Biomarkers of CKD progression and mortality in HIV

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Why Study Kidney Disease in HIV?

- Early onset of kidney disease
- Chronic inflammatory state
- Viral suppression improves kidney function
- Racial differences in progression rates
- Potential benefits and harms from treatment
HIV Increases ESRD Risk

Danish Cohort Study (5,300 HIV+; 53,000 controls)

Any dialysis

HR = 4.7 (4.0-6.0)

Chronic dialysis

HR = 3.59 (2.0-6.0)

Kidney Disease Accelerated in HIV

FRAM, NHANES comparison of cystatin C

**HIV+**

**HIV-**

16-year acceleration in kidney decline
Risks of Kidney Disease Begin Early in HIV

WIHS Cohort (N=\sim 1,100)

10 year mortality risk

eGFRcys

![Graph showing 10 year mortality risk vs. baseline eGFRcys.](image)
Risks of Kidney Disease Begin Early in HIV

WIHS Cohort (N=\sim 1,100)

10 year mortality risk

![Graph showing baseline eGFRcr vs probability of mortality](image)
Determinants of Kidney Injury in HIV

Virus (HIV, HCV)

Antiretroviral medications

Age and Race

Traditional kidney risk factors (diabetes, hypertension)

Genetic Factors (AP0L1)
Risk Factors for ESRD in the VA

- N = 22,156 participants with active follow-up
- ESRD cases: N = 366
- Median follow-up: 69 months
- Mean Age: 45
- Male (98%)
- Race: White (36%), Black (42%), Other (22%)
- 7% eGFR < 60
- 31% proteinuria

*Jotwani V et al. AJKD 2012*
# Risk Factors for End-Stage Renal Disease

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Multivariate Adjusted</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic Risk Factors:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td>3.06 (2.22-4.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Metabolic/Vascular Risk Factors:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.87 (1.46-2.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.69 (1.32-2.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>2.17 (1.72-2.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>HIV Risk Factors:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 Count &lt;200</td>
<td>1.54 (1.17-2.02)</td>
<td>0.002</td>
</tr>
<tr>
<td>Viral Load ≥30,000</td>
<td>2.01 (1.46-2.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>1.90 (1.52-2.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoalbuminuria (&lt;3.5)</td>
<td>2.14 (1.80-2.54)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Jotwani V et al. AJKD 2012*
Tenofovir and Kidney Risk

Over half of current anti-retroviral regimens include tenofovir.

We conducted analysis of new users of anti-retrovirals

Timeframe: 1997-2007

Primary predictor: tenofovir

Outcomes:
- New onset proteinuria (1+ or higher)
- Rapid decline in kidney function (>3/year)
- New onset CKD (eGFR<60)

Scherzer R et al. AIDS 2012
## Tenofovir Exposure and Risk of Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proteinuria (n = 3400 events)</td>
</tr>
<tr>
<td><strong>Ever Exposure to Tenofovir (versus never)</strong></td>
<td>1.68 (1.52-1.85)***</td>
</tr>
</tbody>
</table>

*** p<.0001, ** p<.001, * p<.01, + p<.05

Scherzer R et al. AIDS 2012
Potential Roles of Novel Biomarkers in HIV

- Early detection of kidney disease
- Specify cause of injury:
  - Metabolic
  - Viral/inflammatory
  - Drug toxicity
- Current methods (creatinine, dipstick proteinuria) only detect established disease and cannot distinguish etiology
WIHS COHORT: HIV⁺ AND HIV⁻ WOMEN

Women’s Interagency HIV Study

Investigations using novel urine biomarkers for kidney injury
Hypotheses

1. Tubule injury predicts GFR decline independent of albuminuria
2. HIV-infection causes chronic tubular injury
3. Tubule injury - 3rd axis of kidney disease and prognosis
4. Tubule dysfunction may be independent predictor of kidney function decline
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV-Infected (N = 1,032)</th>
<th>HIV-Uninfected (N = 371)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>41 (36-45)</td>
<td>38 (32-44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>610 (59%)</td>
<td>228 (61%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Caucasian</td>
<td>198 (19%)</td>
<td>53 (14%)</td>
<td></td>
</tr>
<tr>
<td>Current Smoker</td>
<td>542 (53%)</td>
<td>221 (60%)</td>
<td>0.063</td>
</tr>
<tr>
<td>Diabetes</td>
<td>102 (10%)</td>
<td>39 (11%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>315 (31%)</td>
<td>67 (18%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current CD4</td>
<td>398 (247-581)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Shlipak MG et al. JAIDS, 2013
Urine Biomarkers Evaluated in WIHS

