Cardiovascular Disease in HIV Patients

Wendy Post, M.D., M.S.

Professor of Medicine and Epidemiology

Ciccarone Center for the Prevention of Heart Disease
Cardiology Division
Johns Hopkins University School of Medicine

Decreases in AIDS and Death Since the Introduction of HAART

Mortality across Europe, Israel and Argentina in 9803 patients: EuroSIDA

Cardiovascular-related Disease is a Leading Cause of Non-HIV-related Death

Age-adjusted Mortality Rate in HIV+ by Underlying Cause of Death, New York City (1999-2004)
Potential CVD Risk in HIV Patients

HIV Infection
Inflammatory Response

Non-HIV Traditional CVD Risk Factors

Treatment of HIV
Anti-retroviral Therapy
Metabolic side effects

HIV and/or ART may increase risk for CHD

Inclusion criteria
1) Active MACS participant (HIV+ and HIV- men)
2) Age 40-70 years at time of enrollment

Exclusion criteria
1) History of cardiac surgery (CABG or valve surgery)
2) History of coronary angioplasty ± stent placement
3) Kidney disease - eGFR < 60 mg/ml/m²
4) Contrast allergy

Mixed Plaque Non-calcified Plaque Calcified Plaque

RO1 HL095129 (Post) 9/25/08-06/30/14 (NCE)
Subclinical Vascular Disease and Metabolic Abnormalities in MACS HIV+ Men Have More Non-calcified Coronary Plaque

Associations between HIV and Presence of Coronary Artery Plaque on CT Angiography

<table>
<thead>
<tr>
<th>N=759</th>
<th>Adjusted Prevalence Ratio* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any plaque present</td>
<td>1.13 (1.04, 1.23)</td>
<td>0.004</td>
</tr>
<tr>
<td>Non-calcified plaque present</td>
<td>1.29 (1.10, 1.43)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mixed plaque present</td>
<td>1.22 (0.98, 1.52)</td>
<td>0.07</td>
</tr>
<tr>
<td>Calcified plaque present</td>
<td>1.02 (0.84, 1.23)</td>
<td>0.88</td>
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</tbody>
</table>

Separate multiple poisson regressions with robust variances comparing HIV+ to HIV- men

*Adjusted for age, race, CT scanning center, MACS cohort (pre- vs. post-2001) and CVD risk factors

**Advanced HIV is related to Coronary Artery Stenosis > 50%**

<table>
<thead>
<tr>
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<th>Adjusted Prevalence Ratio* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable current HIV RNA &gt; 50 copies/mL</td>
<td>1.43 (0.84, 2.43)</td>
<td>0.19</td>
</tr>
<tr>
<td>Duration of HAART (yrs)</td>
<td>1.09 (1.02, 1.17)</td>
<td>0.007</td>
</tr>
<tr>
<td>History of AIDS</td>
<td>1.40 (0.87, 2.28)</td>
<td>0.17</td>
</tr>
<tr>
<td>Current CD4+ T cell count (per 100 cell increase)</td>
<td>1.00 (0.92, 1.08)</td>
<td>0.97</td>
</tr>
<tr>
<td>Nadir CD4+ T cell count (per 100 cell increase)</td>
<td>0.80 (0.69, 0.94)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**MACS CVD2 Summary/Conclusions**

- Non-calcified plaque is more prevalent and extensive in HIV-infected men, suggesting increased risk for cardiovascular events.

- Men with more advanced HIV infection, as demonstrated by low nadir CD4+ T cell count and a greater number of years on HAART have a higher prevalence of clinically significant coronary stenosis > 50%.

**MACS CVD2 Summary/Conclusions**

- Additional studies are needed to identify how best to prevent progression of atherosclerosis in this unique population and correlation with future events.

- Although coronary CT angiography is not indicated as a screening test in asymptomatic individuals, these results emphasize the importance of assessing and modifying traditional cardiovascular risk factors in this population, especially in men with a history of a low nadir CD4+ T cell count.
Does coronary atherosclerosis progress more rapidly in HIV Patients?

