HIV–associated nephropathy (HIVAN)

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SIMPOSIO KDIGO
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The extent of HIV worldwide

Source: World Health Organization
The extent of HIV worldwide II

**In 2018:**

- 37.9 million people living with HIV
- 1.7 million newly infected people
- 0.77 million HIV-related deaths
- 79% of people with HIV know their status
The extent of HIV worldwide III

Approx. 62% on medication (2018)

↑ life expectancy

Source: World Health Organization
Increase of renal disease in HIV infected patients

- Prevalence of CKD in HIV-infected individuals varies broadly
  - Africa: 38% Nigeria, 20% Uganda, 11.5% Kenya
  - Asia: 16.8% Hong Kong, 27% India
  - Americas: 7%
  - Europe: 1%

- HIV as etiologic factor of CKD
  - Spain: 0.5-1.1%
  - Cameroon: 6.6%
  - South Africa: 28.5%

Source: Phair et al. 2012
HIV-associated nephropathy

• **AIDS-associated nephropathy**  
  • First described in early 1980s associated with AIDS  
  • Aggressive form of FSGS in African-Americans

• **HIV-associated nephropathy (HIVAN)**  
  • Appears in a progresses HIV infection  
  • Major cause of ESRD in HIV patients  
  • Characterized by significant proteinuria and progressive kidney failure.  
  • Prevalence  
    • 1% to 10% in HIV-infected patients  
    • HIVAN histology in 50% of HIV positive patients  
    • 90% of HIVAN patients are of African descent.

Source: Post et al. (2008)
HIV-associated nephropathy

- Key features/parameters of HIVAN
  - Advanced HIV disease
  - Heavy proteinuria
  - Rapid decline in kidney function

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>32 (52)</td>
</tr>
<tr>
<td>At HIVAN diagnosis</td>
<td></td>
</tr>
<tr>
<td>Age, mean years</td>
<td>36.1</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Black African</td>
<td>48 (79)</td>
</tr>
<tr>
<td>Black British/Caribbean</td>
<td>13 (21)</td>
</tr>
<tr>
<td>HIV risk (n = 60)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>57 (95)</td>
</tr>
<tr>
<td>Homosexual/bisexual</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Hepatitis B surface Ag</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Hepatitis C antibody</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (7)</td>
</tr>
<tr>
<td>AIDS (CDC stage C)</td>
<td>29 (48)</td>
</tr>
<tr>
<td>CD4+ T cell count, median cells/μL (IQR)</td>
<td>66 (29–147)</td>
</tr>
<tr>
<td>HIV-1 RNA level, mean log copies/mL</td>
<td>5.2</td>
</tr>
<tr>
<td>Serum creatinine level, median mg/dL (IQR)</td>
<td>3.4 (2.1–7.9)</td>
</tr>
<tr>
<td>GFR, median mL/min (IQR)</td>
<td>21 (9–37)</td>
</tr>
<tr>
<td>Proteinuria level, median g/24-h period (IQR)</td>
<td>5.4 (3.4–8.9)</td>
</tr>
</tbody>
</table>

Source: Post et al. (2008)
HIVAN Pathophysiology

**FSGS**
- Collapsing glomerulopathy
- Foot process effacement

**Tubulointerstitial Nephritis**
- Microcystic dilations
- Tubular atrophy + proteinaceous casts
- Immune infiltrate
HIVAN risk factors

- Genetic predispositions
- Direct viral effects
- Comorbidity disease
- cART-related kidney toxicity

Source: World Health Organization
Genetic predispositions

- 18- to 50-fold higher prevalence of HIVAN in black HIV patients

- **APOL1 G1 and G2 risk variants**
  - Frequency
    - Both 22%
    - Single 45%
  - Strongly associated with development of FSGS and HIVAN
    - 5-fold higher odds of proteinuria
    - 3.5 fold higher odds of HIVAN
    - 3-fold higher risk of progressing to ESRD
    - 29- to 89-fold higher odds of HIVAN (both alleles)

Source: Kopp et al. (2013)
Genovese et al. (2010)
Dummer et al. (2015)
Mechanisms of APOL1-mediated disease

Limited data:
• Higher expression of APOL1 variants in glomeruli and podocyte

• Expression of APOL1 variants in transgenic mouse cause proteinuria, glomerulosclerosis and podocyte effacement

• The estimated lifetime risk with both APOL1 alleles
  • 50% for HIV+
  • 4% for HIV-

Source: Beckermann et al. (2017)
Nicols et al. (2015)
Direct viral effects

Kidney as site of HIV infection

• Renal epithelial cells are infected by HIV

Source: Bruggeman et al. (2000)
Direct viral effects

Kidney as site of HIV infection

- Role of accessory proteins in disease pathogenesis
  - vpr, nef
Direct viral effects

