THE KIDNEYS IN HIV INFECTION

3rd National AIDS Conference

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12th October 2014
OUTLINE

• Diagnosis of Renal Disease in HIV patients
• Risk Factors for kidney disease in HIV patients
• Epidemiology and causes of kidney diseases in HIV patients
• HIVAN, HIVICKD, HIV ASSOCIATED THROMBOTIC MICROANGIOPATHY
• Antiretroviral treatment and potential side effects
• Renal replacement therapy in HIV patients
• Renal transplantation in HIV patients
• Management Strategies
DIAGNOSIS OF RENAL DISEASE IN HIV PATIENTS

AKI
- AKIN
- RIFLE
- KDIGO AKI Guidelines 2012

CKD
- eGFR
- Serum Cystatin C
- Urine albumin to creatinine ratio / Urine protein to creatinine ratio
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ACUTE KIDNEY INJURY

• Highly prevalent among HIV infected individuals → particularly in those who have had AIDS-defining illness including opportunistic infection.

• **Ten percent** of patients experienced at least 1 episode of AKI over a 2-year period. (71 patients out of 754 patients)\(^1\)

• More than half were attributed to underlying infections, 76% of which were AIDS-defining illness, and ~75% needed hospitalization.\(^2\).

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Table 2. Etiology of acute renal failure (ARF) in ambulatory human immunodeficiency virus (HIV)-infected patients, 2000–2002, North Carolina

<table>
<thead>
<tr>
<th>Causes</th>
<th>ARF events&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% by subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td></td>
</tr>
<tr>
<td>Prerenal</td>
<td>43 (38)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea, nausea, vomiting, dehydration</td>
<td>18</td>
<td>42</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Cirrhosis or hepatorenal syndrome</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sepsis or infection</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Erythroderma</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Renal</td>
<td>48 (46)</td>
<td></td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>22</td>
<td>46</td>
</tr>
<tr>
<td>Nephrotoxic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>17</td>
<td>35</td>
</tr>
<tr>
<td>Radiocontrast</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemolytic uremic syndrome</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Obstructive</td>
<td>9 (7)</td>
<td>22</td>
</tr>
<tr>
<td>Kidney stones</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Crystalluria</td>
<td>6</td>
<td>67</td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (9)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Seventy-one patients with 111 episodes of ARF.

<table>
<thead>
<tr>
<th>Type of renal injury</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute tubular necrosis</td>
<td>Pentamidine(^{115})</td>
</tr>
<tr>
<td></td>
<td>Foscarnet(^{116-118})</td>
</tr>
<tr>
<td></td>
<td>Cidofovir(^{119})</td>
</tr>
<tr>
<td></td>
<td>Adefovir(^{119})</td>
</tr>
<tr>
<td></td>
<td>Amphotericin B(^{120,121})</td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides(^{120})</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim-sulfamethoxazole(^{118,122})</td>
</tr>
<tr>
<td>Intratubular obstruction secondary to crystal precipitation</td>
<td>Sulfadiazine(^{123,124})</td>
</tr>
<tr>
<td></td>
<td>Foscarnet(^{125})</td>
</tr>
<tr>
<td></td>
<td>Acyclovir(^{126,127})</td>
</tr>
<tr>
<td>Interstitial nephritis(^{101,128,129})</td>
<td>β-Lactam antibiotics</td>
</tr>
<tr>
<td></td>
<td>Quinolones</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Crescentic glomerulonephritis</td>
<td>Foscarnet(^{130})</td>
</tr>
<tr>
<td></td>
<td>Rifampicin(^{131})</td>
</tr>
<tr>
<td>Nephrogenic diabetes insipidus</td>
<td>Foscarnet(^{132,133})</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
<td>Trimethoprim-sulfamethoxazole (trimethoprim component)(^{134-136})</td>
</tr>
<tr>
<td></td>
<td>Foscarnet(^{133})</td>
</tr>
</tbody>
</table>
DIAGNOSIS OF RENAL DISEASE IN HIV PATIENTS

AKI
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- KDIGO AKI Guidelines 2012

CKD
- eGFR
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- Urine albumin to creatinine ratio / Urine protein to creatinine ratio
MEASURING KIDNEY FUNCTION

• The Infectious Disease Society of America recommends that, at the time of HIV diagnosis:
  • **ALL** patients should be assessed for evidence of CKD, and, if present, be appropriately **staged** for kidney disease. ¹

• The best way to measure the GFR involves administering a foreign substance like **inulin** or radio-isotopes that the glomeruli will filter **completely as waste**, without **reabsorption** by the tubules, and measuring its **clearance** over time. ²

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¹ Kalyesubula R, Perazella MA. Nephrotoxicity of HAART. AIDS Research and Treatment Volume 2011, Article ID 562790
# MEASURING KIDNEY FUNCTION

## Table 2. Commonly Used Glomerular Filtration Rate Estimating Equations Based on Serum Concentration of Creatinine or Cystatin C

