Renal issues in the patient with HIV

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Renal disease in the context of HIV

- HIV associated nephropathy (collapsing FSGS)
- IgA nephropathy
- Lupus-like glomerulonephritis
- Thrombotic microangiopathy (TTP/HUS)
- Membranous nephropathy
- Membranoproliferative GN
- Rhabdomyolysis with AKI (statins, newer ARV, cocaine)
- Nephropathy assoc with concurrent infections (hep B,C)
- Acute interstitial nephritis
- Acute kidney injury (AKI) from prerenal azotemia or ATN
- Crystal induced nephropathy
- Renal failure and Fanconi’s syndrome
- Infiltrative diseases (lymphoma or KS)
- Chronic kidney disease

Adapted from Balow KI 2005
- Routine monitoring of renal function
- Medications
  - Tenofovir and other antiretroviral agents
- HIV nephropathy
- CKD and ESKD
### Routine monitoring of pt with HIV

<table>
<thead>
<tr>
<th></th>
<th>Basic chemistry</th>
<th>urinalysis</th>
<th>other</th>
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<tbody>
<tr>
<td>Entry to care</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Q 6 months</td>
<td></td>
<td></td>
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<tr>
<td>Initiation of ART</td>
<td>✔</td>
<td>✔</td>
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</tr>
<tr>
<td>2-8 weeks after</td>
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<tr>
<td>initiation or</td>
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<tr>
<td>modification</td>
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<tr>
<td>Q 3-6 months</td>
<td>✔</td>
<td>(on TDF) (annual if</td>
<td>Serum phosphate on TDF?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>other)</td>
<td></td>
</tr>
</tbody>
</table>

Guidelines for use of antiretroviral agents in HIV-1-infected adults and adolescents, revised 5/1/14
1. All formulas for eGFR perform poorly when renal function is close to normal.
2. All formulas are meant for the steady state, not AKI.
MEASUREMENT OF URINARY PROTEIN

- Dipstick Method
- 24 hour urine collections
- Urinary “ratios”
  - Protein to creatinine ratio
  - Microalbuminuria (albumin to creatinine ratio)
URINARY PROTEIN:CREATININE RATIO

- ALIQUOT OF RANDOM SPECIMEN
- USES SSA (DETECTS ALL PROTEINS)
- IN STEADY STATE, CORRELATES WITH 24 HR URINARY PROTEIN EXCRETION
- NORMAL RATIO IS <0.2
Correlation of protein: creatinine ratio and 24 hour urine protein

Schwab Arch Int Med 1987
Increasing albuminuria

- **NORMAL**: <30 mcg alb/mg creat
- **MICROALBUMINURIA**: 30-300 mcg alb/mg creat
- **OVERT PROTEINURIA**: >3000 mcg alb/mg creat
- **NEPHROTIC RANGE**: >3000 mg alb/mg creat
Presence of microalbuminuria in HIV may predict future proteinuria

Baseline

685 subjects without abnormal urinary protein 69.4%
191 subjects with Microalbuminuria 20.2%
99 subjects with Proteinuria 10.4%

2nd follow up During 2 years
Normal 79% 47% 35%
Microalbuminuria 16% 40% 14%
Proteinuria: 5% 14% 50%

Szczech L et al. HIV Medicine 2010: 11 419-426
Staging HIV+ patients by eGFR AND proteinuria provides risk stratification

