Renal Disease and Kidney Transplant

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Financial Relationships With Commercial Entities

Dr Locke has no financial relationship with commercial entities to report. (Updated 11/21/19)

Learning Objectives

• Describe risk for acute kidney injury among people living with HIV (PLWH)
• Describe chronic kidney disease and end-stage renal disease in PLWH
• Describe the role for kidney transplant among PLWH
Risk Factors and Common Etiologies

Risk factors for AKI
- Male gender, CD4<200, VL>10,000, HCV co-infection, ART use (not traditional)

Most common etiologies
- 38% Prerenal (due to infection, predominantly OIs)
- 46% Intrinsic (ischemic ATN or nephrotoxic medications)

AKI in HIV - Incidence

Ambulatory patients (Francheschini et al. KI 2002)
- Prospective cohort study of 754 HIV+ patients followed for 2 years
- Mean age 40, 61% black, 68% on ART, 3% have GFR<60ml/m at enrollment
- ARF defined as increase in Scr
- Etiologies categorized: prerenal, intrinsic, obstructive
- 111 episodes AKI in 71 subjects; incidence rate 5.9 per person years

Hospitalized patients (Wyatt et al. AIDS 2006)
- AKI a strong predictor of in hospital mortality in the general population
- Examine hospital discharge billing data/codes for NYS in 2003
- 25,114 patients admitted with HIV compared with 2,010,847 non-HIV admissions
- Risk factors for AKI?
## AKI in HIV - Incidence

<table>
<thead>
<tr>
<th>HIV</th>
<th>No HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>25,116</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.4 (11.1)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>49.1</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>10.3</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>19.2</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>13.2</td>
</tr>
<tr>
<td>Cytomegalovirus (%)</td>
<td>5.1</td>
</tr>
<tr>
<td>Acute HIV infection (%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Acute HIV encephalitis (%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Intravenous injection (%)</td>
<td>5.5</td>
</tr>
</tbody>
</table>

\( p<0.001 \)

Wyatt et al. AIDS 2005

**Similar results were found in an observational cohort study from the VA:**

- Even mild AKI is associated with a significant increase in risk for ESRD and death (37%).
- Those who do not recover to baseline renal function do worse.

Choi et al 2010

### Causes of AKI in HIV

#### Prerenal causes
- hypovolemia

#### Intrinsic renal injury
- ATN (ischemic v. nephrotoxic)
- Parenchymal infection (TB, CMV, fungus)
- Interstitial nephritis
- Glomerular disease

#### Postrenal causes
- Tubular obstruction
- Ureter/bladder obstruction

Wyatt et al. AIDS 2005

**Risk factors for AKI among HIV+ patients:**

- Older age
- Black race
- DM
- CKD
- HCV (traditional)
Prerenal

- Most common etiology
- Hypovolemia due to GI losses
- Poor oral fluid intake
- Adrenal insufficiency/hypoaldosteronism
- Sepsis
- CHF
- Cirrhosis

Acute Tubular Necrosis (ATN)

- Hypoperfusion injury (ischemic)
- Medications (most common)
  - NSAIDs
  - Amphotericin B
  - Pentamidine
  - Cidofovir, foscarnet
  - Aminoglycides
  - AIN: bactrim, rifampin, β-lactam antibiotics

Parenchymal infection

- Fungal infections
- Granuloma formation from TB
- CMV, EBV, BK – cause interstitial nephritis
Glomerular Diseases

HIVAN
- HIV associated immune complex GN
  - Lupus-like nephritis, IgAN, MPGN, MN
- Thrombotic microangiopathy
- AA Amyloid
- HCV co-infection
  - MPGN, fibrillary GN, immunotactoid GN

Non-HIV associated renal disease
- Diabetic nephropathy

HIV Associated Nephropathy (HIVAN)
- First described in the 1984 as a series of patient with advanced AIDS and RPGN
- Almost exclusively found in African Americans (90%) or mixed ethnicity Hispanics (10%)
- Third leading cause of ESRD in African Americans ages 20-64

Rao TK et al NEJM 1984

HIVAN- Presentation
- Rapidly progressive renal failure
- Moderate-nephrotic range proteinuria
- Bland urinary sediment
- Enlarged, echogenic kidneys on renal US
- Progression to ESRD and/or death nearly universal
- Associated with end-stage AIDS, but there are reports of HIVAN with seroconversion or asymptomatic HIV infection
- Diagnosis - renal biopsy; clinical predictors?
HIVAN – Pathology