- Primary outcome: Relative change in total volume of non-calcified plaque over time.
  - State-of-the-art, validated, semi-automatic plaque analysis software
  - More precise data regarding plaque composition and volume than the semi-quantitative method available previously for our cross-sectional analysis
  - Assessment of "vulnerable" plaque characteristics
    - Low attenuation plaque
    - Positive remodeling
    - Spotty calcification

Development of focal calcification in LAD (2010-2015)

SMART Study: HIV Viremia Can Contribute to CV Risk

- 5472 HIV-infected patients with a CD4+ cell count >350/mm³

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, any cause</td>
<td>1.8 (1.2-2.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Major cardiovascular, renal or hepatic disease</td>
<td>1.7 (1.1-2.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Fatal or non-fatal CVD</td>
<td>1.6 (1.0-2.5)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Treatment Interruption vs. Continuous Treatment

**Biomarkers of Immune Activation:**

The SMART Study — CRP, IL-6, D-dimer

Higher levels of biomarkers of inflammation and coagulation are associated with increased risk of CVD in HIV-infected patients

### Quartile 1 (low) Quartile 2 Quartile 3 Quartile 4 (high)

<table>
<thead>
<tr>
<th></th>
<th>IL-6 (n=5037)</th>
<th>hsCRP (n=5095)</th>
<th>D-dimer (n=5069)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 4</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Cumulative Participants With CVD Event, %**: 15, 5, 10, 0

**Time From Randomization, Months**: 0 8 16 24 32 4 12 20 28 36 44 40 48

**Higher levels of biomarkers of inflammation and coagulation are associated with increased risk of CVD in HIV-infected patients**


**HIV Is Associated With Increased Arterial Inflammation**

- 27 HIV patients on ART matched on Framingham Risk Score to 27 uninfected controls
- Arterial inflammation measured with FDG-PET in the aorta
- FDG accumulates within metabolically active macrophages (TBR=target to background ratio)
- FDG uptake was higher in the HIV vs non-HIV FRS matched controls

HIV+ TBR 2.23 (95% CI, 2.07-2.40)
HIV- TBR 1.89 (95% CI, 1.80-1.97)

P < 0.001

Also seen in those with undetectable viral load and those with low FRS


**Aortic Inflammation is Associated with sCD163 levels in HIV+ Patients**

Monocyte Activation Markers Are Elevated in HIV-infected Men in MACS

Serologic markers of monocyte activation measured at time of cardiac CT scanning in the MACS:

- Soluble CD163 (sCD163)
- Soluble CD14 (sCD14)
- Monocyte chemoattractant protein-1 (CCL2)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>HIV-Uninfected</th>
<th>HIV-Infected</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCD163 (ng/mL)</td>
<td>547 (393-693)</td>
<td>680 (519-879)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sCD14 (ng/mL)</td>
<td>1282 (1114-1458)</td>
<td>1619 (1406-1899)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCL2 (pg/mL)</td>
<td>236 (184-303)</td>
<td>276 (219-354)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Monocyte Activation Markers Associated with Immunodeficiency and HIV Viremia

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>CD4+ T-cell count</th>
<th>Nadir CD4+ T-cell count</th>
<th>Undetectable HIV RNA</th>
<th>% of visits with detectable HIV RNA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>0.80 (0.71, 0.89)</td>
<td>0.82 (0.73, 0.94)</td>
<td>0.85 (0.76, 0.97)</td>
<td>0.80 (0.71, 0.89)</td>
<td>0.30</td>
</tr>
<tr>
<td>N (95% CI)</td>
<td>0.78 (0.65, 0.93)</td>
<td>0.68 (0.54, 0.84)</td>
<td>0.75 (0.62, 0.90)</td>
<td>0.78 (0.65, 0.93)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
| Models were adjusted for age, race, HIV serostatus and CVD risk factors

Elevated Monocyte Activation Markers Associated with Coronary Artery Stenosis Among HIV-infected Men

n=566 for coronary artery calcium
n=426 for coronary plaque subtypes

Odds Ratio and 95% CI for associations between biomarkers (quintile 5 compared to quintile 1) and prevalence of coronary plaque, including coronary stenosis ≥50%, among HIV-infected men

Models were adjusted for age, race, HIV serostatus and CVD risk factors

Red lines indicate p<0.05.

Trend across quintiles of biomarker p<0.05.