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>0 mg/dL</th>
<th>30-100 mg/dL</th>
<th>300-1,000 mg/dL</th>
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<tbody>
<tr>
<td>eGFR ≥60 ml/min/1.73m²</td>
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<tr>
<td>Number of Patients at Risk</td>
<td>15,348</td>
<td>2,390</td>
<td>185</td>
</tr>
<tr>
<td>ESRD Rate per 1,000 Person-Years</td>
<td>1.0</td>
<td>6.6</td>
<td>35.4</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)†</td>
<td>Reference</td>
<td>6.3 (4.6-8.6)</td>
<td>24.6 (16.0-37.7)</td>
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<tr>
<td>eGFR 30-59 ml/min/1.73m²</td>
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<tr>
<td>Number of Patients at Risk</td>
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<td>350</td>
<td>85</td>
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<td>ESRD Rate per 1,000 Person-Years</td>
<td>5.5</td>
<td>31.1</td>
<td>115.6</td>
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<tr>
<td>Hazard Ratio (95% CI)†</td>
<td>7.4 (4.0-13.8)</td>
<td>37.1 (25.3-54.6)</td>
<td>88.7 (56.0-140.5)</td>
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<tr>
<td>eGFR &lt;30 ml/min/1.73m²</td>
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<tr>
<td>Number of Patients at Risk</td>
<td>38</td>
<td>106</td>
<td>60</td>
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<tr>
<td>ESRD Rate per 1,000 Person-Years</td>
<td>46.1</td>
<td>111.1</td>
<td>192.9</td>
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<tr>
<td>Hazard Ratio (95% CI)†</td>
<td>42.6 (18.3-99.4)</td>
<td>132.8 (87.1-202.5)</td>
<td>523.0 (323.6-845.4)</td>
</tr>
</tbody>
</table>

Jotwani V et al. AJKD 2012 59(5): 628
Which protein should we measure?

- Urinary albumin to creatinine ratio (ACR) for low levels of proteinuria in DIABETES MELLITUS

- Urinary protein to creatinine ratio for overt (dipstick +) and heavy proteinuria

- Other proteins measured can reflect tubular damage including retinol binding protein and $\beta_2$ microglobulin but the role of these tests in monitoring patients has not yet been defined
Case
Case

- 45 year old man with well controlled HIV referred for discolored urine
- Undetectable HIV viral load, CD4 446
- Began ARV in 1996 indinivir and AZT and then with atazanavir (liver disease), current regimen since 2009
- Meds: omeprazole, rosvuastatin
  - Darunavir 400 mg
  - Emtricitabine-tenofovir (Truvada) 200-300mg
Initial visit:

- BP 113/81 HR 69
- Serum creatinine 0.8-1.1 from 1999 to 2010,
  then 3/2012 1.2
  5/2012 1.3
  8/2012 1.5
  9/2012 1.6

urine protein to creatinine ratio 0.9 g/g (nl <0.2)
Urine albumin: creatinine ratio 229 mcg/mg
Serum

- Na$^+$ 138 mEq/L
- Cl$^-$ 114 mEq/L
- K$^+$ 4.3 mEq/L
- HCO$_3^-$ 26 mEq/L
- BUN 28 mg/dL
- creat 1.6 mg/dL
- glucose 109 mg/dL
- Phos 2.3 (2.7-4.5 mg/dL)
- Uric acid 1.9 mg/dL (nl 3.4-7.0)
Causes of low serum phosphate?

Routine biochemistry in vitamin D deficiency
Peacey SR J R Soc Med 2004; 97; 322-325

**SERUM PHOSPHATE**
- 2.47 mg/dl
- 1.24 mg/dl

**SERUM CALCIUM**

**ALKALINE PHOSPHATASE**
Urine dipstick: glu 100, “protein” 100, pH 6.5
- Alb/creat 229 mcg/mg creat
- prot/creat 0.9 mg/mg
- Urine Phos 144 mg/dL
- Urine creatinine 445 mg/dL
FE PO$_4$: % filtered load Phosphate excreted

\[
\text{FE PO}_4 = \frac{U_{\text{phos}}}{P_{\text{phos}}} \frac{P_{\text{creat}}}{U_{\text{creat}}} \times 100
\]

\[
= \frac{144}{2.3} \times 1.6 \times 445
\]

\[
= 23 \%
\]

(normal is $<<15\%$ if serum PO$_4$ low and kidney normal)

Some use fractional tubular reabsorption or $[1 - \text{FEPO}_4]$  
(normal is $>>85\%$)*
Tenofovir nucleotide analogue RTI