- Pattern of focal segmental glomerular sclerosis on LM, often with global sclerosis of affected glomeruli
- Podocyte hypertrophy and hyperplasia
- Visceral epithelial cells form pseudocrescents
- Tubular atrophy, simplification, microcystic changes and proteinaceous casts
- Inflammatory interstitial infiltrate of lymphocytes, plasma cells and monocytes
ARS Question 1: Which of the following is an effective treatment for HIVAN?
A. Prednisone
B. HAART
C. ACE inhibitor
D. All of the above

HIVAN treatment
- HAART
- ACEI
- Prednisone

HAART
- Incidence of HIVAN and HIVAN-related ESRD has declined since the introduction of HAART in 1996
- In a retrospective study of 42 patients with bx proven HIVAN ART use delayed progression to ESRD (Szczech et al. KI 2004)
- Similar results were found in a study of 36 patients from Johns Hopkins (Atta et al. NDT 2006)
- In a prospective cohort study from Baltimore HAART use was estimated to reduce HIVAN risk by 60% (Lucas et al. AIDS 2004)
- HIVAN is an indication to start HAART
ACEI

- No RCTs exist; usage extrapolated from other proteinuric kidney diseases
- Series of 22 patients with HIVAN, fosinopril use was associated with preservation of renal function at 12 wks (Scr 1.7–2.0) improvement of proteinuria (5.4–2.5g/day) compared with untreated patients. Burns et al. JASN 1997
- A small case/control series of 44 patients with HIVAN demonstrated decreased progression to ESRD (479 v. 146 days) in patients treated with fosinopril. Wei et al. KI 2003
- ACEI usage is likely beneficial; monitor for increases in Scr and hyperkalemia

Both kidney and patient survival were improved by ACEI use

Prednisone

- No RCT data; standard FSGS treatment
- May diminish the inflammatory infiltrate noted on HIVAN biopsies
- Case report of 4 patients treated with prednisone 60mg qd x6wks. Mean Scr decreased from 9.3mg/dl but proteinuria was unchanged; increased OIs Smith et al. Ann J Med 1994
- Series of 21 patients, 13 treated with prednisone. Proteinuria decreased in all and renal function was preserved in 50% of treated patients at 2 years. Eustace et al. KI 2003
- Prednisone may ameliorate renal function but risk of infection needs to be considered
Immune Complex Renal Disease

- Not all renal disease in HIV is HIVAN
- In a multicenter observational study of 89 HIV patients with a renal bx, 50% had a disease other than HIVAN
- Non-HIVAN patients: better renal outcome, Caucasian, higher CD4, more often co-infected with HCV

Obstruction

Intrarenal:
- Due to drug precipitation out of the urine and formation of crystals in the tubules
- Associated with: Sulfadiazine, acyclovir, indinavir, foscarnet, atazanavir
- Risk factors: volume depletion, hypoalbuminemia and CKD

Extrarenal:
- Atazanavir nephrolithiasis
- Retroperitoneal fibrosis
- Pelvic lymphadenopathy - Lymphoma, histoplasmosis, MAC
- Fungus balls - Candida, aspergillus

Indinavir Crystals
CKD in HIV

- CKD is an important complication of HIV infection and treatment.
- As patients live longer and HIV spreads among populations at high risk for renal disease, it is expected the number of patients with HIV related ESRD will increase.
- ART decreased HIVAN related ESRD but is itself nephrotoxic.
- Although only a small percentage of patients may progress to ESRD, proteinuria has been shown in 30% of HIV patients, indicating widespread occult kidney injury.

CKD negatively affects delivery of HIV care

In a retrospective observational study from the VA:

- 9% of patients had CKD stage III or higher
- HAART exposure was 14-49% less as GFR declined
- 15% of patients did not have HAART adjusted for renal dysfunction
- Undereposure and inappropriate dosing was associated with a 35% excess mortality

CKD stage III + also predicted mortality in the WIHS

Choi et al. CID 2007
HIV and ESRD

- Mortality rates for HIV+ patients on dialysis were initially very high
- In a review of the USRDS, 1 year survival of HIV+ dialysis patients improved from 56% in 1990 to 74% in 1999; attributed to introduction of ART
- Race did not predict survival

Ahuja et al. JASN 2002

Mono-infected Co-infected
- Higher mortality rates on dialysis among HIV+ compared to uninfected
- Highest dialysis mortality among co-infected and non-Caucasian

Sawinski & Locke et al. KI 2017, accepted publication.

