>
Challenges in Patient Management

Short Term Issues

• Drug interactions
• Monitoring of levels and toxicities
• Standard target immunosuppression trough levels result in more toxicity
• Rejection and Infection
• Psychosocial
Pharmacodynamic Interactions and Medical Complexity

Highly Active Antiretroviral Therapy

Triple Immunosuppression to Prevent Graft Rejection
Drug Interactions

• Cyclosporine doses:
  – low with PIs/PI+NNRTI
  – typical to high with NNRTIs
• Tacrolimus and sirolimus are similar
• PI and NNRTI levels affected but have largely remained within adequate treatment ranges
Problems in HIV Transplantation: CNI & ARV interactions

Comedication(s):   | EFV | NVP | PI w/ RTV | PI w/o RTV | NNRTI+PI w/RTV | NNRTI+PI w/o RTV |
-------------------|-----|-----|-----------|------------|----------------|-----------------|
N                  | 20  | 11  | 13        | 7          | 8              | 5               |
CsA dose (mg/dose) |      |     |           |            |                |                 |
Wk 2               | 275 ± 129 | 189 ± 44 | 25 ± 0 | 57 ± 31 | 25 ± 0 | 42 ± 30 |
Wk 12              | 279 ± 123 | 147 ± 52 | 25 ± 0 | 75 ± 63 | 25 ± 0 | 39 ± 28 |
CsA Cmin (ng/ml)   |      |     |           |            |                |                 |
Wk 2               | 91 ± 57  | 130 ± 61 | 156 ± 67 | 128 ± 45 | 168 ± 77 | 173 ± 25 |
Wk 12              | 84 ± 60  | 116 ± 57 | 111 ± 77 | 185 ± 177 | 104 ± 61 | 154 ± 21 |
Challenges in Patient Management
Long Term Issues

- Cardiovascular disease
- Bone Diseases
- Malignancies: skin cancers, anorectal cancers due to HPV disease
- Metabolic syndrome
  - Dyslipidemia
  - PTDM
  - Hypercholesterolemia/ hypertriglyceridemia
- Life Adjustment
Potential long-term problems

Long-term renal function

- increased nephrotoxicity from CNIs
- increased graft loss from rejection

Bone disease

- HIV-associated low androgen levels in M & F
- ARV- & tx medication- induced low BMD

Cardiovascular disease

- ARV- & tx medication- induced dyslipidemia and insulin resistance
Cardiovascular Disease

<table>
<thead>
<tr>
<th>Transplant</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common cause of morbidity and mortality</td>
<td>Incidence increasing in the past 10 years</td>
</tr>
<tr>
<td>75-85% Hypertensive post tx</td>
<td>Risk Factors: dyslipidemia, DM, metabolic syndrome, smoking</td>
</tr>
<tr>
<td>60 % develop hyperlipidemia</td>
<td>30% with Hypertension</td>
</tr>
</tbody>
</table>
Bone Disorders: Osteopenia, Osteoporosis, Osteonecrosis

**Transplant**
- Pre tx renal insufficiency
- Hyperparathyroidism
- Smoking
- Poor dietary calcium intake
- Corticosteroid use

**HIV**
- Alcohol intake
- Smoking
- Prolonged use of PIs
- Lack of weight bearing exercises
- Body wt <20% or >20% IDW
HPV Disease

• HPV-related cervical and anorectal disease, already accelerated in people with HIV infection, may be exacerbated by post-transplant immunosuppression

• Preliminary experience at UCSF: common, with progression, but not obviously more aggressive than in non-transplant population

• First case – anal CA in situ post-transplant
Challenges of Living with...

Managing two complex medical problems
- multiple medications and drug interactions
- managing and coping with side effects

Adjusting pre transplant expectations to post transplant realities
- overestimating the benefits
- unmet expectations
- minimizing the new challenges

Emotional adjustment
- depression/ post traumatic stress disorder
Possibilities to Live into…. 

Living with a chronic illness can transform life in a positive way

– Personal transformation
– Acceptance of death leads to more meaningful living
– Freedom from pre-existing expectations
Growing experience with renal transplantation in HIV-infected subjects

<table>
<thead>
<tr>
<th>Country</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>218</td>
</tr>
<tr>
<td>France</td>
<td>7</td>
</tr>
<tr>
<td>Spain</td>
<td>13</td>
</tr>
<tr>
<td>Italy</td>
<td>4</td>
</tr>
<tr>
<td>Canada (BC only)</td>
<td>2</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1</td>
</tr>
<tr>
<td>South Africa</td>
<td>1</td>
</tr>
</tbody>
</table>
Take home points

Renal transplant in HIV-infected patients appears safe and effective

Progression of HIV disease is not common

Problem areas include:

- drug interactions
- HCV
- rejection
- bone and cardiovascular disease?

Transplant in HIV subjects is increasing worldwide
A Big Thanks to:

- Laurie Carlson RN
- Peter Stock MD
- Linda Frassetto MD
- Entire NIH Multicenter study sites
Transplant Study
For People with HIV Infection

Specific Site & Study information
Study Related Presentations &
Published Literature

can be found at:

www.hivtransplant.com