- Renally cleared by filtration and tubular secretion
- In initial large scale trials for efficacy and safety, tenofovir did not cause significant renal disease
- Post FDA approval has identified nephrotoxicity by case reports and cohort studies:
  - Acute tubular necrosis
  - Fanconi’s syndrome
    (glycosuria, $\text{PO}_4$ wasting +/- ↓ renal function)
  - Nephrogenic diabetes insipidus
  - Proteinuria and chronic kidney disease
- Increased risk in patients with underlying renal disease or boosted with protease inhibitor
Tenofovir is transported into the cell by organic anion transporters and secreted by the apical transporters—multidrug resistance proteins.
An increase in OAT or decreased MRP can increase proximal tubule concentrations.
Improvement in creatinine after stopping tenofovir

Mean creatinine 5.7mg/dL
(1.1 to 13 range)

Mean baseline creatinine 1.3 (range 0.8 to 1.8) mg/dL

Herlitz LC et al. KI 2010
Metanalysis on change in GFR (by CG) +/- TDF.

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Total</th>
<th>MD [95% CI], mL/min</th>
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<tbody>
<tr>
<td><strong>Total</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>MD [95% CI], mL/min</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>RCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART naive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BICOMBO 2009</td>
<td>333</td>
<td>-0.70 [-2.73, 1.33]</td>
</tr>
<tr>
<td>De Jesus 2009</td>
<td>300</td>
<td>-0.60 [-1.71, 0.51]</td>
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<tr>
<td>ART experienced</td>
<td></td>
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</tr>
<tr>
<td>HEAT 2009</td>
<td>672</td>
<td>-3.00 [-9.06, 3.06]</td>
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<tr>
<td>Arribas 2008</td>
<td>458</td>
<td>-3.00 [-6.77, 0.77]</td>
</tr>
<tr>
<td>Gallant 2004</td>
<td>600</td>
<td>-5.00 [-8.80, -1.20]</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td>-1.50 [-2.96, -0.005]</td>
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<td><strong>Cohort</strong></td>
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<tr>
<td>ART naive</td>
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<tr>
<td>Kinai 2009</td>
<td>63</td>
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<tr>
<td>Goicoechea 2008 NNRTI</td>
<td>62</td>
<td>-0.22 [-11.18, 10.74]</td>
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<tr>
<td>Goicoechea 2008 RPI</td>
<td>84</td>
<td>-7.88 [-18.66, 2.90]</td>
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<td>HOPS 2007</td>
<td>736</td>
<td>-4.40 [-6.97, -1.83]</td>
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<tr>
<td>Winston 2006</td>
<td>948</td>
<td>-6.33 [-14.85, 2.19]</td>
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<tr>
<td>ART experienced</td>
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<tr>
<td>Fux 2007</td>
<td>284</td>
<td>-4.90 [-8.58, -1.22]</td>
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<tr>
<td>Fux 2007 N</td>
<td>569</td>
<td>-8.20 [-13.13, -3.27]</td>
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<tr>
<td>Gallant 2005</td>
<td>658</td>
<td>-5.80 [-8.70, -2.90]</td>
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<tr>
<td><strong>Subtotal</strong></td>
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<td>-5.45 [-7.02, -3.89]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>-3.90 [-5.66, -2.14]</td>
</tr>
</tbody>
</table>

Nephrotoxicity likely ↔ Less likely

Recommendations for use of tenofovir

- Monitor patients on TDF for tubular toxicity (serum creatinine and serum phosphate, urinary protein:creatinine ratio vs. albuminuria? phosphaturia, uricosuria, glycosuria) q 6 months (or 3?)
- If hypophosphatemia, r/o vitamin D deficiency
- When there are clear proximal tubular defects, the medication must be discontinued
- Dose reduce TDF for CKD and avoid combination therapy with GFR <30 ml/min
1. Tenofovir
2. Emtricitabine
3. Elvitegravir
   (new integrase inhibitor)
4. Novel “boosting” agent, cobicistat --inhibits P450 (CY3A) and “boosts elvitegravir levels

ATRIPLA

1. Tenofovir
2. Emtricitabine
3. Efavirenz
Cobicistat effects serum creatinine not the GFR
Cobicistat effect seen in STRATEGY study (single tablet regimens for virologically suppressed patients)

