The Complex Patient: HIV Plus a Whole Lot Else

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Outline

• Case presentation
• CVD risk in HIV
  – Virus vs. meds?
• Challenges to achieving lipid goals in the HIV patient
  – Additional cholesterol lowering options
  – Fatty liver disease
  – Diet and Exercise
• Summary/Take-home message
Case 4

- 49 yo AA male HIV+ long-term non-progressor with near-elite control of viremia (CD4+ 907, viral load <50 with occasional blips <500), not on ART.
- Several months of an atypical intermittent stabbing chest pain lasting seconds, unrelated to exertion. Tends to be worse at night, but not related to food. No dyspnea, PND, orthopnea, or edema. No palpitations or syncope. Functional status limited by chronic low back pain.
- **Risk factors:**
  - prior smoker (15 pack-years, quit 3 years ago)
  - Hypertension
  - Dyslipidemia (LDL 240, modest TGL 167, normal HDL 56)
  - No diabetes or pertinent family history. BMI 28.
  - Lives in a neighborhood (East Cleveland) with limited access to nutritious food and safe exercise options
- **Meds:** amlodipine 10mg, atorvastatin 40mg, aspirin 81mg
- **Other labs:** Hgb A1c 5.8%; AST/ALT normal; TSH normal; CK normal
Studies

- **ECG**: normal
- **Echo**: normal EF, normal LA size, normal RV, and normal PA pressures
- **Nuclear perfusion imaging**: normal
- **CT angio in ED**: No dissection or pulmonary embolism
  - No coronary calcification
  - Hepatic steatosis

- What to make of his chest pain?
- What should I do next?
Lipid Goals

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Criteria</th>
<th>Treatment goal</th>
<th>Consider drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0–1 major ASCVD risk factors</td>
<td>&lt;130, &lt;100</td>
<td>≥190, ≥160</td>
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<tr>
<td></td>
<td>Consider other risk indicators, if known</td>
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<td></td>
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<tr>
<td>Moderate</td>
<td>2 major ASCVD risk factors</td>
<td>&lt;130, &lt;100</td>
<td>≥160, ≥130</td>
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<tr>
<td></td>
<td>Consider quantitative risk scoring</td>
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<tr>
<td></td>
<td>Consider other risk indicators</td>
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<td></td>
</tr>
<tr>
<td>High</td>
<td>≥3 major ASCVD risk factors</td>
<td>&lt;130, &lt;100</td>
<td>≥130, ≥100</td>
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<tr>
<td></td>
<td>Diabetes mellitus (type 1 or 2)†</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0–1 other major ASCVD risk factors and</td>
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<tr>
<td></td>
<td>No evidence of end-organ damage</td>
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<tr>
<td></td>
<td>Chronic kidney disease stage 3B or 4‡</td>
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<tr>
<td></td>
<td>LDL-C of ≥190 mg/dL (severe hypercholesterolemia)§</td>
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<tr>
<td></td>
<td>Quantitative risk score reaching the high-risk threshold¶</td>
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<tr>
<td>Very high</td>
<td>ASCVD</td>
<td>&lt;100</td>
<td>≥100</td>
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<tr>
<td></td>
<td>Diabetes mellitus (type 1 or 2)</td>
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<tr>
<td></td>
<td>≥2 other major ASCVD risk factors or</td>
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<tr>
<td></td>
<td>Evidence of end-organ damage</td>
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</tbody>
</table>

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

Jacobson et al, J Clin Lipidol 2015
2013 ACC/AHA Statin benefit groups

1. Clinical ASCVD
   - Age >75: Moderate dose statin
   - Age <75: High dose statin

2. LDL > 190mg/dL
   - LDL 240 \rightarrow 
     - High dose statin
   - <7.5% risk: Moderate dose statin
   - >7.5% risk: High dose statin

3. Diabetes
   - Age 40-75
     - <7.5% risk: Moderate dose statin
     - >7.5% risk: High dose statin

4. >7.5% estimated risk
   - Age 40-75
     - Moderate-High dose statin

Stone et al, Circulation, 2014
Can imaging improve risk stratification in HIV?

