HIV and Cardiovascular Disease in Sub-Saharan Africa

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Outline

• **Context**
• **Epidemiology**
  – Coronary heart disease
  – Stroke
• **Pathogenesis**
• **Clinical care**
• **Public health and operational considerations**
• **Future directions**
An Intersection of Epidemics

• Twice in history, the United Nations General Assembly has met specifically on a health issue

AIDS (2001)

NCDs (2011)
### HIV and CVD in South Africa: Impact on Mortality

<table>
<thead>
<tr>
<th>Year</th>
<th>Men aged 50-64 years</th>
<th>Women aged 50-64 years</th>
<th>Men aged 65+</th>
<th>Women aged 65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992-94</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disease</td>
<td>13 (17%)</td>
<td>7 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasms</td>
<td>6 (9%)</td>
<td>5 (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other NCDs</td>
<td>6 (9%)</td>
<td>5 (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/tuberculosis</td>
<td>4 (6%)</td>
<td>3 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>3 (4%)</td>
<td>2 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>168</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995-97</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disease*</td>
<td>20 (21%)</td>
<td>5 (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/tuberculosis</td>
<td>8 (9%)</td>
<td>7 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other NCDs</td>
<td>8 (9%)</td>
<td>8 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998-2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disease*</td>
<td>34 (27%)</td>
<td>15 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other NCDs</td>
<td>11 (9%)</td>
<td>10 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002-05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disease*</td>
<td>30 (29%)</td>
<td>12 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other NCDs</td>
<td>12 (11%)</td>
<td>13 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Centrovascular disease, blemish, heart disease, and hypertensive disease. All malignant neoplasms, excluding those of female genital organs, and cases of diseases not included in other categories such as anemia, dementia, chronic obstructive pulmonary disease, asthma, peptic ulcer disease, etc. Will include primary causes of death, hypertension, heart disease, and cerebrovascular disease. Excludes all infectious causes.

Table: Five most common causes of death in men and women aged 50-64 years and 65 years and older in Agincourt subdistrict, 1992-2005.

HIV and CVD Globally: Projected Impact on Morbidity

<table>
<thead>
<tr>
<th>2030 global mortality</th>
<th>2030 low-income country mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ischemic heart disease (13)</td>
<td>1. Ischemic heart disease (13)</td>
</tr>
<tr>
<td>2. Cerebrovascular disease (11)</td>
<td>2. HIV/AIDS (13)</td>
</tr>
<tr>
<td>3. HIV/AIDS (9)</td>
<td>3. Cerebrovascular disease (8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2030 global DALYs</th>
<th>2030 low-income country DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HIV/AIDS (12)</td>
<td>1. HIV/AIDS (15)</td>
</tr>
<tr>
<td>2. Unipolar depressive disorders (6)</td>
<td>2. Perinatal conditions (6)</td>
</tr>
<tr>
<td>3. Ischemic heart disease (5)</td>
<td>3. Unipolar depressive disorders (5)</td>
</tr>
<tr>
<td>[5. Ischemic heart disease (5)]</td>
<td>[5. Ischemic heart disease (5)]</td>
</tr>
</tbody>
</table>

DALY = disability-adjusted life year
Percentage attributable to disease in parentheses

Outline

• Context
• Epidemiology
  – Coronary heart disease
  – Stroke
• Pathogenesis
• Clinical care
• Public health and operational considerations
• Future directions
# CVD Rates Increased in HIV