<table>
<thead>
<tr>
<th>Name</th>
<th>Equation</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Cockcroft-Gault [383]                                        | $\text{CrCl} = \frac{[140 - \text{age}] \times \text{weight (kg)}}{72 \times S_\text{Cr}} \times 0.85$ (if female) | • Least accurate or precise of available equations [205, 384]  
• May be useful for older, cachectic patients  
• FDA has traditionally required this equation be used for recommended drug dose modifications in kidney disease |
| MDRD, 4-variable, using standardized serum creatinine concentration [205] | $\text{GFR} = 175 \times S_\text{Cr}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ (if black) $\times 0.742$ (if female) | • Widely used by clinical laboratories to estimate GFR  
• Accurate GFR estimates at GFR $<60$ mL/min/1.73 m²  
• Underestimates GFR in patients with GFR $>60$ mL/min/1.73 m² [386] |
| CKD-EPI creatinine equation, using standardized serum creatinine concentration [15, 30] | $\begin{align*} 
\text{Female, } S_\text{Cr} \leq 0.7: \quad & \text{GFR} = 144 \times S_\text{Cr}^{-0.411} \times (0.993)^{0.8} \times 1.159$ (if black) \\
\text{Male, } S_\text{Cr} \leq 0.9: \quad & \text{GFR} = 141 \times S_\text{Cr}^{-0.411} \times (0.993)^{0.8} \times 1.159$ (if black) \\
\text{Male, } S_\text{Cr} > 0.9: \quad & \text{GFR} = 141 \times S_\text{Cr}^{-0.411} \times (0.993)^{0.8} \times 1.159$ (if black) \\
\end{align*}$ | • More accurate than MDRD equation, particularly at GFR $>60$ mL/min/1.73 m² [30, 386] |
| CKD-EPI cystatin C equation, using standardized serum cystatin C concentration [15] | $\begin{align*} 
\text{S_Cys} \leq 0.8: \quad & \text{GFR} = 133 \times S_\text{Cys}^{-0.498} \times (0.996)^{0.8} \times 0.932$ (if female) \\
\text{S_Cys} > 0.8: \quad & \text{GFR} = 133 \times S_\text{Cys}^{-0.498} \times (0.996)^{0.8} \times 0.932$ (if female) \\
\end{align*}$ | • Race not required for estimate  
• Similar accuracy and precision to CKD-EPI creatinine equation [15] |
| CKD-EPI creatinine-cystatin C equation, using standardized serum creatinine and cystatin C concentrations [15] | $\begin{align*} 
\text{Female, } S_\text{Cr} \leq 0.7, S_\text{Cys} \leq 0.8: \quad & \text{GFR} = 130 \times S_\text{Cr}^{-0.48} \times S_\text{Cys}^{-0.375} \times (0.995)^{0.8} \times 1.08$ (if black) \\
\text{Female, } S_\text{Cr} \leq 0.7, S_\text{Cys} > 0.8: \quad & \text{GFR} = 130 \times S_\text{Cr}^{-0.48} \times S_\text{Cys}^{-0.375} \times (0.995)^{0.8} \times 1.08$ (if black) \\
\text{Female, } S_\text{Cr} > 0.7, S_\text{Cys} \leq 0.8: \quad & \text{GFR} = 130 \times S_\text{Cr}^{-0.48} \times S_\text{Cys}^{-0.375} \times (0.995)^{0.8} \times 1.08$ (if black) \\
\text{Female, } S_\text{Cr} > 0.7, S_\text{Cys} > 0.8: \quad & \text{GFR} = 130 \times S_\text{Cr}^{-0.48} \times S_\text{Cys}^{-0.375} \times (0.995)^{0.8} \times 1.08$ (if black) \\
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\text{Male, } S_\text{Cr} \leq 0.9, S_\text{Cys} > 0.8: \quad & \text{GFR} = 135 \times S_\text{Cr}^{-0.375} \times S_\text{Cys}^{-0.375} \times (0.995)^{0.8} \times 1.08$ (if black) \\
\text{Male, } S_\text{Cr} > 0.9, S_\text{Cys} \leq 0.8: \quad & \text{GFR} = 135 \times S_\text{Cr}^{-0.375} \times S_\text{Cys}^{-0.375} \times (0.995)^{0.8} \times 1.08$ (if black) \\
\text{Male, } S_\text{Cr} > 0.9, S_\text{Cys} > 0.8: \quad & \text{GFR} = 135 \times S_\text{Cr}^{-0.375} \times S_\text{Cys}^{-0.375} \times (0.995)^{0.8} \times 1.08$ (if black) \\
\end{align*}$ | • Currently the most accurate method to estimate GFR  
• Requires measurement of both serum creatinine and cystatin C |

MEASURING KIDNEY FUNCTION

• Studies found the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation to be more accurate than the older Modification of Diet in Renal Disease (MDRD) equation in HIV-infected individuals.¹

• The CKD-EPI equation that uses both creatinine and cystatin C has been found to be somewhat more accurate and precise than equations based on a single biomarker in both the general population and in HIV-infected persons.²,³,⁴