Kidney Transplantation

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
Long-term Outcomes among Mono-infected

A National Study of Outcomes among HIV-infected Kidney Transplant Recipients


- Long-term outcomes similar to matched HIV-counterfactuals

Long-term Outcomes among Co-infected

A National Study of Outcomes among HIV-infected Kidney Transplant Recipients


- Co-infected HIV outcomes worse than matched HIV/HCV+ counterfactuals

Kidney Transplantation is Associated with a Significant Survival Benefit among HIV+ Candidates

- Benefit achieved 194 days post-transplant
Kidney Transplantation is Associated with a Significant Survival Benefit among Co-infected HIV+ Candidates

Can Increased Risk Associated with HCV Infection be Mitigated among HIV+ Candidates?

ARS Question 2: What is the optimal timing for HCV treatment?
A. Always pre-transplant
B. Depends only on fibrosis stage
C. Depends only on waiting time
D. Depends on both fibrosis stage and waiting time
Pre vs. Post Transplant HCV Treatment?

Panel A (Life Years):
Red: pre-transplant treatment yields fewer life years — do not treat.
Green: pre-transplant treatment yields more life years — treat now.

Panel B (QALYs):
Red: pre-transplant yields fewer quality-adjusted life years — do not treat.
Green: pre-transplant yields more quality-adjusted life years — treat now.

Panel C (ICERS):
Red: pre-transplant treatment yields fewer quality-adjusted life years and is not cost-effective (dominated) — do not treat.
Yellow: pre-transplant provides more quality-adjusted life years but is not cost-effective (ICER ≥ $100,000/QALY) — consider delaying treatment.
Green: pre-transplant treatment provides more quality-adjusted life years and is cost-effective (ICER < $100,000/QALY) — treat now.

ART/DAA/IS interactions must be considered

- LDV/SOF and GLE/PIB compatible with most contemporary ART regimens and TAC-based IS
- ELB/GRZ and GLE/PIB should not be given with CYA
- ELB/GRZ and GLE/PIB have no GFR restrictions
- ART should only be modified in consultation with an ID specialist
- Consultation with Hepatology is advised

High Rates of Acute Rejection

Potential Etiologies for High Rates of Acute Rejection

1. Reluctance to use lymphocyte depleting agents

<table>
<thead>
<tr>
<th>Induction Immunosuppression</th>
<th>HIV Negative (%)</th>
<th>HIV Positive (%)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>21.4</td>
<td>35.1</td>
<td>&lt;0.001</td>
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<td>Anti-thymocyte globulin</td>
<td>43.5</td>
<td>25.8</td>
<td></td>
</tr>
<tr>
<td>Anti-interleukin 2</td>
<td>23.1</td>
<td>33.5</td>
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<tr>
<td>Alemtuzumub</td>
<td>12.0</td>
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Lower Risk of Acute Rejection at 1-year with ATG Induction among HIV-infected Recipients

Table 1. Rate of AS within the first posttransplantation year among HIV-infected RT recipients

<table>
<thead>
<tr>
<th>Induction Therapy</th>
<th>Reference</th>
<th>ATG</th>
<th>IL-2</th>
<th>维持性 therapy</th>
<th>CNI based</th>
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</table>

The multivariable adjusted Pearson regression model adjusted for recipient age, sex, BMI, degree of HLA match, and history of prior non-HIV transplantation donor, age, and center experience.

No Difference in Risk of Acute Rejection among ATG Induced HIV+ & HIV- Recipients

Table 2. Rate of AS within the first posttransplantation year among HIV-infected RT recipients

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<td></td>
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</tbody>
</table>

Matched Control analysis among HIV-infected and non-HIV-infected anti-thymocyte globulin induced kidney transplant recipients.