Kidney as site of HIV infection

- transgenic mice expressing *nef* and *vpr* in podocytes

Source: Zuo et al. 2006
Direct viral effects

Kidney as site of HIV infection

- Expression of *nef* in human podocytes in vitro
cART-related kidney toxicity

Combined antiretroviral therapy

Drug classes:
1. Entry inhibitors
2. RT inhibitors
3. Integrase inhibitors
4. Protease inhibitors
cART-related kidney toxicity

Combined antiretroviral therapy

A Untreated

CD4 T Cell Count

Viral Load

Plasma HIV RNA (log)

Week

HIV RNA <200 copies/mL  CD4 count > 350 cells/μl

B Incidence of ESRD from HIVAN (1989–2011)

C Antiretroviral Treated

CD4 T Cell Count

Viral Load

Plasma HIV RNA (log)

Week

Source:
cART-related kidney toxicity

- Kidney injuries due to reverse transcriptase (RTI) and protease (PI) inhibitors are reported

- **Tenofovir (RTI)**
  - 33% higher risk of CKD
  - characterized by Fanconi syndrome
  - tubular accumulation and mitochondria injury
  - recovery can be incomplete

- **Atazanavir (PI)**
  - 20% higher CKD incidence
  - Crystalluria, tubulointerstitial nephritis
  - Poorly soluble → crystal formation, inflammation
  - Persistent risk for kidney injury

Source: Cooper et al. (2011)  
Swanepoel et al. (2017)
## Other risk factors

**Cohort study:**
22,156 HIV-infected patients
366 developed ESRD

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>No ESRD (n=21,790)</th>
<th>ESRD (n=366)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 +/- 10</td>
<td>45 +/- 8</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.2%</td>
<td>2.2%</td>
<td>0.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>36%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>42%</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>13%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.9 +/- 4.5</td>
<td>24.6 +/- 4.4</td>
<td>0.6</td>
</tr>
<tr>
<td>eGFR &lt;60 ml/min/1.73m²</td>
<td>5%</td>
<td>46%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0 mg/dL</td>
<td>84%</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>30-100 mg/dL</td>
<td>13%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>300-1000 mg/dL</td>
<td>1%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>30%</td>
<td>67%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5%</td>
<td>20%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>5%</td>
<td>8%</td>
<td>0.01</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>8%</td>
<td>8%</td>
<td>0.7</td>
</tr>
<tr>
<td>CD4 Count (cells/mm³)</td>
<td>285 (289)</td>
<td>236 (243)</td>
<td>0.008</td>
</tr>
<tr>
<td>Viral Load (copies/mL)</td>
<td>82,009 (166,484)</td>
<td>96,007 (146,947)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hepatitis C Virus Infection</td>
<td>20%</td>
<td>30%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypalbuminemia</td>
<td>18%</td>
<td>37%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiretroviral Therapy</td>
<td>25%</td>
<td>21%</td>
<td>0.06</td>
</tr>
<tr>
<td>Statin Use</td>
<td>2%</td>
<td>1%</td>
<td>0.09</td>
</tr>
<tr>
<td>ACE Inhibitor Use</td>
<td>2%</td>
<td>4%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Source: Jotwani et al. (2012)
HIVAN Treatment

- No specific HIVAN treatment available

- Assessment of CKD risk scores:

  ![KDIGO Diagram]

  - Low risk: eGFR > 90, uPCR < 200, Age < 50
  - High risk: eGFR < 70, uPCR > 500, Age > 60

  - Hepatitis C co-infection
  - Immunodeficiency
  - Diabetes mellitus
  - Uncontrolled hypertension
  - History of cardiovascular disease

  - Standard ART (local guidelines)
  - Avoid nephrotoxic ART* (TDF, IDV, ATV, LPV)

Source: World Health Organization
Management of ESRD in HIV Infected Persons

Risk of renal disease in HIV infected individuals

- Effective cART
  - Prolonged life expectancy
  - Risk of comorbidity

- cART
  - Reduced prevalence of HIVAN
  - Declined ESRD complications

→ Increase need of HIV+ patients for dialysis and kidney transplantation

Source: Chaudhary et al. (2015)
Management of ESRD in HIV Infected Persons

1. Dialysis

Main risk factors:
- Ineffective control of viral load (41%)
- Side infections

Source: Chaudhary et al. (2015)
Ndlovu et al. (2019)
Trullas et al (2011)
Management of ESRD in HIV Infected Persons

2. Transplantation

• Criteria:
  • Effective HIV suppression for $\geq 6$ months
  • Undetectable plasma HIV-1 RNA
  • CD4+ cell count $> 200$ cells/mm$^3$

• Risks:
  • Immunsuppressiva and low CD4 count
  • Interactions of Immunsuppressiva with cART

Source: Malat et al. (2019)
Summary

1. HIV can cause kidney injury
   - Control of kidney parameters
   - Biopsy of required

2. Risk factors:
   - Genetic depositions
   - Direct viral effects
   - Drug nephrotoxicity

3. Therapy
   - Adjustment of cART
   - Dialysis
   - Transplantation
Thank you for your attention