WHY IS KIDNEY DISEASE IMPORTANT?
• 17,235 patients
• Followup for 5.7 years

Figure 1. Outcomes in HIV-infected patients with no acute kidney injury (AKI) or AKI of increasing severity. Adapted from Choi et al.⁴
• Observational Cohort Study
• 7 large HIV cohorts in UK – 20,132 patients
• Followup 5.3 years (median)

Figure 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality and estimated glomerular filtration rate (eGFR) categories according to spline. Data were adjusted for age, sex, ethnicity, risk group, and years since entry into the cohort as fixed covariates and CD4 cell count, HIV (human immunodeficiency virus) RNA level, combination antiretroviral therapy use, AIDS, and hepatitis B surface antigen and hepatitis C antibody status as time-updated covariates. The diamond symbol represents the reference point of eGFR of 95 mL/min/1.73 m² (knots at eGFRs of 45, 60, 75, 90, and 105 mL/min/1.73 m²).
**CKD CLASSIFICATION**

- **Very high risk**
- **High risk**
- **Moderately increased risk**
- **Low risk**

### Albuminuria categories

**A1** (≤30 mg/g)
- Normal to mildly increased

**A2** (30 – 300 mg/g)
- Moderately increased

**A3** (>300 mg/g)
- Severely increased

<table>
<thead>
<tr>
<th>G1 (≥90)</th>
<th>Normal or high</th>
</tr>
</thead>
<tbody>
<tr>
<td>G2 (60–89)</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>G3a (45–59)</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b (30–44)</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4 (15–29)</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5 (&lt;15)</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

Adapted from Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected With HIV: 2014 Update by the HIV Medicine Association of the Infectious Diseases Society of America
In the USA, 1.5% (range 0.3–3.4%) of dialysis patients → HIV infection 0.4% (range 0–1.0%) of dialysis patients → AIDS.¹

However, as dialysis patients in the USA have not necessarily undergone routine screening for HIV infection since then, true incidence and prevalence estimates are probably higher than those reported.²

Black persons account for 10% of the general population in the USA but account for > 30% of patients with ESRD.²

Among persons with HIV infection who receive dialysis, 91% are Black.


Fig. 1 Comparisons of prevalence of proteinuria (a), albuminuria (b), CKD stages 1–5 (c), and CKD stages ≥3 (d) across previous studies. The number in brackets indicates the reference number.
The prevalence of CKD among the HIV seropositive patients in Sg Buloh Hospital was 9.47%.

- CKD stage 1 (16 patients) 77.9%
- CKD stage 2 (9 patients) 17.6%
- CKD stage 3 (15 patients) 3%
- CKD stage 4 (7 patients) 1.4%
- CKD stage 5 (One patient) 0.2%
# RISK FACTORS FOR KIDNEY DISEASE IN HIV PATIENTS

Adapted from Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected With HIV: 2014 Update by the HIV Medicine Association of the Infectious Diseases Society of America

<table>
<thead>
<tr>
<th>Factor</th>
<th>CKD (GFR &lt;60 mL/min/1.73 m² or Proteinuria)</th>
<th>ESRD or (GFR &lt;15 mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk Range</td>
<td>Reference(s)</td>
</tr>
<tr>
<td>African descent</td>
<td>1.7–2.4</td>
<td>[36, 42, 44, 54, 122]</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.5–1.7</td>
<td>[44, 46]</td>
</tr>
<tr>
<td>Family history of ESRD</td>
<td>NR</td>
<td>[44, 46]</td>
</tr>
<tr>
<td>Age</td>
<td>1.2–5.5 per 10 y older</td>
<td>[35, 36, 38, 44, 46, 391]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.5–2.6</td>
<td>[38, 42, 46, 54, 121, 122]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.4–3.5</td>
<td>[35, 38, 42, 46, 54, 121, 122, 122, 156]</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>1.1–1.25 per 100 cells/μL lower</td>
<td>[42, 46, 54, 121, 122, 156, 394]</td>
</tr>
<tr>
<td></td>
<td>1.4–2.2 for CD4 &lt;200 vs ≥200 cells/μL</td>
<td>[42, 46, 54, 121, 122, 156, 394]</td>
</tr>
<tr>
<td>HIV RNA</td>
<td>1.3–2.2 for detectable or higher vs undetectable or lower HIV RNA</td>
<td>[36, 38, 54, 122]</td>
</tr>
<tr>
<td>Hepatitis C coinfection or history of injection drug use</td>
<td>1.3–2.2</td>
<td>[36, 38, 42, 44, 46, 51, 54, 121, 122, 156]</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>1.2–1.3 per year of exposure</td>
<td>[35, 46, 156, 157]</td>
</tr>
<tr>
<td></td>
<td>1.6–2.2 for any or recent exposure vs no or remote exposure</td>
<td>[35, 46, 156, 157]</td>
</tr>
<tr>
<td>Tenofovir plus a ritonavir-boosted protease inhibitor</td>
<td>3.4 vs an NNRTI-based regimen without tenofovir</td>
<td>[54]</td>
</tr>
<tr>
<td>Indinavir</td>
<td>2.0–2.5 for any or recent exposure vs no or remote exposure</td>
<td>[35, 156]</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>1.2 per year of exposure</td>
<td>[46]</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>1.1 per year of exposure</td>
<td>[46]</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NR, not reported.
CAUSES OF CKD IN HIV PATIENTS