SCr rose and eGFR declined at Week 48

Median change from baseline in SCr at week 48: E/C/F/TDF, 6.19 μmol/L vs. PI + RTV + FTC/TDF, -0.88 μmol/L

Arribas J, et al. CROI 2014; Boston. #551LB
Cobicistat may ↑ serum creatinine

**Diagram:**
- **Basolateral**
  - Creatinine
  - Dolutegravir
  - Cobicistat
  - Ritonavir
  - Cimetidine
  - Trimethoprim

- **Apical**
  - OCT2
  - MATE1
  - MATE2-K
  - OCTN1
  - OCTN2
  - Pgp
  - CRP
  - MRP2

**Note:**
- ATP indicates ATP-driven transporters.
- Arrows indicate direction of transport.
Dolutegravir

Brand Name: Tivicay
Other Names: DTG
Drug Class: Integrase Inhibitors
Approved Use: Treatment of HIV Infection

Drug Image:
Click image to enlarge

Chemical Image:
Click image to enlarge

dolutegravir
Molecular Weight: 419.3821
- Abacavir
- Dolutegravir
- Lamivudine
New prodrug **tenofovir alafenamide** (TAF) may lead to less renal exposure to drug.

→ TAF does not appear to be a substrate for OAT.
Tenofovir Alafenamide is not a substrate for renal organic anion transporter 1 and does not exhibit OAT dependent cytotoxicity. Bam RA, Yant SR and Cihlar T. CROI 2013; 540.
Crystal induced renal disease

- Protease inhibitors
  - Indinivir (insoluble in acid pH)
  - Atazanavir (Reyataz) insoluble in alkaline pH
  - Nelfinivir
  - Amprenavir
  - NRTI Efavirenz

- Other medications
  - Acyclovir
  - Foscarnet

Nelfinivir crystals
Crystal induced renal disease

Urine with crystals from acyclovir
Sawyer MH AmJ Med 1988 84(6) 1002

Renal Tissue in an HIV+ patient Treated with Indinavir
Acute interstitial nephritis
Drugs that may cause AIN

- Antibiotics
  - β lactam antibiotics
  - Sulfonamides (tmp/smz, dapsone)
  - Quinolones
  - rifampin

- Proton pump inhibitors***

- NSAIDS

- Allopurinol

- ARV: Abacavir, ritonovir, atazanavir, indinivir,
  - efavirenz * (hypersensitivity RXN)

- cocaine

- HIV, BK virus and other infectious agents

Review in CJASN 2010 5(5): 798
Renal dosing of ARV

- Dose reduction for nucleoside/tide reverse transcriptase inhibitors
- Caution with combination pills
- Some PI need dose alteration
- NNRTI extensive hepatic metabolism
- Newer agents (darunavir, etravirine, raltegravir, maraviroc) primarily hepatic metabolism but not extensively tested in patients with CKD
- Reports of inadequate treatment in many patients with CKD or ESKD

Double check at http://www.aidsinfo.nih.gov/
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ARV Agent(s)/Drug Class</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td><strong>Renal Effects</strong></td>
<td>Switch from</td>
<td>Switch to</td>
</tr>
<tr>
<td>Including proximal renal tubulopathy, elevated creatinine</td>
<td>TDF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ABC&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ATV/r, LPV/r</td>
<td>DTG, RAL, or NNRTI</td>
</tr>
<tr>
<td><strong>Stones</strong></td>
<td></td>
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</tr>
<tr>
<td>Nephrolithiasis and cholelithiasis</td>
<td>ATV, ATV/r</td>
<td>DRV/r, INSTI, or NNRTI</td>
</tr>
</tbody>
</table>

**Table 15. Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent**

- **Comments**: Phosphate wasting as a consequence of TDF nephrotoxicity may lead to osteomalacia.
- **Comments**: cobi and DTG, and to a lesser extent RTV, RPV, and RAL, can increase SCR soon after treatment initiation because of inhibition of tubular secretion of creatinine. This effect does not affect glomerular filtration. However, assess for renal dysfunction, especially if SCR increases by >0.4 mg/dL.
- **Comments**: Nephrolithiasis (a frequent complication of IDV) has been observed with ATV. Cholelithiasis is also reported with ATV.