** Trend across quintiles of biomarker p<0.01.
Predictors of Atherosclerosis in MACS CVD2 (separate manuscripts)

- Adiponectin
- Epicardial adipose tissue
- Race
- Monocyte Activation Markers (sCD163, sCD14, MCP-1)
- HCV infection
- Chronic Kidney Disease
- Osteoprotegerin
- Subcutaneous and Visceral Adipose Tissue

- Insulin Resistance
- Lipids
- ART
- Inflammation markers (IL-6, sTNFRα1 and 2)
- Smoking
- TMAO and microbiome
- HDL Function
- Testosterone

Published Manuscripts, Submitted for Publication, Working on Pen Draft, Data Analyses

HIV and Risk of Heart Failure

Veterans Aging Cohort Study

8486 participants
28.2% HIV-infected
7.3 years of follow-up
Adjusted HR 1.81 (95% CI, 1.39-2.36)

Limited data on myocardial function


Myocardial fibrosis on cardiac MRI more common in HIV

No. of Risk
HP estimated
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0

Figure 1. Kaplan-Meier survival analysis of the risk of heart failure (HR failure for this cohort).


HIV+ (on cART) 76%
HIV- 13%

Peak myocardial longitudinal systolic and diastolic strain were lower in HIV+
Small sample size
**Myocardial disease in HIV**

Do HIV+ patients have a greater prevalence of myocardial abnormalities that can predispose to sudden cardiac death or heart failure than HIV- individuals? Does use of drugs and alcohol confound these associations?

- N = 400
- MACS (Baltimore/DC and Chicago), WHS (DC), ALIVE (Baltimore)

**ABCs of Heart Disease Risk Management**

**A** Assessment of Risk
- Aspirin/antiplatelet therapy when indicated

**B** Blood Pressure Control

**C** Cholesterol Management
- Cigarette Smoking Cessation

**D** Diabetes and Pre-Diabetes Management

**E** Exercise/diet/weight loss

**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 to date in small studies, there are no data from large RCTs in HIV investigating tolerability, AE's and efficacy
- How will statins uniquely work in HIV
  - LDL lowering
  - Effects on inflammatory pathways
REPRIEVE: A Randomized Trial to Prevent Vascular Events in HIV
Steven Grinspoon, M.D.

• Primary Clinical Hypothesis
Statin therapy will prevent atherosclerotic cardiovascular disease (ASCVD)-related MACE events in HIV-infected persons on antiretroviral therapy (ART) in whom traditional CVD risk is not significantly increased.

• Primary Mechanistic Hypothesis
Statin therapy will reduce progression of non-calcified coronary atherosclerotic plaque volume as measured by serial coronary CT angiography (CTA).

REPRIEVE-Inclusion criteria

• Documented HIV infection
• Receiving stable ART
• CD4 > 100 cells/mm³
• Age 40 - 75 years
• Not recommended to receive statins by 2013 ACC/AHA guidelines
  - no CVD or DM
  - 10-year ASCVD risk score < 7.5%
  - LDL < 190

REPRIEVE- Study Design
Low Dose MTX and HIV

- Randomized double blinded placebo controlled study in treated and suppressed HIV-infected individuals with CVD or 1 CV risk factor (N=200)
- Occurring simultaneously as the trial in infected pts with CVD (Ridker)
- Primary endpoints are safety, impact on inflammatory markers/immune activation, and endothelial function

Hsue P, Currier JS, Stein JH NHLBI and ACTG

Case 1

A 50-year-old African American man with HIV infection.
Meds: tenofovir, emtricitabine, raltegravir
No known CVD.
BP 124/78 mm Hg.
Current smoker- 20-pack-year history.

Labs (fasting):
- Total cholesterol level 210 mg/dL
- Triglyceride level 310 mg/dL
- HDL-C level 38 mg/dL
- Calculated LDL-C level 110 mg/dL
- Glucose level 99 mg/dL

Should this patient initiate lipid-lowering therapy?

A  Yes. He should start a fibrate.
B  Yes. He should start a statin.
C  No. He should be counseled regarding diet and exercise only.

Should this patient initiate lipid-lowering therapy?
10-years ASCVD Risk is 9.4%

The Pooled Cohort Equation calculates his risk of a cardiovascular event within the next 10 years at 9.4%. Lifetime risk 50%.