Traditional HIV-specific glomerular disease

HIVAN

HIVICKD

HIV-related TMA

Comorbidities

Hypertension

Diabetes Mellitus

Hepatitis C / Hepatitis B

Drugs

# HIV-SPECIFIC AND HIV NON-SPECIFIC GLOMERULAR DISEASES OBSERVED IN HIV-INFECTED PATIENTS

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV-specific disease</strong></td>
<td></td>
</tr>
<tr>
<td>HIVAN</td>
<td>Detectable viral load, high amount of proteinuria, rapid progression of renal failure</td>
</tr>
<tr>
<td>HIVIC (HIV-associated immune complex kidney disease)</td>
<td>Proteinuria and/or haematuria, variable manifestation including AKI</td>
</tr>
<tr>
<td>TMA (Thrombotic microangiopathy)</td>
<td>AKI, proteinuria, haematuria with microangiopathic haemolytic anaemia and thrombocytopaenia</td>
</tr>
<tr>
<td><strong>HIV nonspecific disease</strong></td>
<td></td>
</tr>
<tr>
<td>HCV-related MPGN/cryoglobulinemia</td>
<td>Proteinuria and/or haematuria, nephritic syndrome, decrease in serum complements</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>Proteinuria (microalbuminuria to nephrotic syndrome), decrease in GFR</td>
</tr>
<tr>
<td>Glomerular sclerosis</td>
<td>Older patients, hypertension, no or low amount of proteinuria, coexistence of atherosclerotic diseases</td>
</tr>
<tr>
<td>Membranous glomerulopathy</td>
<td>Nephrotic syndrome, idiopathic and secondary causes associated with HBV or cancers</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>Nephrotic syndrome, use of NSAIDs</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>Haematuria and/or proteinuria with or without renal failure</td>
</tr>
<tr>
<td>Postinfectious glomerulonephritis</td>
<td>Haematuria and/or proteinuria with or without renal failure</td>
</tr>
</tbody>
</table>

Figure comparing HIV-positive with HIV-negative patients biopsied during study period of 1 year (2003-2004) at Chris Hani Baragwanath Hospital, South Africa.

COMORBIDITIES OF DIABETES, HYPERTENSION

- **Diabetes** and **hypertension** account for more than 70% of all ESRD in the general US population.¹

- Aging of the HIV infected population and prolonged exposure to antiretroviral regimens → promote the development of diabetes and hypertension²

- **Diabetes** and **hypertension** have also been identified as **independent risk factors for CKD** among HIV-infected individuals in Europe.³

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HEPATITIS C CO-INFECTION

• An estimated 10 million individuals worldwide are coinfected with HIV and HCV.¹

• Hepatitis C coinfection is associated with a significant increase in risk of CKD progression among HIV-infected individuals


Traditional HIV-specific glomerular disease

HIVAN

HIVICKD

HIV-related TMA
HIV ASSOCIATED NEPHROPATHY

- First described in New York in 1984.¹
- The estimated prevalence of HIVAN has ranged from 3.5% in clinical studies to 12% in autopsy studies.²
- Renal biopsy is the only means to establish the diagnosis of HIVAN.³


Figure 1 | Classic pathological features of HIV-associated nephropathy (HIVAN). Kidney biopsy performed in a 28-year-old African American man with untreated HIV/AIDS presenting with proteinuria, hypertension, and progressive renal failure. a) Low-power view showing diffuse interstitial fibrosis and tubular atrophy. b) High-power view demonstrating hyalinizing arteriolosclerosis and mesangial matrix expansion.
Table 2. Proximate CD4+ cell count, HIV-1 RNA level and risk of developing HIV-1-associated nephropathy.

<table>
<thead>
<tr>
<th>CD4+ cell count &lt; 200 × 10⁶ cells/l</th>
<th>HIV-1 RNA &gt; 100,000 copies/ml</th>
<th>Rate ratioᵃ (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>3.5 (1.8–7.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>2.0 (0.7–6.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>6.1 (3.2–11.8)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

ᵃAdjusted for race.
PATHOGENESIS OF HIVAN AND OTHER HIV-RELATED KIDNEY DISEASES

Single-nucleotide polymorphisms in the apolipoprotein L1 (APOL1) gene

TREATMENT OF HIVAN

• HAART

* Diagnosis of HIVAN is an indication for antiretroviral therapy regardless of viral load.