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<sup>a</sup> For patients with chronic active HBV infection, another agent active against HBV should be added to substitute for TDF.

<sup>b</sup> ABC should be used only in patients known to be HLA-B*5701 negative.

<sup>c</sup> TDF reduces ATV levels; therefore, unboosted ATV should not be co-administered with TDF. Long term data for unboosted ATV are unavailable.

**Key to Abbreviations**: ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; BMD = bone mineral density; CNS = central nervous system; cobi = cobicistat; d4T = stavudine; did = didanosine; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FPV/r = ritonavir-boosted
Renal disease in the context of HIV

- HIV associated nephropathy (collapsing FSGS)
- IgA nephropathy
- Lupus-like glomerulonephritis
- Thrombotic microangiopathy (TTP/HUS)
- Membranous nephropathy
- Membranoproliferative GN
- Rhabdomyolysis with AKI (with statin use)
- Nephropathy assoc with concurrent infections (hep B,C)
- Acute interstitial nephritis
- Acute kidney injury (AKI) from prerenal azotemia or ATN
- Crystal induced nephropathy
- Renal failure and Fanconi’s syndrome
- Infiltrative diseases (lymphoma or KS)
- Chronic kidney disease

Adapted from Balow KI 2005
Table 1. Clinical Data on 11 Patients with AIDS and Renal Disease.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Race/Sex</th>
<th>Risk Factor</th>
<th>Renal Manifestation</th>
<th>Renal Histology *</th>
<th>Time to Severe Uremia</th>
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</thead>
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<tr>
<td></td>
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<td>Renal</td>
<td></td>
<td>Time to Severe Uremia</td>
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<td></td>
<td></td>
<td></td>
<td>Renal</td>
<td></td>
<td>ml/min</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Renal</td>
<td></td>
<td>wk</td>
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<tr>
<td>28/B/F</td>
<td>Heroin</td>
<td>Nephrotic syn.</td>
<td>FSGS</td>
<td>90</td>
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<tr>
<td>38/B/M</td>
<td>Heroin, homosexual</td>
<td>Nephrotic syn.</td>
<td>FSGS (A)</td>
<td>(1.4)</td>
<td>8–10</td>
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<tr>
<td>27/B/M</td>
<td>Heroin</td>
<td>Nephrotic syn.</td>
<td>FSGS</td>
<td>75</td>
<td>16</td>
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<td>33/B/M</td>
<td>Heroin</td>
<td>Nephrotic syn.</td>
<td>FSGS (A)</td>
<td>90</td>
<td>12</td>
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<tr>
<td>8</td>
<td>26/B/M</td>
<td>Homosexual</td>
<td>Nephrotic syn.</td>
<td>FSGS (1.3)</td>
<td>16</td>
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<tr>
<td>9</td>
<td>46/B/M</td>
<td>Haitian</td>
<td>Azotemia, proteinuria</td>
<td>Mesangial increase</td>
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<tr>
<td>10</td>
<td>36/B/M</td>
<td>Homosexual</td>
<td>Nephrotic syn.</td>
<td>FSGS (A) (1.2)</td>
<td>8–10</td>
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<tr>
<td>11</td>
<td>22/B/F</td>
<td>Haitian</td>
<td>Nephrotic syn.</td>
<td>FSGS (A)</td>
<td>8</td>
</tr>
</tbody>
</table>

* Histology codes: FSGS: Focal segmental glomerular sclerosis
  A: Active
HIV nephropathy/ HIV associated FSGS

- Classically, presents with nephrotic syndrome
- Typically normotensive
- Ultrasound with enlarged kidneys
- Historically-poor prognosis $\rightarrow$ ARV therapy has changed the landscape
- Usually late manifestation (can occur throughout course of HIV)
- Presentation with well controlled HIV more subtle, may have mild proteinuria
- Marked predilection for individuals of African ancestry
Typical histopathologic findings in HIVAN

FSGS with segmental collapse

Tubular microcystic changes

Ross JASN 2002; 13:2997
In situ hybridization of HIV mRNA

Ross M J, Klotman P E JASN 2002;13:2997-3004
Pathogenesis of HIV AN

HIV-1 infection (nef, vpr, genes!)