Progressive radius matching (1:1):
- Death, Factors e type Diabetes or deceased
- Recipient Factors: age, sex, PRA, number HLA mismatches, k, previous transplant, HCV

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• Infection common > 50% first year (AIDS-defining ~10%)
• Neither ATG or IL2 associated with higher infection risk
• ATG associated with lower risk of CMV, CDI, pneumonia

Potential Etiologies for High Rates of Acute Rejection

2. Drug interactions resulting in altered exposure to IS

Pharmacokinetic curve of tacrolimus in HIV patients receiving protease inhibitors does not show the normal peak-and-trough pattern. Resembles a flat line with half-life of up to 20 days secondary to strong inhibition of CYP3A.

Trough levels of tacrolimus in patients receiving protease inhibitors should be higher to achieve AUCs equal to patients not on protease inhibitors.

- 17.5 ng/mL at 1-month
- 10 ng/mL at 1-year


Antiretroviral Therapy & Risk for Graft Loss

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease inhibitors</td>
<td>1.84 (1.02-3.77)</td>
<td>0.03</td>
</tr>
<tr>
<td>Male</td>
<td>1.91 (1.05-3.47)</td>
<td>0.03</td>
</tr>
<tr>
<td>African American</td>
<td>1.88 (1.11-3.12)</td>
<td>0.02</td>
</tr>
<tr>
<td>HCV antibody +</td>
<td>2.46 (1.49-6.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRA ≥30%</td>
<td>1.43 (1.09-1.86)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Donor Characteristics</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDPI &gt; 85%</td>
<td>1.93 (0.95-3.89)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥365 days post-transplant</td>
<td>4.46 (1.75-11.48)</td>
<td>0.002</td>
</tr>
<tr>
<td>≥365 days post-transplant</td>
<td>1.40 (0.84-2.32)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Why are Integrase Inhibitors preferred?

**Table:**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Effect on CNI/mTOR levels</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>none</td>
<td>Non CYP3A4</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Decrease*</td>
<td>CYP3A4 variable</td>
</tr>
<tr>
<td>PI</td>
<td>Increase</td>
<td>CYP3A4 inhibitor</td>
</tr>
<tr>
<td>Fusion Inhibitors</td>
<td>none</td>
<td>CYP3A4 substrate</td>
</tr>
<tr>
<td>CCR5 R Antagonist</td>
<td>none</td>
<td>Non CYP3A4</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td>none</td>
<td>Non CYP3A4</td>
</tr>
</tbody>
</table>

*exceptions: delavirdine and rilpivirine (increases) - rilpivirine has the greatest effect of PIs

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**Slide 50**

**TDF use posttransplant**

- 104 HIV+ KTx 2001-2014
- 3yr graft loss: 26% TDF vs 28% non TDF
- TDF associated with AKI and CKD
- Fanconi's syndrome – mitochondrial toxicity
- TAF – prodrug, intracellular conversion to TDF in lymphocytes, lower plasma exposure

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**Slide 51**

**HIV control does not prevent renal infection**

- 68% of HIV+ recipients with undetectable VL had HIV detectable in their kidneys
- Infection had 2 forms: podocyte and tubular
- Podocyte infection was associated with more rapid decline in renal function and graft loss
- Urine HIV RNA and DNA screening test developed – correlates with biopsy
- Rationale for protocol biopsies?
Access to Kidney Transplantation among HIV+ Waitlist Candidates

<table>
<thead>
<tr>
<th>Rate per 100 PY</th>
<th>HIV+ Candidates</th>
<th>HIV- Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waitlist Mortality</td>
<td>5.61</td>
<td>6.62</td>
</tr>
<tr>
<td>Transplantation</td>
<td>14.32</td>
<td>26.70</td>
</tr>
</tbody>
</table>


South African Experience – HIV to HIV KT

Patient Survival

- 1-year: 86%
- 3-year: 73%

Graft Survival

- 1-year: 91%
- 3-year: 81%
HOPE Act Signed into Law – November 21, 2013

- Mandate for research on the use of HIV-infected deceased donors (HIVOD)
- Guidelines for research in November 2015
- Specifically, develop and publish criteria for the conduct of research relating to transplantation of organs from donors infected with HIV to HIV-end-stage patients
Summary

- AKI is prevalent in HIV and a risk factor for both CKD and death.
- HIV confers a risk of CKD that can rival DM.
- Renal transplant is a good option for HIV+ patients with outcomes comparable to HIV- recipients
- Continued efforts are needed to realize full potential of HOPE Act
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Recommended additional reading

Question-and-Answer