• ACE inhibitors

HIVAN TREATMENT WITH HAART

Hopkins Nephrology HIV Cohort
ARV Treatment of HIVAN:
Dialysis Free Survival Estimates
Atta et al., Nephrol Dial Transpl, 2006

Time (days)

Dialysis-free Survival

ARV Treatment (n=26)

P = (0.025)

No ARV (n=10)
HAART AND HIVAN INCIDENCE
12-YEAR COHORT STUDY

- Risk of HIVAN low in patients without AIDS
- NO HIVAN when HAART used without AIDS occurrence
- Lower HIVAN associated with NRTI and HAART use compared with no ART in patients with AIDS
- (p < 0.001 for trend)

Numbers in bars represent point estimates for HIV-associated nephropathy incidence in cases per 1000 person-years. Brackets above bars represent upper limits of 95% confidence intervals.

Traditional HIV-specific glomerular disease

- HIVAN
- HIVICKD
- HIV-related TMA
HIV-ASSOCIATED IMMUNE COMPLEX KIDNEY DISEASE

• The prevalence of HIV-associated, immune complex–mediated glomerulonephritides has been estimated to be 15%–80%. ¹

• May present as:
  • postinfectious glomerulonephritis,
  • membranous nephritis,
  • IgA nephritis,
  • fibrillary glomerulonephritis,
  • immunotactoid glomerulopathy
  • membranoproliferative glomerulonephritis
  • lupus-like syndrome ²,³

TREATMENT OF HIV-ASSOCIATED IMMUNE COMPLEX KIDNEY DISEASE

• No RCT

• Seem to benefit from treatment with:
  • **ACE-inhibitors**
  • **Glucocorticoids**
  • **Antiretroviral therapy.**

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Traditional HIV-specific glomerular disease

- HIVAN
- HIVICKD
- HIV-related TMA
HIV-ASSOCIATED THROMBOTIC MICROANGIOPATHY

• Predominantly affects white populations, children and young males.¹

• Compared with HIVAN, TMA is rare, but **HIV-related TMA** may account for up to 35% of all TMA cases.²,³

• Occurs late in the course of HIV infection and its incidence has dropped markedly since the advent of antiretroviral therapy.

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HIV-ASSOCIATED THROMBOTIC MICROANGIOPATHY

- Haemolytic uraemic syndrome
  - Microangiopathic anemia and renal impairment
- Thrombotic thrombocytopenic purpura
  - Microangiopathic anemia,
  - Thrombocytopenia
  - Renal impairment
  - Fever
  - Neurologic features

HIV-ASSOCIATED THROMBOTIC MICROANGIOPATHY

- Pathogenesis unclear
- Probably due to **endothelial injury** caused by:
  - exposure to circulating viral proteins, and/or
  - many other factors including:
    - medications,
    - circulating proinflammatory molecules,
    - antiphospholipid antibodies.

HIV-ASSOCIATED THROMBOTIC MICROANGIOPATHY

- There are no clinical trials to guide the treatment of HIV-TMA.
- Treatment:
  - plasma infusion and plasmapheresis,\(^1\)
  - Splenectomy reserved for refractory disease.\(^1\)
  - Antiretroviral therapy.\(^2\)
  - Anectodal experience with corticosteroids, and vincristine.\(^1\)
- Mortality exceeds 60% in HIV-associated TMA.\(^1\)

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IMPACT OF ANTIRETROVIRAL THERAPIES ON KIDNEY FUNCTION
REVERSE TRANSCRIPTASE INHIBITORS

• There are two main categories of reverse transcriptase inhibitors (RTI).

• **Nucleoside (NRTI) and nucleotide (NtRTI) analogs,**
  - inhibit *reverse transcription* of viral RNA to DNA by *becoming incorporated* into the viral DNA → termination of DNA chain elongation.

• **Non-nucleoside RTI, do not** become incorporated into viral DNA but **directly binds to** and inhibit reverse transcriptase function.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

• Nearly all NRTI → capable of causing systemic lactic acidosis with the highest risk being associated with stavudine and didanosine.

• NRTI cause type B lactic acidosis by inhibiting function of DNA polymerase - γ

→ reduced cellular mitochondrial DNA content
→ reduced expression of proteins necessary for oxidative phosphorylation → increased oxidative stress due to mitochondrial injury.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

• This mechanism of mitochondrial dysfunction in proximal tubular cells explains the association of stavudine and lamivudine with Fanconi syndrome.¹

• Another report described acute kidney injury and biopsy proven interstitial nephritis after exposure to abacavir.²

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

- **Adefovir** and **cidofovir**, are approved for treatment of hepatitis B and cytomegalovirus, respectively.

- **Adefovir**, which is approved for use against hepatitis B, was initially developed as an anti-HIV medication, it was never approved for use because of **nephrotoxicity** when used at high dose (10-fold higher dose than for hep B) necessary for antiHIV efficacy.

- **Tenofovir**, **adefovir** and **cidofovir** are all capable of inducing **renal tubular injury**.