Podocyte dysregulation (esp if genetic predisposition)
- Disruption of cytoskeleton
- Loss of foot process architecture
- Proliferation
- Immature collagen IV

Glomerular capillary loop collapse

Loss of filtration barrier
- Massive proteinuria
- Secondary damage to podocytes
- Glomerulosclerosis

Tubular epithelial cell dysregulation

Tubular destruction and regeneration with microcyst formation

Adapted from Kimmel Annals 2003
Zhou Kidney Int 2005
Klotman FASEB 2007
Many questions?

- If kidney is a reservoir for HIV, why don’t more have this disorder
- What host factors are important in HIVAN
  - MYH9? Apo L1? Others?
- Treatment?
APO L1 alleles G1 and G2 confer risk for HIVAN

<table>
<thead>
<tr>
<th>Risk Allele</th>
<th>Stratum</th>
<th>Number Case/Control</th>
<th>1 vs. 0 Risk Allele</th>
<th>2 vs. 0 Risk Allele</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (CI)</td>
<td>P</td>
</tr>
<tr>
<td>HIV-associated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>collapsing</td>
<td>G1</td>
<td>27/180</td>
<td>1.9 (0.5, 8)</td>
<td>0.37</td>
</tr>
<tr>
<td>glomerulopathy</td>
<td>G2</td>
<td>11/150</td>
<td>1.4 (0.2, 7.5)</td>
<td>0.70</td>
</tr>
<tr>
<td>(n = 54) and</td>
<td>G1/G2</td>
<td>26/113</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>hyper-normal</td>
<td>G1 or G2</td>
<td>54/237</td>
<td>1.8 (0.5, 6.8)</td>
<td>0.42</td>
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<tr>
<td>controls (n = 237)</td>
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<td></td>
</tr>
<tr>
<td>African American</td>
<td>G1</td>
<td>125/286</td>
<td>1.9 (1, 3.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>idiopathic FSGS</td>
<td>G2</td>
<td>56/234</td>
<td>1.0 (0.4, 2.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>cases (n = 217)</td>
<td>G1/G2</td>
<td>82/186</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>and controls (n =</td>
<td>G1 or G2</td>
<td>217/383</td>
<td>1.4 (0.8–2.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>383)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The APOL1 risk alleles are referred to as follows: G1, S342G mutation; G2, 6 bp deletion (N388del/Y389del). Stratum refers to African American and controls with stratum codes of hypertension (2), chronic kidney disease (3), and non-renal outcomes (4). The strata do not add to the total due to overlap between strata. G1/G2 compound heterozygotes were determined by Fisher exact test. As shown, the data best fit a recessive mode of inheritance, with marginal evidence for the G1 allele.
ApolL1 and Trypanosomes

**A** *T. b. brucei*

- ApoL1 (WT)
- HDL3
- ApoA1
- Hb-Hpr ligand
- Lysosomal swelling
- Parasite dies

**B** *T. b. rhodesiense*

- ApoL1 (WT)
- Serum resistance assoc protein (SRA)
- No lysosomal swelling
- Parasite survives

**C** *T. b. rhodesiense*

- ApoL1 (G1 or G2)
- Lysosomal swelling
- Parasite dies

Current opinion in immunology
Patient and renal survival in HIVAN

% alive

% without ESKD

Therapy for HIVAN

- Current era → HAART
  - Case reports of clinical and histological remission from therapy
- Prednisone if HAART does not improve renal function or deterioration is rapid
- Blockade of renin angiotensin aldosterone system
- Epidemiology suggests reduction in incidence of HIVAN but data lags
Relative proportion of patients on ARV in chronic kidney disease

Adapted from Choi AI et al 2007 Clin Inf Dis 45:1633
What about HIV with CKD?

