HIV-1 and Kidney Disease

Mohamed G. Atta, MD, MPH

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Learning Objectives

• Assess current markers to identify individuals with kidney disease in your practice.
• Discuss the spectrum of kidney disease in HIV infected individuals and its clinical implications for your practice.
• Utilize current guidelines to screen for and manage renal disease in individuals with HIV in your practice.
Off-Label Disclosure

This presentation will not discuss any non-FDA-approved or investigational uses of any products/devices.
Markers of Kidney Disease

• Protein and/or blood in the urine
• Elevated serum creatinine and/or BUN
• Decreased glomerular filtration rate (GFR)
• Anemia

Is Serum Creatinine Enough?

- Abnormal kidney function may not be recognized in patients with lower relative muscle mass using serum creatinine alone
  - Females
  - Older patients
  - Wasted (decreased lean muscle mass)

Estimating Equations

• **Cockcroft-Gault**

\[
\text{CrCl (mL/min)} = (140-\text{age}) \times \frac{\text{weight}}{\text{sCr} \times 72} \times (0.85 \text{ if F})
\]

• **MDRD**

\[
\text{GFR (mL/min per 1.73 m}^2\text{)} = 186 \times \text{sCr}^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})
\]

A New Equation to Estimate Glomerular Filtration Rate (CKD-EPI)

<table>
<thead>
<tr>
<th>Race and Sex</th>
<th>Serum Creatinine Level, µmol/L (mg/dL)</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>≤62 (≤0.7)</td>
<td>GFR = 166 × (Scr/0.7)^{-0.329} × (0.993)^{Age}</td>
</tr>
<tr>
<td></td>
<td>&gt;62 (&gt;0.7)</td>
<td>GFR = 166 × (Scr/0.7)^{-1.209} × (0.993)^{Age}</td>
</tr>
<tr>
<td>Male</td>
<td>≤80 (≤0.9)</td>
<td>GFR = 163 × (Scr/0.9)^{-0.411} × (0.993)^{Age}</td>
</tr>
<tr>
<td></td>
<td>&gt;80 (&gt;0.9)</td>
<td>GFR = 163 × (Scr/0.9)^{-1.209} × (0.993)^{Age}</td>
</tr>
<tr>
<td><strong>White or other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>≤62 (≤0.7)</td>
<td>GFR = 144 × (Scr/0.7)^{-0.329} × (0.993)^{Age}</td>
</tr>
<tr>
<td></td>
<td>&gt;62 (&gt;0.7)</td>
<td>GFR = 144 × (Scr/0.7)^{-1.209} × (0.993)^{Age}</td>
</tr>
<tr>
<td>Male</td>
<td>≤80 (≤0.9)</td>
<td>GFR = 141 × (Scr/0.9)^{-0.411} × (0.993)^{Age}</td>
</tr>
<tr>
<td></td>
<td>&gt;80 (&gt;0.9)</td>
<td>GFR = 141 × (Scr/0.9)^{-1.209} × (0.993)^{Age}</td>
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</tbody>
</table>

National Kidney Foundation (NKF) Definition of Chronic Kidney Disease (CKD)

• Glomerular filtration rate (GFR) <60 mL/min/1.73 m² for ≥3 months with or without kidney damage

  OR

• Kidney damage for ≥3 months, with or without decreased GFR, manifested by either
  – Pathologic abnormalities; or
  – Markers of kidney damage, ie, proteinuria

### CKD

#### National Kidney Foundation Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with Mild ↓ GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>
Renal disease is an important complication of HIV

- Proteinuria may occur in untreated HIV infection at a rate of up to 30%.
  