• 0.7-10% of patients may develop tenofovir-induced AKI

• 22-81% may develop subclinical signs of tubulopathy → hyperphosphaturia


Figure 4 | Tenofovir-induced nephrotoxicity is characterized by proximal tubular injury, which is often accompanied by intracytoplasmic inclusions that appear reddish on hematoxylin and eosin (a) and trichrome staining (b). These inclusions correspond to accumulation of markedly enlarged mitochondria with increased matrix density.
Figure 1. TDF-induced epithelial cell dysfunction is due to mitochondrial damage. Enlarged mitochondria (*) are visible adjacent to normal-size mitochondria (+). Large mitochondria appear devoid of cristae, while other mitochondria show normal cristae content. When cristae are visible in dysmorphic mitochondria, they are usually grouped at a pole. (Original magnification ×8000.) Photograph kindly provided by Leal C. Herlitz, MD, Department of Pathology, Columbia University Medical Center in New York, New York.
RISK FACTORS FOR TENOFOVIR INDUCED RENAL TOXICITY

• Background renal dysfunction

• African American ethnicity

• Female gender

• CD4⁺ nadir < 200 cells / mm³

• Concomitant nephrotoxic medications
  • acyclovir, ganciclovir, cidofovir, aminoglycosides, pentamidine, amphotericin

• Comorbid conditions
  • Diabetes, hypertension, co infection with Hep B/C

• Older age


HIV PROTEASE INHIBITORS

- Inhibit the ability of the viral protease to process Gag structural polyproteins → inhibiting viral maturation, rendering virions noninfectious.

- Most protease inhibitors are poorly soluble in aqueous solution → promote crystalluria and/or nephrolithiasis when concentrated in the urine.

HIV PROTEASE INHIBITORS

• **Indinavir** reported to be associated with:
  • Nephrolithiasis
  • AKI due to acute tubular obstruction by indinavir crystals and
  • Chronic tubulointerstitial nephritis due to chronic occlusion of renal tubules by indinavir crystals.¹

• The HIVMA-IDSA guidelines recommend that individuals receiving indinavir should drink at least 1.5 L of water per day and that periodic monitoring of creatinine and urinalysis for pyuria be performed in the first 6 months of treatment.²

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NONNUCLEOSIDE REVERSE-TRANSCRIPTASE INHIBITORS

- **Nevirapine**, **efavirenz**, and **delavirdine** have been demonstrated to have a safe renal profile in controlled trials. ¹

- A single case report linked **efavirenz** to renal toxicity on the basis of a hypersensitivity reaction involving pneumonitis, hepatitis, and **interstitial nephritis**. ²

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FUSION INHIBITORS

- **Enfuvirtide** has not been associated with severe renal adverse effects. ¹

- In a safety analysis of 663 patients in the T-20 versus Optimized Regimen Only (TORO)–1 and TORO-2 trials, one patient who had a history of diabetes, proteinuria, and hematuria developed **membranoproliferative glomerulonephritis**.²

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# Renal Syndromes Associated with Antiretroviral Agents

<table>
<thead>
<tr>
<th>Type of Agent</th>
<th>Drug (Trade Name)</th>
<th>Clinical Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors</td>
<td>Abacavir, Didanosine, Lamuvidine, Stavudine</td>
<td>AKI (AIN) Fanconi Syndrome</td>
</tr>
<tr>
<td>Nucleotide reverse transcriptase inhibitors</td>
<td>Tenofovir fumarate</td>
<td>Fanconi syndrome, Nephrogenic DI, AKI (prox tubule damage)</td>
</tr>
<tr>
<td>Other reverse transcriptase inhibitors</td>
<td>Delavirdine, Efavirenz, Nevarapine</td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Indinavir, Nelfinavir, Ritonavir</td>
<td>Renal colic, urolithiasis, obstructive uropathy, AKI and CKD from interstitial nephritis and crystallisation Renal colic AKI</td>
</tr>
<tr>
<td>HIV-1 fusion inhibitor</td>
<td>Enfurvirtide</td>
<td>Membranoproliferative GN</td>
</tr>
</tbody>
</table>

Daugas E et al, KI 2005;67:393-403
### Table 4

Association of cumulative antiretroviral exposure (per year) with risk* of kidney disease outcomes, ordered by prevalence of use

