Risk Stratification for ASCVD in the Patient Living with HIV

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38 year-old White man who was found to be HIV+ six years ago when he was admitted to the hospital with fevers. He has been on anti-retroviral medication since diagnosis. His viral load is undetectable and his CD 4 count in the 600s.

He has no personal history of CVD or family history of premature CAD. He follows a Mediterranean Diet, does not smoke, has a glass of wine with dinner and denies use of illicit drugs. He engages in no regular exercise but walks to and from work (2 miles each way) as a school teacher.

He denies chest pain, discomfort, shortness of breath, palpitations, syncope.
Case Presentation
Risk Stratification

Medical History:
HIV, Hypertension (well controlled), dyslipidemia (attempting to control by diet).

Exam:
BMI 27  BP 132/75  Waist circumference 42 inches
No JVD, normal carotid upstroke
CV: S1, S2, no S3 or S4, no murmurs
Chest: clear  Extremities: warm, no edema
Good distal pulses, no bruit over arterial beds
Fasting Lab Results:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>normal</td>
<td>Total cholesterol</td>
</tr>
<tr>
<td>CBC with diff</td>
<td>normal</td>
<td>LDL-C (calculated)</td>
</tr>
<tr>
<td>TSH</td>
<td>normal</td>
<td>HDL-C</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>normal</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>HbA1c</td>
<td>normal</td>
<td>non-HDL-C</td>
</tr>
<tr>
<td>AST, ALT</td>
<td>normal</td>
<td>Lp(a)</td>
</tr>
</tbody>
</table>
Case Presentation
Risk Stratification

Medications

Antiretroviral
Complera one tablet daily
- Emtricitabine 200 mg (NRTI)
- Rilpivirine 25 mg (NNRTI)
- Tenofovir disoproxil fumarate 300 mg (NRTI)

HCTZ 12.5 mg daily
Lisinopril 10 mg daily
## Profile of Patient

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
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<tbody>
<tr>
<td>Age</td>
<td>38</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>Hypertension</td>
<td>yes (controlled on medication)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>yes</td>
</tr>
<tr>
<td>BMI</td>
<td>27</td>
</tr>
<tr>
<td>HIV positive status</td>
<td>yes</td>
</tr>
</tbody>
</table>
Risk Score

Framingham 10-year Risk = 1%

age, total cholesterol, HDL-C, systolic blood pressure, gender, smoking status
Risk Score

**Pooled Cohort Equations**
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Gender, race (Black or White), age, total cholesterol, HDL-C, systolic blood pressure, blood pressure medication, smoking, diabetes

Our patient = **3.5% ten year risk for a first ASCVD event***
* Used age 40 as risk prediction for ages 40-79

Elevated Risk ≥ 7.5%
Does not qualify for statin treatment
No targets for LDL-C in 2013 ACC/AHA Guideline
## Risk Schemes for the General Population

<table>
<thead>
<tr>
<th>Population</th>
<th>Framingham Risk Score</th>
<th>POOLED COHORT EQUATIONS (ACC/AHA)</th>
<th>REYNOLDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>General population from one area. Framingham MA (USA)</td>
<td>Population-based cohort studies funded by NHLBI</td>
<td>Men and Women from USA, no known CVD (men were non-diabetic)</td>
</tr>
<tr>
<td>Age</td>
<td>30-74 years</td>
<td></td>
<td>Men 57-80?; Women ≥45</td>
</tr>
<tr>
<td>Years risk prediction</td>
<td>10-year risk of CHD events 30-year risk of CHD and stroke</td>
<td>10-year risk of ASCVD</td>
<td>10-year risk for CVD</td>
</tr>
<tr>
<td>Variables</td>
<td>sex, age, total cholesterol, HDL-C, smoking status, systolic blood pressure (treated/not treated), diabetes</td>
<td>Sex, age, race (White or Black), total cholesterol, HDL-C, Systolic blood pressure, treatment for high blood pressure (if systolic &gt; 120 mmHg), Diabetes, smoking status</td>
<td>Sex, age, smoking status, total cholesterol, HDL-C, CRPhs, parental history of MI &lt; 60 years of age, HbA1c (if diabetic)</td>
</tr>
<tr>
<td>Discrimination and Calibration in HIV+</td>
<td>c-statistic: 0.65, 0.71, 0.77 O/E: 1.18, 1.51</td>
<td>c-statistic: 0.65, 0.71 O/E: 1.20; may be better than FRS at higher categories of predicted risk</td>
<td>unknown</td>
</tr>
<tr>
<td>Notes</td>
<td>Risk scores account for White and Black Race Eliminated targets for LDL-C</td>
<td></td>
<td>Men were in the Physicians Health Study and Women in the Women’s Health Study</td>
</tr>
</tbody>
</table>
## Risk Schemes: HIV Populations