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Population</th>
<th>N (HIV)</th>
<th>Primary Result</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein</td>
<td>2002</td>
<td>Kaiser</td>
<td>4159</td>
<td>↑ MI and CHD in HIV vs. control</td>
<td>1.5 (MI) 1.7 (CHD)</td>
</tr>
<tr>
<td>Currier</td>
<td>2003</td>
<td>CA Medicaid</td>
<td>28513</td>
<td>↑ CHD in HIV (age 18-33) vs. control</td>
<td>2.06</td>
</tr>
<tr>
<td>Triant</td>
<td>2007</td>
<td>Partners</td>
<td>3851</td>
<td>↑ MI in HIV vs. control</td>
<td>1.75</td>
</tr>
<tr>
<td>Obel</td>
<td>2007</td>
<td>Danish cohort</td>
<td>3953</td>
<td>↑ CHD in HIV (on ART) vs. control</td>
<td>2.12</td>
</tr>
<tr>
<td>Lang</td>
<td>2010</td>
<td>FHDH</td>
<td>74958</td>
<td>↑ MI in HIV vs. 3 population registries</td>
<td>1.5</td>
</tr>
<tr>
<td>Klein</td>
<td>2011</td>
<td>Kaiser</td>
<td>20775</td>
<td>↑ MI and CHD in HIV vs. 10:1 matched control</td>
<td>1.4 (MI) 1.2 (CHD)</td>
</tr>
<tr>
<td>Freiberg</td>
<td>2011</td>
<td>VA</td>
<td>27379</td>
<td>↑ MI in HIV vs. 2:1 matched control</td>
<td>1.86</td>
</tr>
<tr>
<td>Durand</td>
<td>2011</td>
<td>Quebec</td>
<td>7053</td>
<td>↑ MI in HIV vs. 4:1 matched control</td>
<td>2.11</td>
</tr>
</tbody>
</table>

Boston: Increased AMI Rates in HIV

- Age Group: 75-84 vs. 35-44, 75-84 vs. 45-54, 75-84 vs. 55-64, 75-84 vs. 65-74
- Gender: Male
- Race: African American vs. Caucasian, Hispanic vs. Caucasian
- Cardiac Risk Factor: Hypertension, Diabetes, Dyslipidemia

Triant JCEM 2007;92:2506-2512.
South Africa: Increasing CVD Rates

Heart of Soweto Study

• Aim to systematically investigate the emergence of heart disease in a large urban South African population
• Urgent need to track heart disease in epidemiologic transition
• Predominantly Black African community of 1 million
• Chris Hani Baragwanath Hospital of Johannesburg
• Initial studies did not include assessment of HIV in relation to cardiac disease
Cardiac Manifestations of HIV Infection

Sliwa Eur Heart J 2012;33:866-874.
Non-AIDS-Defining Events: Botswana vs Tennessee

- Comparison of incidence of non-AIDS-defining events in 2 HIV cohorts from 2002-2007
  - Nashville, TN observational cohort (N=1129)
  - Botswana urban area clinical trial cohort (N=650)
- Rates standardized to U.S. population for age and sex
- Botswana cohort had higher rates CVD events and non-AIDS-defining malignancies
- Non-AIDS defining events were caused of death in:
  - 30% Botswana cohort
  - 4% Nashville cohort
- Significance of CVD and NCD events for HIV patients on ART in resource-limited settings

Non-AIDS-Defining Events: Incidence Rates

<table>
<thead>
<tr>
<th></th>
<th>Botswana</th>
<th>Tennessee</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NADE</td>
<td>19</td>
<td>12</td>
<td>0.20</td>
</tr>
<tr>
<td>CVD</td>
<td>8</td>
<td>5</td>
<td>0.20</td>
</tr>
<tr>
<td>Renal</td>
<td>2</td>
<td>3</td>
<td>0.92</td>
</tr>
<tr>
<td>Hepatic</td>
<td>0</td>
<td>4</td>
<td>N/A</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8</td>
<td>.5</td>
<td>0.015</td>
</tr>
<tr>
<td>CD4 count at time of event</td>
<td>274</td>
<td>224</td>
<td></td>
</tr>
</tbody>
</table>

NADE = non-AIDS-defining event

Clinical and Angiographic Features of ACS in South Africa

- Prospective study comparing HIV positive ART-naïve vs. HIV negative patients
- 60 patients with acute coronary syndrome 2004-2008
- Characteristics of HIV patients with ACS vs controls:
  - Younger
  - Lower rates HTN, DM
  - Lower TC, LDL
  - Lower HDL
  - Higher rates smoking
  - Lower atherosclerotic burden
  - Higher thrombotic burden
Clinical and Angiographic Features of ACS in South Africa

- HIV pts had higher levels:
  - Target lesion revascularization
  - Major adverse cardiac events
  - In-stent restenosis (nonsignificant)

- In multivariate analysis adjusted for age/smoking, HIV was independent predictor of large thrombus burden