- ACR
- Interleukin-18
- KIM-1
- NGAL
- α-1 microglobulin
### Biomarker Correlation Matrix

<table>
<thead>
<tr>
<th></th>
<th>ACR</th>
<th>IL-18</th>
<th>KIM-1</th>
<th>NGAL</th>
<th>α-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-18</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIM-1</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGAL</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>α-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

- Red: 0.1-0.2
- Blue: 0.2-0.3
- Green: >0.3

All biomarkers standardized to urine creatinine
Urine Biomarker and Kidney Decline in HIV+

- **Single Injury Marker: Multivariate-Adjusted**
  - ACR
  - IL-18
  - KIM-1
  - NGAL

- **Additional Adjustment for Other Injury Biomarkers**
  - ACR
  - IL-18
  - KIM-1
  - NGAL

Adjusted Effect on $\Delta$ eGFR

Shlipak MG et al. JAIDS, 2013
Urine Biomarkers and Kidney Decline in HIV-

Single Injury Marker: Multivariate-Adjusted

- ACR
- IL-18
- KIM-1
- NGAL

Additional Adjustment for Other Injury Biomarkers

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- IL-18
- KIM-1
- NGAL

Adjusted Effect on $\Delta$ eGFR

Shlipak MG et al. JAIDS, 2013
<table>
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<tr>
<th>Cutoff Points</th>
<th>ACR &gt;15.7 mg/g</th>
<th>IL-18 &gt;196 pg/mL</th>
<th>KIM-1 &gt;721 pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% (N=381)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2**</td>
<td>1.32 (0.91 to 1.91)</td>
<td>1.74 (1.25 to 2.43)**</td>
<td>1.10 (0.77 to 1.57)</td>
</tr>
<tr>
<td>10% (N=138)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2**</td>
<td>1.50 (0.74 to 3.03)</td>
<td>2.46 (1.32 to 4.57)+</td>
<td>2.05 (1.17 to 3.58)#</td>
</tr>
</tbody>
</table>

*N= number of participants with at least one outcome

**Model 2: multivariate-adjusted full model controls for model 1 plus traditional risk factors, HIV-related risk factors, and ACR

+p<0.01

++p<0.001

#p<0.05
## High Tertile of ACR, IL-18, and KIM-1 and Rapid Kidney Decline in HIV-Uninfected (N=289)

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<th>IL-18 &gt;196 pg/mL</th>
<th>KIM-1 &gt;721 pg/mL</th>
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</thead>
<tbody>
<tr>
<td>5% (N=67)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2**</td>
<td>0.92 (0.56 to 1.53)</td>
<td>1.76 (0.90 to 3.44)</td>
<td>1.40 (0.79 to 2.49)</td>
</tr>
<tr>
<td>10% (N=21)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2**</td>
<td>1.28 (0.46 to 3.55)</td>
<td>5.93 (1.34 to 26.13)#</td>
<td>4.25 (1.06 to 17.09)#</td>
</tr>
</tbody>
</table>

* N= number of participants with at least one outcome  
** Model 2: multivariate-adjusted full model controls for model 1 plus traditional risk factors, HIV-related risk factors, and ACR  
+p<0.01  
++p<0.001  
#p<0.05
Urine Biomarker Levels: HIV vs. Controls

Adjusted Differences:

1. IL-18 (pg/mL): ↑ 38%
2. NGAL (ng/mL): ↑ 17%
3. KIM-1 (pg/mL): ↑ 12%
4. ACR (mg/g): ↑ 47%

Jotwani V. et al. In Press, AVT
### Independent Predictors of Each Biomarker

<table>
<thead>
<tr>
<th>Demographic Risk Factors:</th>
<th>ACR % Estimate (95% CI)</th>
<th>IL-18 % Estimate (95% CI)</th>
<th>KIM-1 % Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Race</td>
<td>↑ 35 (5, 72)</td>
<td>↑ 59 (34, 88)</td>
<td>↓ 5(-22, 16)</td>
</tr>
<tr>
<td>Metabolic/Vascular Risk Factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>↑ 81 (38, 136)</td>
<td>-</td>
<td>↑ 31(12, 54)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>↑ 47 (7, 101)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HIV Risk Factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 Count</td>
<td>-</td>
<td>↓ 8(-13,-3)</td>
<td>↓ 8 (-13,-2)</td>
</tr>
<tr>
<td>Viral Load</td>
<td>↑ 15 (7, 25)</td>
<td>↑ 15 (8, 22)</td>
<td>-</td>
</tr>
<tr>
<td>HCV Infection</td>
<td>-</td>
<td>↑ 30 (13, 49)</td>
<td>↑ 20(3, 40)</td>
</tr>
</tbody>
</table>