<table>
<thead>
<tr>
<th></th>
<th>D:A:D</th>
<th>VACS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>D:A:D cohort of HIV+ men in Europe, Argentina, Australia, USA</td>
<td>HIV+ USA veterans, men</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>16-85</td>
<td>≥18</td>
</tr>
<tr>
<td><strong>Data collection</strong></td>
<td>1999-2008; followed for median 4.8 years</td>
<td>2000-2007</td>
</tr>
<tr>
<td><strong>Years risk prediction</strong></td>
<td>5-year risk of CVD</td>
<td>5 year mortality</td>
</tr>
<tr>
<td><strong>Variables</strong></td>
<td>Number of years on IDV, LPV currently on IND, LPV, ABC, Sex, age, current/previous cigarette smoker, diabetes, family history of CVD, systolic BP, total cholesterol, HDL-C</td>
<td>Age, CD4 count, HIV-1 RNA (viral load), hemoglobin, FIB-4, estimated GFR, Hepatitis C infection status</td>
</tr>
<tr>
<td><strong>Guidelines using score</strong></td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Discrimination and Calibration in HIV+</strong></td>
<td>c-statistic(^{6,8}): 0.72, 0.77 O/E(^{6,8}): 1.33, 0.95</td>
<td>c-statistic(^{14}) (for CHD death): 0.77 O/E: unknown</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Predicts mortality and CHD death for HIV+ who have been treated with ART for at least one year.</td>
<td>Fris-Moller, N. European J Cardiovascular Prevention Rehab 2010; Tate, AIDS 2013</td>
</tr>
</tbody>
</table>
CVD Risk Prediction: Framingham Applied to Patients with HIV

Objectives

• Evaluate agreement between the CVD risk using Framingham risk score and the presence of subclinical atherosclerosis (carotid IMT)

• Investigate the relationships between CVD and plasma biomarkers of oxidation and inflammation

CVD Risk Prediction
Framingham Applied to Patients with HIV

Methods
• N = 187 had carotid IMT

Results
• Weak but significant association between Framingham Risk Score and carotid IMT
• A high proportion of patients with estimated low risk had subclinical atherosclerosis by cIMT
• Multivariate analysis: presence of subclinical atherosclerosis associated with age, BMI, MCP-1, oxidized LDL
• FRS underestimated the presence of subclinical atherosclerosis
Zanni, et al: Compared who would be treated with a statin among HIV-infected subjects by 2013 ACC/AHA Guideline and the 2004 NCEP ATP III (Framingham-based)

108 HIV-infected subjects without known CVD and not on lipid therapy underwent CT Angiography. Plaque was characterized as having “high-risk morphology (HRM)”

Who Would be treated with statin?

<table>
<thead>
<tr>
<th>HRM</th>
<th>ACC/AHA</th>
<th>NCEP ATP III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>26%</td>
<td>10%</td>
</tr>
<tr>
<td>No</td>
<td>19%</td>
<td>7%</td>
</tr>
</tbody>
</table>
CVD RISK PREDICTION
ACC/AHA Guidelines
Applied to Patients with HIV

Zanni, et al.

• The 2013 ACC/AHA Guidelines recommend statin therapy for a higher percentage of subjects with and without high-risk morphology coronary plaque relative to the 2004 NCEP ATP III Guidelines

• Even by 2013 Guidelines, statin therapy would not be recommended for the majority (74%) of the HIV-infected subjects with subclinical high-risk morphology plaque

Zanni MV. AIDS 2014;28:2061
## How good is the ACC/AHA calculator in HIV?

