Statin Use and Cardiovascular Disease in HIV

Steven K. Grinspoon, MD
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

IAS–USA
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(Updated 04/25/16)
Learning Objectives
After attending this presentation, participants will be able to:
- Describe the current epidemiology of cardiovascular disease (CVD) in HIV
- Describe the unique pathophysiology of CVD in HIV
- Describe the potential utility and limitations of statin use to prevent CVD in HIV

Most Epidemiological Studies Suggest that Rates of CVD in HIV are:
1. Equal to that seen in non-HIV
2. 10% higher
3. 50-100% higher
4. 200% higher

Current Status of CVD Prevention in HIV
- Even as rates of death and mortality related to HIV have decreased with use of more potent ART, CVD rates remain increased among HIV patients and are a leading cause of morbidity and mortality
- There is limited understanding of the mechanisms and treatment strategies for CVD in HIV
- No large scale primary CVD prevention strategy has been tested in HIV
CVD Risk in HIV-Infected Patients is Beyond That Predicted by Traditional Risk Factors

In the VACS cohort, the HR of MI was 1.48 in HIV vs. non-HIV veterans after adjusting for FRS, comorbidities, and substance use (95% CI 1.27-1.72). (Freiberg, 2013)

Which of the Following is Not a Common Feature of Coronary Plaque in HIV Patients?

- 1. Eccentric high risk fatty plaque lesions (74%)
- 2. Inflamed plaque (7%)
- 3. Heavily calcified plaque (19%)

Increased Traditional Risk Factors Account for Only a Portion of CVD Risk in HIV

- DM, HTN, and dyslipidemia, though increased, accounted for 25% of excess risk
- Newer studies suggest importance of genetics, inflammation and immune dysfunction, as non traditional risk factors

Dyslipidemia
Hypertension
Diabetes
HIV+ non-HIV+

HIV: a State of Immune Activation and Suppression

- HIV infection
- Decrease in CD4+ T cells
- Microbial translocation
- Viral reactivation (CMV) and co-infection (HCV)
- Chronic activation of T cells and monocytes
- Endothelial cell activation

Adapted from Hsue JID 2012

Immune Activation Relates to Novel Atherosclerotic Phenotype in HIV

- In the general population, MI does not typically result from gradual expansion of subclinical coronary plaque, but rather from rupture of vulnerable high risk plaque in 75% of cases.
- Recent studies in HIV+ patients without known CVD demonstrate that atherosclerotic plaques are indeed:
  - Inflamed
  - Non-calcified, high risk morphology features (vulnerable)
  - Associated with immune activation markers

Increased Arterial Inflammation in HIV

- Aortic TBR by PET

- HIV
- Framingham Matched Controls
- CVD Controls

p = 0.0003

Control HIV
Arterial Inflammation Linked to Immune Activation in HIV

\[ \rho = 0.53; P\text{-value} < 0.03 \]

5.5
6.0
6.5
7.0
7.5
8.0
8.5

Natural Log of sCD163 (ng/ml)

Inflamed High Risk Plaque Identified by FDG Composed of Activated Macrophages

Increased Rates of Atherosclerosis in HIV by Coronary CT Angiography

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HIV</th>
<th>Lo AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of plaque</td>
<td>94%</td>
<td>89%</td>
<td>94%</td>
</tr>
<tr>
<td>Mean plaque volume (µl)</td>
<td>170</td>
<td>170</td>
<td>170</td>
</tr>
<tr>
<td>Agatson Score</td>
<td>0 (0, 9.9)</td>
<td>0 (0, 17.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Segments with plaque</td>
<td>1.2</td>
<td>2.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-calcified segments</td>
<td>0.46±0.98</td>
<td>0.99±1.57</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Calcified segments</td>
<td>0.29±0.81</td>
<td>0.26±0.77</td>
<td>0.87</td>
</tr>
<tr>
<td>Any stenosis &gt; 70%</td>
<td>0%</td>
<td>6.5%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

• Young HIV-infected men and matched controls
• Baseline FRS, FH CHD, and smoking rates similar
• Similar data observed from the MACS cohort

Lo AIDS 2010; Post Annals 2014
Increased High Risk Morphology Plaque in HIV Patients

- Low Attenuation Plaque (LAP)
- Positively Remodeled (PR) Plaque
- Mean minimal attenuation < 40 Hounsfield Units
- Plaque segment/reference segment > 1.05

Increased High Risk Morphology Plaque in HIV Patients


A New Paradigm for Atherogenesis in HIV

- Persistent Viral Replication
- Microbial Translocation
- T-cell activation
- Monocyte Activation
- High Risk Plaque
- Inflammation

Current Challenges in Preventing and Treating CHD in HIV

- Understanding the optimal timing and use of ART to maximize effects on immune function and minimize metabolic effects
- Identifying patients with disease: current risk identification strategies are not adequate
- Developing a safe and effective strategy for primary prevention, especially for those not identified by current algorithms, but with substantial subclinical disease
- Developing an intervention that addresses both traditional and immune-related risk factors
SMART and START- Effects on CVD

- SMART - Randomized trial of continuous vs. intermittent ART guided by CD4 count (begun when <250 and stopped when >350). Stringent viral suppression reduced AIDS and CVD events.