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>% of participants with any exposure at end of study</th>
<th>Proteinuria</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Rapid Decline***</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Chronic Kidney Disease</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>39.7</td>
<td>1.34 (1.25, 1.45)</td>
<td>&lt;0.0001</td>
<td></td>
<td>1.11 (1.03, 1.18)</td>
<td>0.0033</td>
<td></td>
<td>1.33 (1.18, 1.51)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>89.5</td>
<td>0.98 (0.94, 1.03)</td>
<td>0.50</td>
<td></td>
<td>1.02 (0.97, 1.06)</td>
<td>0.44</td>
<td></td>
<td>0.93 (0.85, 1.02)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>68.3</td>
<td>0.98 (0.93, 1.03)</td>
<td>0.42</td>
<td></td>
<td>0.98 (0.93, 1.02)</td>
<td>0.29</td>
<td></td>
<td>0.89 (0.81, 0.98)</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>49.0</td>
<td>0.94 (0.90, 0.99)</td>
<td>0.026</td>
<td></td>
<td>1.01 (0.97, 1.05)</td>
<td>0.64</td>
<td></td>
<td>0.88 (0.79, 0.98)</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>43.0</td>
<td>1.02 (0.97, 1.07)</td>
<td>0.54</td>
<td></td>
<td>1.02 (0.97, 1.06)</td>
<td>0.43</td>
<td></td>
<td>0.98 (0.89, 1.07)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Ritonavir†</td>
<td>35.7</td>
<td>1.18 (1.09, 1.27)</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.96 (0.89, 1.04)</td>
<td>0.34</td>
<td></td>
<td>0.97 (0.84, 1.14)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>31.6</td>
<td>0.99 (0.95, 1.04)</td>
<td>0.68</td>
<td></td>
<td>1.02 (0.98, 1.06)</td>
<td>0.39</td>
<td></td>
<td>1.01 (0.92, 1.11)</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>29.6</td>
<td>1.01 (0.96, 1.07)</td>
<td>0.73</td>
<td></td>
<td>1.01 (0.96, 1.06)</td>
<td>0.65</td>
<td></td>
<td>1.07 (0.97, 1.18)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>24.6</td>
<td>1.04 (0.99, 1.09)</td>
<td>0.15</td>
<td></td>
<td>0.99 (0.95, 1.04)</td>
<td>0.67</td>
<td></td>
<td>**1.16 (1.06, 1.27)</td>
<td>0.0019</td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>23.0</td>
<td>0.94 (0.88, 1.00)</td>
<td>0.051</td>
<td></td>
<td>0.98 (0.93, 1.04)</td>
<td>0.49</td>
<td></td>
<td>0.95 (0.84, 1.07)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>22.8</td>
<td>1.01 (0.96, 1.06)</td>
<td>0.69</td>
<td></td>
<td>1.02 (0.97, 1.06)</td>
<td>0.52</td>
<td></td>
<td>0.93 (0.84, 1.03)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>17.1</td>
<td>0.93 (0.79, 1.08)</td>
<td>0.34</td>
<td></td>
<td>**1.22 (1.07, 1.40)</td>
<td>0.0035</td>
<td></td>
<td>0.96 (0.77, 1.18)</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>15.3</td>
<td>0.77 (0.68, 0.86)</td>
<td>&lt;0.0001</td>
<td></td>
<td>1.05 (0.94, 1.17)</td>
<td>0.39</td>
<td></td>
<td>1.21 (0.91, 1.60)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Saquinavir</td>
<td>10.7</td>
<td>0.91 (0.83, 0.99)</td>
<td>0.035</td>
<td></td>
<td>1.00 (0.92, 1.08)</td>
<td>0.97</td>
<td></td>
<td>0.89 (0.72, 1.09)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Amprenavir</td>
<td>4.3</td>
<td>0.90 (0.78, 1.05)</td>
<td>0.20</td>
<td></td>
<td>1.03 (0.90, 1.18)</td>
<td>0.67</td>
<td></td>
<td>1.17 (0.94, 1.46)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>3.3</td>
<td>0.91 (0.63, 1.32)</td>
<td>0.63</td>
<td></td>
<td>1.29 (0.90, 1.85)</td>
<td>0.16</td>
<td></td>
<td>1.00 (0.67, 1.47)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>1.5</td>
<td>1.11 (0.92, 1.35)</td>
<td>0.29</td>
<td></td>
<td>0.91 (0.72, 1.14)</td>
<td>0.41</td>
<td></td>
<td>1.24 (0.70, 2.19)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>1.5</td>
<td>1.10 (0.90, 1.35)</td>
<td>0.35</td>
<td></td>
<td>0.85 (0.66, 1.10)</td>
<td>0.21</td>
<td></td>
<td>1.24 (0.84, 1.81)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Tipranavir</td>
<td>0.6</td>
<td>0.87 (0.29, 2.68)</td>
<td>0.81</td>
<td></td>
<td>0.34 (0.05, 2.34)</td>
<td>0.27</td>
<td></td>
<td>0.06 (0.00, 66.0)</td>
<td>0.43</td>
<td></td>
</tr>
</tbody>
</table>
METABOLIC ALTERATIONS ASSOCIATED WITH ANTIRETROVIRAL TREATMENT

- Metabolic alterations associated with HAART may cause:
  - Significant elevations in serum lipid levels \(^1\)
  - Increase in diabetic renal disease
  - Increase in hypertensive renal disease as well as vascular complications.

- A controlled study evaluated 1689 patients demonstrated a 4-fold risk of developing diabetes.

---

\(^1\) Roling J, Schmid H, Fischereider M et al. HIV-Associated Renal Diseases and Highly Active Antiretroviral Therapy–Induced Nephropathy. Clinical Infectious Diseases 2006; 42:1488–95

METABOLIC ALTERATIONS ASSOCIATED WITH ANTIRETROVIRAL TREATMENT

• A cohort study (5578 patients) during 1984–2003
  → incidence of hypertension in 7.3% HIV patients
  → incidence began to increase significantly after 2 years of antiretroviral therapy.