**Centers for AIDS Research Network of Integrated Clinical Systems**

<table>
<thead>
<tr>
<th></th>
<th>Discrimination (Harrell’s C: 95% CI)</th>
<th>Calibration (Hosmer-Lemeshow X²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OVERALL</strong></td>
<td>0.71 (0.67-0.75)</td>
<td>214 (p&lt;0.01)</td>
</tr>
<tr>
<td><strong>White Men</strong></td>
<td>0.76 (0.71-0.81)</td>
<td>34.3 (p&lt;0.01)</td>
</tr>
<tr>
<td><strong>Black Men</strong></td>
<td>0.74 (0.68-0.79)</td>
<td>29.2 (p&lt;0.01)</td>
</tr>
<tr>
<td><strong>White Women</strong></td>
<td>0.64 (0.48-0.79)</td>
<td>31.6 (p&lt;0.01)</td>
</tr>
<tr>
<td><strong>Black Women</strong></td>
<td>0.74 (0.64-0.84)</td>
<td>212.7 (p&lt;0.01)</td>
</tr>
</tbody>
</table>

Feinstein et al, AHA Epi-Lifestyle Sessions, 2016
Risk Assessment Scheme

2015 National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia

Very high risk
• Known ASCVD
• Diabetes + ≥ 2 other major RF or end organ damage
  → non-HDL-C goal < 100 mg/dL
  → LDL-C goal < 70 mg/dL

High risk
• Diabetes with 0-1 major ASCVD risk factors or LDL ≥ 190 or ≥ 3 major RF
• Option for those with 2 major RF → 10-year risk scoring with
  1) ATP III Framingham ≥ 10% 10-year risk or
  2) Pooled Cohort Equations ≥ 15% 10-year risk
  → non-HDL-C goal < 130 mg/dL
  → LDL-C goal < 100 mg/dL
Risk Assessment Scheme

2015 National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia

**Moderate Risk**
- 2 major RF
- May consider additional RF to reclassify as high risk: multipack smoking, strong family history of premature CAD, CAC ≥ 300, LDL-C ≥ 160, non-HDL-C ≥ 190, CRPhs ≥ 2.0, Lp(a) ≥ 50 mg/dL, urine albumin:creatinine ≥ 30 mg/g
  - LDL-C goal < 100 mg/dL
  - Non-HDL-C goal < 130 mg/dL

**Low risk**
- 0-1 major ASCVD risk factors
- May consider additional risk factors to reclassify as moderate or high
  ** consideration may be given to pharmacotherapy in those with non-HDL-C 190-219 or LDL-C 160-189
  - LDL-C goal < 100 mg/dL
  - Non-HDL-C goal < 130 mg/dL
CVD Risk Prediction: What to do?

National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia:
Part II section on “Patients with Human Immunodeficiency Virus”

Judith A. Aberg, Chair. ID, Mount Sinai
Carl Fichtenbaum, ID, University of Cincinnati
Joel Gallant, ID, Southwest Care
Michael Hochberg: General Medicine, Kaiser Permanente
Chris Longenecker, Cardiology, Case Western
Merle Myerson, Cardiology, Mount Sinai
Turner Overton, ID University of Alabama

Guidelines and Recommendations
National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part II

• All HIV-infected patients should be assessed for cardiovascular risk, including measurement of a fasting lipid panel with total-C, HDL-C, TG, LDL-C, and non-HDL-C, and should be counseled about lifestyle interventions, including smoking cessation, diet, and exercise.

• At this time there has not been sufficient research to formulate comprehensive, evidence-based guidelines and validated risk stratification schemes for HIV-infected patients.
D:A:D Study: Is the Framingham Risk Estimation Valid in HIV-Infected Patients?