- START - Randomized trial of immediate vs. delayed ART in naïve HIV patients with CD4 > 500 (vs. initiation at CD4 < vs. 350). Earlier initiation reduced AIDS events but not CVD events.

Statins Have the Unique Potential to Work in HIV Because:

1. They reduce triglycerides
2. They improve glucose simultaneously with lipids
3. They lower LDL
4. They lower LDL and may have anti-inflammatory effects

Potential Interventions For CVD in HIV

- Traditional Risk Modification Strategies
  - Antihypertensive
  - Antidiabetic
  - ASA
  - Statins
- Immune/Inflammatory Modulators
  - ART
  - CCR5 Antagonists
  - IL Antagonists
  - Methotrexate
  - Statins
Statin Effects on CVD in non HIV Population

- In a meta-analysis of 26 studies with 170,000 patients, statins were shown to reduce events by 22% per 39 mg/dL lowering in LDL

2013 ACC/AHA Statin Guidelines

- Unclear how these guidelines pertain to HIV Patients
- Need for a discussion between patients and providers
- Need for more data

Many HIV Patients with High-Risk Plaque would not Receive Recommendation for Statin by 2013 Guidelines:

CHD risk underestimated by traditional risk scores

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Statins Reduce Vascular Events in Non HIV Patients with Low LDL and Increased CRP

- LDL was reduced 47 mg/dL, and should have resulted in a HR of 0.73 based on LDL lowering alone, according to CTTC meta-analysis.
- Instead, JUPITER showed a HR of 0.56, greater than expected based on LDL lowering alone.

Statins Address Both Traditional and Immune Risk Factors in HIV

LDL Lowering:
- LDL lower LDL by similar amounts in patients with and without HIV. (HIV-infected: 26.2%; HIV-uninfected: 26.9%)

Dampening of Immune Activation:
- Decrease monocyte activation reflected in decreased circulating levels of sCD14 and the macrophage-derived phospholipase Lp-PLA2.

Statins are Generally Safe and Well-Tolerated in HIV

- Absolute rates of grade 3 or 4 adverse effects on liver and muscle – low (Silverberg Ann Int Med 2009).
- Despite immune suppressant effects, no adverse effects on viral replication (Moncunill AIDS 2005, Negredo AIDS 2006).
Newer Statins May Not Increase Glucose and Not Interact with PIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>PI Interaction</th>
<th>Effects on Glucose</th>
<th>LDL Lowering and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin (40 mg/d)</td>
<td>-</td>
<td>-</td>
<td>-33 mg/dL, -25%</td>
</tr>
<tr>
<td>Atorvastatin (20 to 40 mg/d)</td>
<td>+</td>
<td>+</td>
<td>-38 mg/dL, -29%</td>
</tr>
<tr>
<td>Rosuvastatin (10 mg/d)</td>
<td>+</td>
<td>+</td>
<td>-28 mg/dL, -28%</td>
</tr>
<tr>
<td>Pitavastatin (4 mg/d)*</td>
<td>-</td>
<td>-</td>
<td>-48 mg/dL, -28%</td>
</tr>
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Pitavastatin metabolized primarily by glucoronidation. Minimally metabolized by CYP3A. No known interactions with antiretroviral therapy → no dose limitations. Included in 2013 ACC/AHA guidelines as a recommended moderate dose statin.

*Among dyslipidemic patients with high starting cholesterol levels.

Statin Effects on Coronary Artery Plaque in HIV

- Decreasing non-calcified plaque in proximal left anterior descending (LAD) coronary artery in patient on atorvastatin for 12 months.

Need for a Large RCT to Inform Clinical Practice

- HIV patients with low traditional risk scores are at increased risk for CVD with subclinical plaque and inflammation
- It is unknown if statins will prevent CVD and should be recommended for the HIV population
- Though largely well tolerated in small studies, there are no data from large RCTs in HIV investigating efficacy and tolerability
- How will statins uniquely work in HIV?
  - LDL lowering
  - Effects on inflammatory pathways
REPRIEVE Schema

Endpoints

- Time to first Major Adverse Cardiovascular Event (MI, Stroke, Angina, Revascularization, PAD, CVD death)
- Secondary Endpoints
  - AIDS events
  - Non AIDS events (liver, kidney, DM)
  - Relationship of immune function and LDL to MACE response
  - Safety
Mechanistic Substudy

Objectives:
• To determine:
  – Effects on high risk coronary plaque
  – Effects on immune function in relationship to plaque

Novelty
• First major CVD prevention trial in HIV
• Largest study to date focused on HIV-related CVD; will inform standard of care
• Represents a new paradigm of long-term prevention trial for chronic co-morbidities
• Partnership between NHLBI, NIAID and Office of AIDS Research to fund an important HIV study

Conclusions and Future Directions
• Traditional and non traditional risk factors contribute to increased CVD risk in HIV, which manifests as inflamed, noncalcified high risk plaque in association with immune activation
• Modulation of traditional and nontraditional risks is necessary to prevent CVD in HIV
• Statins may be an effective strategy to prevent CVD in HIV and should be tested in large trials to determine optimal practice patterns