- Address underlying disorders
- Dose medications for reduced GFR
- Address HTN with goal <130/80 if there is proteinuria and preference for ACE I/ARB (if proteinuria)
- Avoid high protein diets
- Management of cardiovascular risk factors
  - hyperlipidemia
  - Glycemic control in diabetes
  - tobacco use!!
- Assess and treat metabolic complications
  - Anemia
  - Metabolic acidosis and hyperkalemia
  - Secondary hyperparathyroidism
ESKD in the HIV positive patient

- Hemodialysis
- Peritoneal dialysis
- Renal transplantation
- “Non selection”
Incidence and prevalence of ESKD from AIDS

Counts (in thousands)

Rate (in millions)

Incident count (thousands)

Incident rate per million

<table>
<thead>
<tr>
<th>Condition</th>
<th>1995</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Congestive heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Ischemic heart disease, CAD*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Cardiac arrest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Cardiac dysrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Pericarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. Cerebrovascular disease, CVA, TIA*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>h. Peripheral vascular disease*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. History of hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>j. Diabetes (primary or contributing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k. Diabetes, currently on insulin</td>
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<tr>
<td>l. Chronic obstructive pulmonary disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>m. Tobacco use (current smoker)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n. Malignant neoplasm, Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o. Chronic obstructive pulmonary disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p. Tobacco use (current smoker)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>q. Drug dependence*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r. Drug dependence*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>s. HIV positive status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t. AIDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>u. Inability to ambulate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>v. Inability to transfer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>w. Non-renal congenital abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>x. Can't Disclose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>y. Can't Disclose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>z. Can't Disclose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Care of patients with ESKD

- Lifestyle modifications
- Vaccination
- Infection prophylaxis
- Malignancy screening
- Appropriate dosing of ARV
- Anemia management
- Bone and mineral management

From Novak and Szczech ACKD 2010
Renal transplantation in recipient with HIV

Patient survival

Graft survival

HIV+
>65 yr

HIV and transplantation requires close coordination of care

- Potential antiretroviral/ immunosuppressive drug-drug interactions
  - Protease inhibitors affect P450 cytochrome isoenzymes (CYP3A4) which affect metabolism of calcineurin inhibitors
  - Nonnucleoside reverse transcriptors affect metabolism of immunosuppressant agents in more complex manner

- Increased risk of rejection but treatment may result in severe infections

- Transplant team must work closely with infectious disease team
Recommendations:

- Assess renal function and measure proteinuria in all patients at diagnosis of HIV and annually (more frequently with ↑ risk factors for CKD)

- Consider referral for patients with eGFR < 60 ml/min, proteinuria and/or hematuria

- Consider a broad differential in assessing kidney disorders

- Dose medications according to eGFR to avoid toxicity AND inadequate treatment

- Attention to modifiable risk factors for CVD in setting of CKD.
Established or hypothesized role of HIV infection or its treatment

- HIV-associated nephropathy (HIVAN)
- Antiretroviral nephrotoxicity
  - Tenofovir (proximal tubulopathy)
  - Indinavir (interstitial nephritis and crystal deposition)
  - Other protease inhibitors?
- HIV-immune complex kidney disease
- IgA nephropathy

Hypothesized additive effect of HIV infection or its treatment
- Diabetic nephropathy

Unclear role of HIV infection or its treatment
- Noncollapsing focal segmental glomerulosclerosis
- Membranoproliferative glomerulonephritis, with or without hepatitis C virus
- Membranous nephropathy, with or without hepatitis B virus
- Arterionephrosclerosis

Mallipatu et al KI 2014
Other resources:

- Guidelines, drug dosing
  http://www.aidsinfo.nih.gov

- Monograph on HIV and CKD from NKF:
  http://www.kidney.org/professionals/tools

- IDSA CKD in HIV guidelines
  (2005 posted, update in 2014)
  http://www.idsociety.org

- CROI conference on retroviral and OI has web/podcasts of recent meetings
  http://retroconference.org
Hello Kidney