Incidence of MIs is low: 345 over 94,469 patient-years’ follow-up (3.7/1,000 patient-years)
For primary prevention of ASCVD, HIV infection may be counted as an additional ASCVD risk factor for risk stratification.
Initial risk stratification based on the number of major ASCVD risk factors (with the caveat that the presence of HIV infection may be counted as an additional risk factor), the use of risk prediction tools, such as the ATP III, Framingham Risk Score or the ACC/AHA Pooled Cohort Equations if two risk factors are present, and the use clinical indicators to help inform clinical judgment, if needed.
Dyslipidemia in Patients with HIV: Discordance

Certain populations of patients such as those with diabetes have been shown to have “discordance” between LDL-C and non-HDL-C, LDL-particle number, and apolipoprotein B. LDL-C may be at or near goal but other measures of atherosclerotic particle burden may be high.

Patients infected with HIV have also been found to have discordance with LDL-C measure lower than LDL-particle number. Myerson M, et al. *Journal of Clinical Lipidology*. 2014;8(3) 332-333.
Discordance in Lipid Measurement in HIV-Infected Patients

- 100 HIV+ patients from the cardiology section of the HIV clinic at Mt. Sinai
- Compared to 50 HIV- patients seen in the Hospital’s Cardiovascular Disease Prevention Program
- Analyzed distribution of LDL-P in Patients with LDL-C <100

- HIV+ group had a higher percentage with LDL-C <100 mg/dL who had discordant levels of LDL-P than the HIV- group (85% discordance vs 61% discordance).

- Among patients with LDL-C >100 mg/dL, comparable numbers had high LDL-P (>1600 nmol/L), independent of HIV status (68% and 67%).

Myerson et al, 2014 NLA Scientific Sessions, Abstract #146
So, let's go back to our patient
<table>
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<td>yes</td>
</tr>
<tr>
<td>BMI</td>
<td>27</td>
</tr>
<tr>
<td>HIV positive status</td>
<td>yes</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>232</td>
</tr>
<tr>
<td>LDL-C (calculated)</td>
<td>150</td>
</tr>
<tr>
<td>HDL-C</td>
<td>32</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>250</td>
</tr>
<tr>
<td>non-HDL-C</td>
<td>200</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>25 (nl)</td>
</tr>
<tr>
<td>Framingham 10-year risk score</td>
<td>1%</td>
</tr>
<tr>
<td>Pooled Cohort Equations score</td>
<td>3.5%</td>
</tr>
<tr>
<td>NLA</td>
<td>low risk</td>
</tr>
</tbody>
</table>
Management Plan
Points to Consider

Patient considered at low risk by three risk schemes although NLA states that for low risk patients:

– May consider additional risk factors to reclassify as moderate or high—but not validated in HIV+ patients
– Consideration may be given to pharmacotherapy in those with non-HDL-C 190-219 or LDL-C 160-189

• Metabolic syndrome
• Discordance of LDL-C and other measures of atherogenic particle burden
• HIV positive status
Initial risk stratification based on the number of major ASCVD risk factors (with the caveat that the presence of HIV infection may be counted as an additional risk factor), the use of risk prediction tools, such as the ATP III, Framingham Risk Score or the ACC/AHA Pooled Cohort Equations if two risk factors are present, and the use clinical indicators to help inform clinical judgment, if needed.
Management Plan

1) Risk Category: Low risk → Moderate risk based on risk profile and HIV positive status

2) Targets and Goals:
   - Non HDL-C < 130+
   - LDL-C < 100*
   - Triglycerides < 150

* Acknowledge that these are aggressive goals
Management Plan

1. Lifestyle Modification
   weight loss, exercise, nutrition counseling
   option to recheck lipid profile

2. Medication
   choose low-dose statin drug

3. Follow up testing
   • recheck fasting lipid panel 6 weeks after initiating therapy.
   • Reasonable to check an apolipoprotein B
Risk Stratification in Patients Living with HIV

Summary

• Patients living with HIV are at increased risk for CVD
• Existing risk scores and schemes have not been validated in this patient population
• In counting risk factors, it is reasonable to consider HIV status and increase one risk category
• Targets and goals are those for the general population.
• Patients infected with HIV may have discordance between LDL-C and other measures of atherosclerotic particle burden. In addition to non HDL-C, consider checking apolipoprotein B