**Table 2. Angiographic Features of HIV Patients and Controls with ACS**

<table>
<thead>
<tr>
<th>Feature</th>
<th>HIV+ve (n = 30)</th>
<th>HIV-ve (n = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic angiogram n (%)</td>
<td>30 (100)</td>
<td>30 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>24 (80)</td>
<td>18 (60)</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean no. of affected vessels</td>
<td>1.3 ± 0.6</td>
<td>1.6 ± 0.8</td>
<td>0.08</td>
</tr>
<tr>
<td>Angiographically normal IRA</td>
<td>14 (47)</td>
<td>4 (13)</td>
<td>0.005</td>
</tr>
<tr>
<td>Thrombus in multiple arteries</td>
<td>3 (10)</td>
<td>0 (0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Large thrombus burden</td>
<td>13 (43)</td>
<td>5 (17)</td>
<td>0.02</td>
</tr>
<tr>
<td>Treatment n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI (PTCA or stent)</td>
<td>18 (60)</td>
<td>18 (60)</td>
<td>1.0</td>
</tr>
<tr>
<td>PTCA alone</td>
<td>9 (30)</td>
<td>7 (23)</td>
<td>0.54</td>
</tr>
<tr>
<td>Stent (bare metal)</td>
<td>9 (30)</td>
<td>11 (37)</td>
<td>0.78</td>
</tr>
<tr>
<td>Medical therapy only</td>
<td>12 (40)</td>
<td>11 (37)</td>
<td>0.60</td>
</tr>
<tr>
<td>CABG</td>
<td>0 (0)</td>
<td>2 (7)*</td>
<td>0.49</td>
</tr>
</tbody>
</table>

HIV and Stroke

• Limited data on association of HIV and stroke
• Early case reports confounded by opportunistic infections and malignancy
• Increased proportion of HIV patients incurring ischemic strokes from 1997-2006
• Increased rate composite cerebrovascular events in Danish HIV versus control patients

Increased Stroke Rates in HIV

- Partners HealthCare System clinical care cohort
- 4308 HIV and 32423 non-HIV patients
- 1996 to 2009
- Primary outcome ischemic stroke
- Identified by specific ICD code and validated by chart review
- Incidence rates
  - 5.27/1000 PY HIV
  - 3.75/1000 PY non-HIV
- **Increased stroke risk in HIV patients under 50**

Chow JAIDS 2012 epub.
HIV is an Independent Risk Factor for Stroke

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted HR</td>
<td>1.40*</td>
<td>2.16*</td>
<td>1.18</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.34*</td>
<td>2.02*</td>
<td>1.17</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.21*</td>
<td>1.76*</td>
<td>1.05</td>
</tr>
</tbody>
</table>

- Model 1 adjusted for age, gender, and race
- Model 2 adjusted for age, gender, race hypertension, diabetes, dyslipidemia, smoking, structural heart disease (cardiomyopathy, valvular heart disease, or heart failure), atrial fibrillation/flutter, aspirin use, warfarin use

- **Increased stroke rate driven by effect among women**

* Indicates statistical significance

Chow JAIDS 2012 epub.
Ischemic Stroke Predictors in HIV Patients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>0.97</td>
<td>0.921</td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White race (vs. all others)</td>
<td>1.40</td>
<td>0.235</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.79</td>
<td>0.451</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.59</td>
<td>0.159</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.99</td>
<td>0.987</td>
</tr>
<tr>
<td>Smoking (ever vs. never)</td>
<td>0.83</td>
<td>0.483</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>1.24</td>
<td>0.544</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.91</td>
<td>0.881</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.15</td>
<td>0.014</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>1.73</td>
<td>0.096</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>0.70</td>
<td>0.484</td>
</tr>
<tr>
<td>NRTI use</td>
<td>1.19</td>
<td>0.681</td>
</tr>
<tr>
<td>NNRTI use</td>
<td>0.38</td>
<td>0.006</td>
</tr>
<tr>
<td>PI use</td>
<td>0.63</td>
<td>0.226</td>
</tr>
<tr>
<td>CD4 count (cells/mm³)</td>
<td>0.97</td>
<td>0.477</td>
</tr>
<tr>
<td>HIV RNA (copies/ml)</td>
<td>1.10</td>
<td>0.001</td>
</tr>
<tr>
<td>CNS infection/malignancy</td>
<td>2.75</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Chow JAIDS 2012 epub.
Stroke in Sub-Saharan Africa