- High Prevalence of co-morbidities adversely affecting renal function
  
  • HTN, DM, HCV, Substance Abuse

- Renal dysfunction contributes to cardiovascular disease in HIV patients (George et. al *AIDS* 2010)
Spectrum of Renal disorders in HIV-1 infected patients

- HIV-1 dependent
  - HIVAN
  - HIVIC (IgA, lupus like)
  - TMA
- Co-infection with other organisms
- Related to therapy
- Unrelated to HIV
HIVAN Glomerular Epithelial Cells Contain HIV-1 Nucleic Acids
(Bruggeman et al. JASN 11: 2079, 2000)

HIV-1 mRNA in situ
HIV-1 DNA in situ PCR
HIVAN: “Classic” clinical characteristics

- Exclusive disease of African Americans
- Proteinuria (often nephrotic range)
- Detectable viremia
- Normal size echogenic kidneys on ultrasound
- Progressive renal failure (weeks to months)
Treatment

Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome

TK Rao et al, NEJM March 1984

Progression to ESRD within 8 to 16 weeks
Death within 6 months
HIVAN Prevention and Treatment

Hopkins Nephrology HIV Cohort ARV Treatment of HIVAN:


Atta et al., Nephrol Dial Transpl, 2006
Recommendations for Initiating ART

Hammer SM et al.

Symptomatic HIV disease

Asymptomatic

- CD4<350
- CD4>350
  - Rapid decline in CD4 count
  - High risk of CVD
  - Active hepatitis B or C coinfection
  - HIVAN

August, 2008
Causes of CKD in the HAART Era

• Non-HIV related
  – Hypertension/cocaine
  – Diabetes mellitus
  – Non-diabetic glomerular disease
  – Cystic kidney disease
  – Tubulointerstitial disease
  – Co-infection with HBV, HCV, or syphilis

• HIV-related
  – ART or OI medications

## Ultrasound Guided Biopsy in 244 HIV individuals
Johns Hopkins, Feb 1995 to Dec 2007

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIVAN</td>
<td>71 [5 with ICGN] (29%)</td>
</tr>
<tr>
<td>FSGS</td>
<td>46 (19%)</td>
</tr>
<tr>
<td>Acute interstitial nephritis</td>
<td>28 (11%)</td>
</tr>
<tr>
<td>HIV Immune Complex GN</td>
<td>18 [8 Lupus-like] (7%)</td>
</tr>
<tr>
<td>Hypertensive Nephropathy</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>Diabetic Nephropathy</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>Post infectious GN</td>
<td>12 (5%)</td>
</tr>
</tbody>
</table>
Etiology of Acute Renal Failure


Pre-renal
- Diarrhea, Nausea, Vomiting, Dehydration
- Sepsis or Infection
- Cirrhosis
- Heart Failure
- Pancreatitis
- Adrenal Insufficiency
- Erythroderma

ARF Events Number
- 43 (38%)

Renal
- Acute Tubular Necrosis, ischemic
- Nephrotoxic Drugs
- Interstitial Nephritis
- Nephrotoxic Radiocontrast
- Thrombotic Thrombocytopenic Purpura
- Hemolytic Uremic Syndrome

ARF Events Number
- 48 (46%)

Obstructive
- Kidney Stones
- Crystalluria
- Gross Hematuria

ARF Events Number
- 9 (7%)

Unknown
- 11 (9%)

Causes
Drug Toxicities in HIV

- ATN/tubular disorder
  - Aminoglycosides, Amphotericin B, Tenofovir, Cocaine, Contrast

- Acute interstitial nephritis
  - Any drug, most often PPI, antibiotics,

- Crystalluria/Stones
  - Indinavir, Atazanavir, Acyclovir and Sulfadiazine, Ciprofloxacin, Bactrim

- Atherosclerotic vascular disease
  - Cocaine
Crystalluria and stone formation
A: Kopp, J. Ann Intern Med 1997; B: courtesy of Perazella M, Yale University.

- Sulfadiazine
- TMP/SMX
- Indinavir
- Atazanavir
- Ciprofloxacin

Indinavir and Atazanivir crystals

Bactrim Crystal

Sulfadiazine Crystal
Kidney Function and the Risk of Cardiovascular Events in HIV-1 Infected Patients

- Nested, matched, case-control study
- 315 HIV-infected patients (63 cases who had cardiovascular events and 252 controls).
- eGFR (CKD-EPI formula/MDRD), and proteinuria were the primary exposures of interest

George et. al AIDS, January 2010
Kidney Function and the Risk of Cardiovascular Events in HIV-1 Infected Patients

- eGFR of <60: unadjusted OR 15.9 for cardiovascular event (p<0.001).