• The risk of developing hypertension was maximally elevated
  (OR, 1.7) after > 5 years of treatment with HAART, compared with the risk among HIV infected patients who did not receive treatment (OR, 0.79).

RENAL REPLACEMENT THERAPY IN HIV-INFECTED INDIVIDUALS

• Hemodialysis
• Peritoneal dialysis
• Kidney transplantation

Options for managing ESRD in HIV patients

• Survival rates with HD and PD are very similar.
• For patients on dialysis, antiretroviral drug regimens and doses should be carefully reviewed and adjusted if necessary.

SURVIVAL OF HIV-INFECTED PATIENTS RECEIVING RENAL REPLACEMENT THERAPY

- IMPROVED and the mortality rate is now approaching that for ESRD in the general population.¹

- A recent study reported survival rates at:
  - 1 year for HIV-infected patients on dialysis of **95.2%**
  - 3 years – **71.7%**
  - 5 years – **62.7%** ²


The risk factors for mortality in the HIV infected dialysis population:

- a lower CD4+ T-cell count,
- a higher viral load,
- the absence of antiretroviral therapy, and
- a history of opportunistic infections. 1,2,3

**RENUMAL TRANSPLANTATION IN HIV PATIENTS**

### Table 4 | Patient and graft survival rates in HIV-positive renal transplant recipients. Differences between pre-cART and cART era

<table>
<thead>
<tr>
<th></th>
<th>Pre-cART era, 1987-1997&lt;sup&gt;a&lt;/sup&gt;</th>
<th>cART era, 2003-2009&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-year survival rates</strong></td>
<td>USRDS (n=63,210)</td>
<td>HIV+ (n=32)</td>
</tr>
<tr>
<td>Patient survival</td>
<td>78%</td>
<td>71%</td>
</tr>
<tr>
<td>Graft survival</td>
<td>61%</td>
<td>44%</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>48.4%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Abbreviations: cART, combined antiretroviral treatment; HIV, human immunodeficiency virus; NS, non significant; SRTR, US Scientific Registry of Transplant Recipients; USRDS, United States Renal Data System.

<sup>a</sup>Swanson et al.55
<sup>b</sup>Stock et al.74
<sup>c</sup>SRTR survival estimates for older kidney transplant recipients (age ≥65 years) and for all kidney transplant recipients.
<sup>d</sup>SRTR 1-year acute rejection rate (SRTR 3-year acute rejection rate not available).
MANAGEMENT STRATEGIES
Qualitative assessment for risk of kidney disease

- Race
- Family history of kidney disease
- CD4$^+$ lymphocyte count
- HIV-1 RNA level
- History of use of nephrotoxic medications
- Comorbidities
  - Diabetes mellitus
  - Hypertension
  - Hepatitis C coinfection

Screening studies at initial HIV documentation

- Urine analysis (for proteinuria)
- Serum creatinine (estimate creatinine clearance or glomerular filtration rate using appropriate formula)
Abnormal values

- Grade ≥ 1+ proteinuria by dipstick
- Cr clearance or GFR < 60mls/min/1.73m²

- Evaluate proteinuria further with spot urine protein/creatinine ratio
  - Perform renal ultrasound
- Consider referral to a nephrologist for further evaluation and potentially biopsy.

IDSA guidelines 2005
No abnormal values

Groups without risk factors for kidney disease should be followed clinically and reassessed based on the occurrence of signs and symptoms or as clinical events dictate.

Groups at risk for development of chronic kidney disease should be rescreened annually.

*Patients on tenofovir may require monitoring every 3 months

GROUPS AT RISK

- Individuals of African American race
- Individuals with diabetes, hypertension or Hep C coinfection
- Individuals with CD4\(^+\) counts < 200 cells/mm\(^3\)
- Individuals with HIV RNA levels > 4000 copies/ml.

IDA guidelines 2005
TAKE HOME MESSAGES

• Renal pathology in HIV-infected persons can be caused by a variety of mechanisms leading to a broad spectrum of clinical disease.

• Long-term survival contributes to an increase in HAART-induced metabolic alterations, diabetes, and hypertension and is likely to be associated with an increase in secondary renal damage, such as hypertensive nephrosclerosis and diabetic glomerulopathy.
TAKE HOME MESSAGES

• HAART and other medical therapies for HIV-related infections have been associated with both short- and long-term toxicities including nephrotoxicity.

• Kidney abnormalities tend to develop in the setting of multiple treatments and cannot be always attributed to a specific drug.

• Renal function should therefore be monitored on a regular basis in patients with HIV receiving any antiretroviral agent.

• Early detection of risk factors, systematic screening for chronic causes of CKD, and appropriate referrals for kidney disease management should be advocated for improved patient care.
THANK YOU