• 8.5% of patients with stroke (WHO-defined) had HIV in a Nigerian cohort from 2008-2010
• The HIV rate in the Durban stroke data bank paralleled that of the background population in a year 2000 analysis, suggesting no increased stroke risk in association with HIV
• In a cohort of 293 black African patients from Durban, KZN, there were no angiographic differences between HIV positive and negative
• In an HIV cohort from Kinshasa, DRC from 2004-2008, patients with ischemic stroke had a significantly lower CD4 count (108 vs 208) compared to those without stroke

Stroke in Sub-Saharan Africa

The role of traditional stroke risk factors in HIV disease

- In a case-control study of 147 patients with stroke in Malawi, HIV patients were younger and less likely to have HTN and DM
- HIV patients with stroke were less likely to have traditional stroke risk factors and more likely to have infection in a Cape Town group of 1087 patients

Causes of stroke in 35 HIV-infected patients in Soweto, South Africa

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• Context
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• Future directions
HIV

ART

HIV

CVD

ENDOTHELIAL DYSFUNCTION

INFLAMMATION

IMMUNE DYSFUNCTION

COAGULATION ABNORMALITIES

CVD

DYSLIPIDEMIA

DIABETES

HYPERTENSION

SMOKING

FAMILY HISTORY

CVD
## Prevalence of CVD Risk Factors in Sub-Saharan Africa

<table>
<thead>
<tr>
<th>Location</th>
<th>HTN</th>
<th>Lipid</th>
<th>DM</th>
<th>Smoking</th>
<th>Obesity</th>
<th>MetS</th>
</tr>
</thead>
<tbody>
<tr>
<td>KwaZulu-Natal, South Africa</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>Nairobi, Kenya</td>
<td></td>
<td>63</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NW South Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Johannesburg, South Africa</td>
<td>19</td>
<td>32 (high TC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>46 (low HDL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (high LDL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rwanda (women)</td>
<td></td>
<td></td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>46</td>
<td>31 (high TC)</td>
<td></td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SW Uganda</td>
<td>23</td>
<td></td>
<td>0.4</td>
<td>14 (M)/1 (F)</td>
<td>1 (M)/4 (F)</td>
<td></td>
</tr>
<tr>
<td>Cameroon</td>
<td></td>
<td>38 (high TC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>46 (high LDL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Kenya</td>
<td>11 (M)/7 (F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 (M)/23 (F)</td>
</tr>
</tbody>
</table>

Lipid Changes and ART in Rural Uganda

- 374 patients in rural Ugandan cohort with CD4 <250 initiating ART
- After 24 months ART, TC, LDL, and HDL significantly increased and TC/HDL ratio significantly decreased
- TG initially decreased but then returned to baseline
- Lipid changes thought unlikely to confer CVD risk

Buchacz JAIDS 2008;47:304
### South Africa: ACS Risk Factors by HIV Status

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>ACS+ HIV +</th>
<th>ACS + HIV –</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43</td>
<td>54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>73</td>
<td>33</td>
<td>0.004</td>
</tr>
<tr>
<td>DM (%)</td>
<td>3</td>
<td>23</td>
<td>0.05</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>23</td>
<td>77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>3.6</td>
<td>4.6</td>
<td>0.003</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>2.2</td>
<td>3.0</td>
<td>0.003</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>0.8</td>
<td>1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25</td>
<td>28</td>
<td>0.008</td>
</tr>
<tr>
<td>Anticardiolipin IgG (%)</td>
<td>47</td>
<td>10</td>
<td>0.003</td>
</tr>
<tr>
<td>Anti-prothrombin IgG (%)</td>
<td>87</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiphospholipid syndrome (%)</td>
<td>44</td>
<td>24</td>
<td>NS</td>
</tr>
</tbody>
</table>

## South Africa: Clinical Characteristics by ACS Status

<table>
<thead>
<tr>
<th></th>
<th>ACS + HIV +</th>
<th>ACS – HIV +</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count (median)</td>
<td>230</td>
<td>125</td>
<td>0.013</td>
</tr>
<tr>
<td>AIDS defining criteria (%)</td>
<td>37</td>
<td>70</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>73</td>
<td>37</td>
<td>0.003</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>0.8</td>
<td>1.0</td>
<td>0.011</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25</td>
<td>21</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Endothelial Dysfunction in South African cohort

- Altered endothelial dysfunction in HIV
  - Increased pulse wave velocity in HIV vs controls over age 50
  - Increasing pulse wave velocity in HIV with aging
  - Increased sICAM-1, sVCAM-1 in HIV vs controls