- Adjusted OR (eGFR 10 ml/min ↓): 1.2 (95% CI 1.1–1.4) for cardiovascular event

- Prevalence of proteinuria: 51% in cases vs. 25% in control, p<0.001).

- Proteinuria: unadjusted OR 3.6 (95% CI 1.9–7.0) and adjusted OR 2.2 (95% CI 1.1–4.8).

George et. al AIDS, January 2010
Relationship between eGFR and cardiovascular event status HIV-1 infected patients

Mean eGFR was 68.4 in cases vs. 103.2 ml/min, in control p<0.001

George et. al AIDS, January 2010
Association Between Kidney Function and Albuminuria With Cardiovascular Events in HIV-Infected Persons

- A national sample of 17,264 HIV-infected persons receiving care in the VA for (1) incident CVD and (2) incident heart failure.

- Rates of CVD and heart failure were at least 6-fold greater in the highest-risk patients with an eGFR 30 mL/min per 1.73 m² and albuminuria 300 mg/dL versus those with no evidence of kidney disease (eGFR 60 mL/min per 1.73 m² and no albuminuria).
HIV and ESRD: Dialysis Outcomes Urban African American Cohort Data

Survival on renal replacement therapy among African Americans infected with HIV-1 in urban Baltimore

162 RRT /4,509 HIV-1-infected AA

Survival Predictors (Adjusted Model)
- Younger Age
- HAART
- Higher CD4
- Higher Albumin

Atta et al, Clin Inf Dis, 2007
Managing Known Risk: Are We Screening Effectively?

Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America

IDSA Guidelines - Screening Algorithm for HIV-Related Renal Diseases

Kidney Disease Risk: Qualitative Assessment
• Race
• Family history of kidney disease
• CD4+ lymphocyte count
• HIV-1 RNA level
• Nephrotoxic medication use (history)
• Comorbidities
  • Diabetes mellitus
  • Hypertension
  • Hepatitis C coinfection
  • Cocaine

Screening Studies at Initial HIV Documentation
• Urine analysis (for proteinuria)
• Serum creatinine (estimate Cl_{cr} or GFR using appropriate formula)

(Continued on next slide)

IDSA Guidelines - Screening Algorithm for HIV-Related Renal Diseases

(Continued)

Abnormal Values
- Grade ≥1+ proteinuria by dipstick
- Clcr or GFR <60 mL/min per 1.73 m²
- Evaluate proteinuria further with spot urine protein/cr ratio
- Perform renal ultrasound
- Consider referral to nephrologist for further evaluation & potential biopsy

No Abnormal Values
- W/O Kidney Disease
  - Risk Factors:
    - Follow clinically
    - Reassess based on signs/symptoms
    - Reassess per clinical events
- With Kidney Disease
  - Risk Factors*:
    - Rescreen annually

*At-risk Groups Include:
- African Americans
- Patients with diabetes, hypertension, or hepatitis C coinfection
- Patients with CD4+ cell counts <200 cells/mm³
- Patients with HIV RNA levels >4000 copies/mL
Selected Major Recommendations

- Patients at the time of diagnosis of HIV be screened for existing kidney disease with a UA, micro, urine protein quantification by spot urine ratio and calculated estimate of GFR
- If > 300 mg est. proteinuria or GFR < 60 consider referral to nephrologist and undergo additional evaluation (renal ultrasound, poss. biopsy)
Bottom Line: What do we do?

- Take a good history to assess for risk factors
- Estimate GFR and measure urine protein
- Assess if acute or chronic renal failure?
- If acute, make sure it is not HIVAN or drug toxicity and then assess for the usual suspects
- If chronic – ask “why?” at least once and then proceed with CKD management
Conclusion

• HIVAN is an ominous diagnosis and must be aggressively treated

• Kidney disease prevalence is increasing, despite decreasing HIVAN rates

• Kidney disease is associated with increased cardiovascular events.

• Always consider drug toxicities

• There is a broad differential diagnosis for renal failure in HIV, so kidney biopsy may be helpful