Risk of first nonfatal myocardial infarction, coronary heart disease death, nonfatal or fatal stroke

http://tools.cardiosource.org/ASCVD-Risk-Estimator/

Statin Therapy Recommended in 4 Groups

1. Individuals with known ASCVD
2. Individuals with LDL-C ≥190 mg/dL
3. Individuals 40 to 75 years of age with diabetes and LDL-C 70-189 mg/dL
4. Individuals 40 to 75 years of age with estimated 10-year ASCVD risk ≥7.5% and LDL-C 70-189 mg/dL.1

*Requires “risk discussion” between clinician and patient before statin initiation


HIV+ Men at Low Calculated CVD Risk Have Excess Atherosclerosis: MACS

Odds of Plaque on Coronary CTA among 754 Men (450 HIV+/304 HIV-) in the MACS Age 40-70 2010-2013

Intensity of Statin Therapy

Table 5. High-Intensity and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately 50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30%</td>
<td>Daily dose lowers LDL-C on average, by approximately 15%</td>
</tr>
<tr>
<td>Atorvastatin (40-80 mg)</td>
<td>Rosuvastatin (5-10 mg)</td>
<td>Simvastatin (20 mg)</td>
</tr>
<tr>
<td>Fluvastatin (20-40 mg)</td>
<td>Pravastatin (40-80 mg)</td>
<td>Fluvastatin (80 mg)</td>
</tr>
<tr>
<td>Lovastatin (40-80 mg)</td>
<td>Fluvastatin (40-80 mg)</td>
<td>Fluvastatin (20 mg)</td>
</tr>
<tr>
<td>Pravastatin (2 mg)</td>
<td>Pravastatin (10-20 mg)</td>
<td>Pravastatin (5 mg)</td>
</tr>
</tbody>
</table>

*Indicated responses to statin therapy noted in the RCTs and should be expected to vary in clinical practice. These might have a biologic basis to an individual patient’s response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

A Statin dosing for persons on antiretroviral therapy is the same as for the general population.
B Persons on antiretroviral therapy should avoid taking all statins.
C PIs inhibit cytochrome P450 CYP3A4, leading to inappropriate levels of certain statins and a higher risk of statin-related adverse effects.
D Simvastatin and lovastatin are safe for use in persons on PI-containing antiretroviral regimens.

Primary Care Guidelines for the Management of Persons Infected With HIV: 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America

Lipids

- Patients with abnormal lipid levels should be managed according to the National Cholesterol Education Program Guidelines (new AHA/ACC guidelines)
- Fasting lipid levels should be obtained prior to and within 1-3 months after starting ART.
- Strong recommendation, moderate quality evidence

Statins and ART

- Caution when prescribing statins with protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors
- Most PIs inhibit the metabolism of statins, increasing potential for statin toxicity.
  - atorvastatin and rosuvastatin should be initiated at low doses and titrated carefully
  - pitavastatin and pravastatin are metabolized by glucuronidation, so little effects when coadministered with a PI
  - Efavirenz induces statin metabolism, resulting in lowering of statin levels
The Problem

- Limited data on proven therapies to reduce CVD risk in HIV+ patients
- Can we translate results in the general population to HIV+ patients?
- Want to practice evidence based medicine
- Who should get Statins?
- Aspirin?
- Other methods to reduce inflammation and immune activation?

Summary

- HIV patients are increased risk for CVD
- Inflammation/immune activation contribute to risk for atherosclerosis and CVD independent of traditional CVD risk factors
- Elevated sCD163 levels are associated with vascular inflammation and also coronary atherosclerosis in patients with HIV
- Lower nadir CD4+ T cell counts associated with coronary stenosis

Conclusions

- Clinical trials are needed to inform HIV guidelines
- REPRIEVE will test statin therapy
- Need an aspirin clinical trial
- Need data about CAC and risk
- Until further data, use guidelines in place for general population (AHA/ACC guidelines)
- Treat HIV+ patients with multiple CVD risk factors most aggressively
Ideal cardiovascular health (all of these)

- Total chol <200 mg/dl (untreated)
- BP <120/80 (untreated)
- Fasting blood glucose <100 mg/dl (untreated)
- BMI <25 kg/m2
- Abstinence from smoking
- Physical activity at goal: ≥150 min/wk moderate intensity, ≥75 min/wk vigorous activity, or combination
- Healthy (DASH-like) diet

All patients should be encouraged to stop smoking regardless of CVD risk

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- RO1HL125053 (Post)
- RO1 HL095129 (Post)
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