Fig. 1. cr-PWV in the HIV-infected and uninfected group with increasing age. Adjusted for gender, BMI, MAP, self-reported alcohol and tobacco use. Values are means ± SEM. *cr-PWV of HIV-infected and uninfected participants differ ($p = 0.057$).
Inflammation and Immune Activation in HIV Pathogenesis

• Patients from northeastern Tanzania
• 229 HIV and 54 control patients
• Cytokines measured at baseline and after 2 and 4 months of ART
• For most markers levels higher in HIV-infected vs HIV-uninfected
• For most markers laves reduced with increasing time on ART
• All cytokines correlated positively with viral load
• ART reduced levels close to those in HIV-uninfected patients
• Implications for CVD which is thought to be related to inflammation/immune activation in HIV patients

Outline

• Context
• Epidemiology
  – Coronary heart disease
  – Stroke
• Pathogenesis
• Clinical care
• Public health and operational considerations
• Future directions
CVD Risk Prediction for HIV Patients

- Framingham Risk Score has not been validated for HIV patients
- Observed AMI rates higher than predicted if on ART
- HIV-specific risk score developed but not externally validated

Managing Dyslipidemia in HIV

- Check fasting lipids at diagnosis, at start or change of ART, and every 6-12 months
- Drug interactions
  - PIs variably inhibit cytochrome P450 CYP3A4
  - NNRTIs decrease some statin levels
- Manage lipids according to NCEP guidelines, HIV lipid guidelines
  - Statin if LDL above goal or TG 200-500 with elevated non-HDL-C
  - Fibrate if TG>500
- Rosuvastatin more effective than pravastatin in several HIV studies
- TG and TC improved with exercise training in trial of Rwandan HIV patients

---

<table>
<thead>
<tr>
<th>Statin</th>
<th>Level w/ PI</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>--</td>
<td>Can use safely</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>↑</td>
<td>Use with caution/low dose</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↑↑</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>↑↑</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>?</td>
<td>Accruing data</td>
</tr>
</tbody>
</table>

Dyslipidemia Difficult to Treat in HIV

• Study assessed response to statins/fibrates in cohort study of 829 HIV and 6941 non-HIV patients started on lipid-lowering therapy between 1996-2005

• Decreased reductions in LDL with statins
  – 26% in HIV vs. 28% decrease at 12 months; P=0.001
  – Largest reductions with simvastatin, smallest with pravastatin

• Decreased reductions in TG with gemfibroizil
  – 44% in HIV vs. 59% decrease at 12 months; P<0.001

• Overall adverse events uncommon but HIV patients had higher risk of liver enzyme and CK elevation

Statins Associated with Decreased Mortality in HIV

- Johns Hopkins HIV Clinical Cohort
- 1538 patients virologically suppressed on ART
- 15.5% received a statin
  - 69% atorvastatin, 24% pravastatin, 7% rosuvastatin
- Statin use significantly associated with a lower mortality risk
  - Relative hazard 0.33
  - Adjusted for demographics, cholesterol, hemoglobin, CD4, viral load, ART use by year and class, hepatitis, AIDS-defining illness
- Unable to specifically assess CVD mortality

Moore PLoS One 2011;6:e21843
Aspirin for Primary Prevention of CVD

<table>
<thead>
<tr>
<th>Population</th>
<th>Men Age 45–79 Years</th>
<th>Women Age 55–79 Years</th>
<th>Men Age &lt;45 Years</th>
<th>Women Age &lt;55 Years</th>
<th>Men and Women Age ≥80 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation</td>
<td>Encourage aspirin use when potential CVD benefit (MIs prevented) outweighs potential harm of GI hemorrhage</td>
<td>Encourage aspirin use when potential CVD benefit (strokes prevented) outweighs potential harm of GI hemorrhage</td>
<td>Do not encourage aspirin use for MI prevention</td>
<td>Do not encourage aspirin use for stroke prevention</td>
<td>No Recommendation</td>
</tr>
<tr>
<td>Grade</td>
<td>Grade: A</td>
<td>Grade: D</td>
<td></td>
<td></td>
<td>Grade: I (insufficient evidence)</td>
</tr>
</tbody>
</table>

Shared decision making is strongly encouraged with individuals whose risk is close to (either above or below) the estimates of 10-year risk levels indicated below. As the potential CVD benefit increases above harms, the recommendation to take aspirin should become stronger.