*all p-values< 0.01

*Jotwani V. et al. In Press, AVT.*
Kidney Biomarkers and Mortality Risk

Shlipak MG et al. JAIDS, 2013.
Adjusted HR: Biomarker Tertiles and Mortality Risk

- IL-18:
  - Tertile 1
  - Tertile 2
  - Tertile 3

- ACR:
  - Tertile 1
  - Tertile 2
  - Tertile 3

- L-FABP:
  - Tertile 1
  - Tertile 2
  - Tertile 3

Note: Fully-adjusted Cox models control for age, ethnicity, traditional kidney risk factors, and HIV-related risk factors (all measured at baseline, except for CD4 and HIVRNA, which are time-updated). Traditional kidney risk factors include smoking, hypertension, diabetes, ACR, and eGFRcystatin. HIV-related risk factors include CD4 count, HIVRNA, and HCV.

Peralta CA. et al. In Press, HIV Medicine
# of Abnormal Biomarkers- Mortality Risk

![Graph showing annual death rate with different number of elevated biomarkers](image)

- **0 elevated (n=136)**: 15 cases, annual death rate (95% CI) with p-value 0.26.
- **1 elevated (n=295)**: 47 cases, annual death rate (95% CI) with p-value 0.012.
- **2 elevated (n=269)**: 64 cases, annual death rate (95% CI) with p-value <0.0001.
- **3+ elevated (n=208)**: 75 cases, annual death rate (95% CI).

*Number of the five biomarkers in the “worst” tertile (IL-18, NGAL, KIM-1, ACR, L-FABP)*

Note: P-values denote comparison with 0 elevated category. Rates above are age-adjusted.

_Peralta CA. et al. In Press, HIV Medicine_
α-1 microglobulin

- Urine marker of proximal tubule dysfunction
- Freely filtered
- Completely metabolized in proximal tubule
- Should not be detectable in urine
Detectable α-1 microglobulin in HIV+ vs. HIV- Controls

Detectable >0.6 mg/dL

Adjusted HR: 1.46 (1.2-1.8); p=0.0004

Jotwani V. et al. In Press, AVT.
Association of urinary α-1 microglobulin and other urine biomarkers with kidney decline among HIV-infected participants

Jotwani V. et al. Manuscript in Progress.
Optimal HIV Biomarker Panel?

- Glomerular Injury – ACR
- Proximal Tubule Injury – KIM-1, IL-18
- Proximal Tubule Dysfunction – α-1 microglobulin
New Users of HAART in WIHS Cohort

_Oboho et al. JAIDS, 2013_

TDF (n=45) vs. No TDF (n=45)

1. NGAL - no difference
2. NAG - small increase in TDF users
3. B$_2$mg - Huge increase in TDF users
   “19-fold OR of abnormal B$_2$mg”

Suggest proximal tubule dysfunction may be early sign of TDF toxicity that is otherwise not detectable
TDF/FTC (n=193) vs. ABC/3TC (n=192) Randomized Control Trial

- 48 week follow-up
- No change in eGFR
- Relative change in TDF/FTC vs. ABC/3TC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR</td>
<td>↑ 8%</td>
<td>p=0.42</td>
</tr>
<tr>
<td>NAG</td>
<td>↑ 5%</td>
<td>p=0.51</td>
</tr>
<tr>
<td>B₂M</td>
<td>↑ 133%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>RBP</td>
<td>↑ 50%</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Post et al. JAIDS, 2010
Clinical definition of “Proximal Tubule Dysfunction”

2 of 3

- Urine glucose > 250 (non-diabetic)
- Serum K < 3mEq/L
- Serum HCO$_3^-$ <19mEq/L

- No cases occurred during follow-up

Post et al. JAIDS, 2010
Markers of injury and dysfunction in the kidney tubules:
- Are elevated in HIV+ persons compared with HIV- persons
- Different biomarkers capture a different risk factor profile
- Are independently associated with declining kidney function over time, complementary with albuminuria
- Appear to be independently associated with mortality risk
- May help in early detection of drug toxicity

Although new and not widely available clinically, these biomarkers could have utility in the management of HIV treatment.
Acknowledgements

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- National Institute on Aging
  - R01AG034853 (HIV population)
  - 5R03AG034871
Thank You!