- Coronary artery calcium
- Non-calcified plaque
  - Higher HIV+ vs. Controls
  - Associated with immune activation markers
- High risk plaque features
  - Higher in HIV+ vs. Controls
  - Reduced by atorvastatin therapy
- Ectopic fat
  - Pericardial fat
  - Liver fat

Longenecker et al, Translational Res, 2012
Lo et al, Lancet HIV, 2015
Traditional risk

HIV risk

ART risk
HIV risk

ART risk

Traditional risk
Virus vs. meds? A lesson from SMART

DC = Drug conservation arm
VS = Viral suppression arm

HR (95% CI) for DC = **1.58** (1.12-2.22; p=0.009)

Phillips et al, Antivir Ther 2008
Virus vs. meds? A lesson from “Elite Controllers”

(a) Age
(b) Hypertension
(c) Ever smoker
(d) CD4>500

Hsue et al, AIDS 2009
Contemporary ART is even less toxic

![Graph A](image1.png)

![Graph B](image2.png)

Ofotokun et al, CID 2015
HIV + Chronic Inflammation

ART
Case 2 – Follow-up

- Diagnoses?
- 10yr vs. Lifetime risk
- Additional agents:
  - Ezetimibe
  - PCSK9 inhibition
  - Apharesis
  - others
- Concerned about hepatic steatosis?

**Graph:**
- Hazard ratio, 0.936 (95% CI, 0.89–0.99)
- P=0.016
- SIMVSTATIN MONOTHERAPY
- SIMVASTATIN–EZETIMIBE

**Source:** IMPROVE-IT Trial. Cannon et al, NEJM, 2015
PCSK9 Inhibition in HIV

- HIV+ associated with 10% higher levels
- N=6 in evolocumab trial → similar LDL response to HIV-uninfected (-61% ON TOP of statin)
- ? Significance of “very high” levels → HCV co-infection
- Switching PI→ RTG may decrease PCSK9 (SPIRAL study)

NAFLD increases CVD risk

HIV

NAFLD progression

NAFLD

↑ Insulin resistance
↓ Insulin clearance
↑ Glucose production
↑ Fetuin-A
↑ FGF-21
↑ RBP-4
↑ CRP
↑ IL-6
↑ TNF
↑ Triglycerides
↑ Small, dense LDL
↓ HDL cholesterol
↑ Fibrinogen
↑ Factor VIII
↑ PAI-1

T2DM

CVD

Free fatty acids
↑ Inflammatory cytokines
↓ Adiponectin
↑ Insulin resistance

Expanded and inflamed adipose tissue

Anstee et al, Nat Rev Gastro Hep 2013
Management of cardiovascular risk in NAFLD

- Lifestyle changes are central to management
- Statins are safe and effective
- 2014 NLA statin safety guidelines
- Consult with liver specialist if necessary

Fig. 4 – Effects of statins on cardiovascular events and on the liver in patients with nonalcoholic fatty liver disease.

Tziomalos et al, Metabolism 2015
Statins are safe in patients with NAFLD
Diet and exercise

• Large disparities across diverse HIV+ populations
• Poor access to healthy food choices in vulnerable communities
• Alcohol may increase drivers of inflammation and immune activation
• Need for interdisciplinary and evidence-based approach to lifestyle change
Key points for this case

- Primary prevention for a 49 year old elite controller not on HIV medications
  - Probable heterozygous FH
  - NASH
- In his case, chronic inflammation/immune activation due to low level viremia likely contributes to higher risk of CV events
- LDL (non-HDL) treatment goal is <100 (130) mg/dL
- I increased atorvastatin to 80mg and added ezetimibe. We plan to recheck LFTs in 3 months.
- We will likely need to consider a PCSK9 inhibitor and/or other alternatives.
Summary

• In regards to cardiovascular risk, antiretroviral drug therapy does more good than harm.
• Newer ART drugs such as integrase inhibitors have less toxic metabolic risk profiles, and little effect on lipids.
• Newer cholesterol drugs such as PCSK9 inhibitors may play a role in some patients.
• HIV is a known cause of fatty liver disease, but most patients with elevated liver enzymes can safely be prescribed a statin.
• HIV-infected patients may experience barriers to achieving ideal diet and exercise behaviors. An interdisciplinary and evidence-based approach to care is needed.
Cardiovascular disease in HIV/AIDS is complex, but YOU can help manage it!