To determine whether the potential benefit of MIs prevented (men) and strokes prevented (women) outweighs the potential harm of increased GI hemorrhage, both 10-year CVD risk and age must be considered.

<table>
<thead>
<tr>
<th>Risk Level at Which CVD Events Prevented (Benefit) Exceeds GI Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>45–59 years</td>
</tr>
<tr>
<td>60–69 years</td>
</tr>
<tr>
<td>70–79 years</td>
</tr>
</tbody>
</table>

The table above applies to adults who are not taking NSAIDs and who do not have upper GI pain or a history of GI ulcers. NSAID use and history of GI ulcers increase the risk for serious GI bleeding events considerably and should be considered in determining the balance of benefits and harms.

NSAID use combined with aspirin use approximately quadruples the risk for serious GI bleeding events compared with the risk with aspirin use alone. The rate of serious bleeding in aspirin users is approximately 2 to 3 times greater in patients with a history of GI ulcers.

Aspirin Use in HIV Infection

• ASA significantly underused in HIV patients who met criteria for its use
  – 31% met criteria
  – 1.6% received ASA

• Unknown role of ASA in primary prevention of AMI or stroke for HIV patients

• Interventions targeted at generalized inflammation and immune activation may better address pathogenesis

Tornero JAIDS 2010;54:560.
ART Strategies

Paradigm shift: treat HIV to reduce cardiovascular risk

• CVD-related benefit from virologic suppression and immune reconstitution achieved by treating HIV thought to outweigh possible proatherogenic effects of individual medications
• Individual ART may have varying risk; consider underlying CVD risk when selecting specific drugs
• Individualized clinical judgment to balance risks

HIV Treatment Guidelines and CVD Risk

• 2010 IAS-USA HIV treatment guidelines
  – Recommend initiation of ART specifically for patients with high cardiovascular risk
  – Endorse aggressive management of modifiable CVD risk factors

• 2012 DHHS HIV treatment guidelines
  – Recommend antiretroviral therapy for all HIV-infected individuals
  – *The recommendation to initiate therapy at CD4 count >500 cells/mm3 (BIII) is based on growing awareness that untreated HIV infection or uncontrolled viremia may be associated with development of many non-AIDS defining diseases, including cardiovascular disease (CVD), kidney disease, liver disease, neurologic complications, and malignancy*

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Public Health Implications

• How to integrate development of health care systems/infrastructure
• Apply models developed for HIV to chronic disease management
• Similar principles specific to community
  – Prevention
  – Care retention
  – Counseling
**HIV**

- HIV education
- Public awareness
- HIV test accessibility

**CVD**

- CVD education
- Public awareness
- CVD risk factor screening

**HIV DIAGNOSIS**

- Individualized education
- Check BP, lipids, glucose
- Assess smoking status
- Calculate FRS

**LINK TO CARE**

- Review CVD risk factor guidelines
- Weigh benefits/risks
- Counsel sodium/diet/exercise
- Counsel smoking cessation
- Start ASA/HTN/lipid/DM rx

**TREATMENT INITIATION**

- Clinical assessment
- Monitor side effects rx
- Lab monitoring

**FOLLOW UP**

- Review HIV rx guidelines
- Weigh benefits/risks
- Counsel adherence
- Start ART

**CONTINUED ENGAGEMENT IN CARE**

- Establish patient relationship
- Continued counseling
- Repeat risk assessment

**CVD**

- Individualized education
- Check BP, lipids, glucose
- Assess smoking status
- Calculate FRS

- Clinical assessment
- Monitor side effects rx
- Lab monitoring

- Review HIV rx guidelines
- Weigh benefits/risks
- Counsel adherence
- Start ART

- Establish patient relationship
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Implications and Future Directions

• Scope of CVD in HIV patients in sub-Saharan Africa remains largely unknown: more outcome data needed
• Traditional CVD risk factor modification important, especially smoking
• Likely role for non-traditional immune-related factors in conferring CVD risk
• Increasing recognition that treating HIV might decrease cardiovascular risk
• To what extent do we need to recapitulate data?
  – General population ➔ HIV ➔ HIV sub-populations
• Integration of HIV and CVD health care systems critical