HIV and Cardiovascular Disease: Unmet Needs

Daniel Duprez, MD, PhD, FNLA
Donald and Patricia Garofalo Chair in Preventive Cardiology
University of Minnesota

Agenda

• Facing the problem
• HIV and CVD: pathological mechanisms
• Unique risks by HIV on overall CV risk
• Lipodystrophy in HIV – therapy
• Lipids and HIV – lipid lowering therapy
• HIV & CVD prevention – scientific gaps
HIV – Facing the Problem

• Tremendous progress in the treatment of HIV has led to increased survival and a dramatic evolution of the disease.

• The clinical challenges confronting the population have now shifted from AIDS-related illnesses to chronic diseases.

• The risk of developing cardiovascular disease in the HIV-positive population is significantly higher, and disease progression may be accelerated compared with in the general population.

Agenda

Facing the problem

• HIV and CVD: pathological mechanisms

• Unique risks by HIV on overall CV risk

• Lipodystrophy in HIV – therapy

• Lipids and HIV – lipid lowering therapy

• HIV & CVD prevention – scientific gaps
Agenda

- Facing the problem
- HIV and CVD: pathological mechanisms
  - Unique risks by HIV on overall CV risk
  - Lipodystrophy in HIV – therapy
  - Lipids and HIV – optimal lipid lowering therapy
  - HIV & CVD prevention – scientific gaps
Comparison of Risk and Age at Diagnosis of Myocardial Infarction in HIV-Infected Versus Uninfected Adults (Veterans Aging Cohort Study)

<table>
<thead>
<tr>
<th></th>
<th># of MI events</th>
<th>PY</th>
<th>IR per 1000 PY</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>398</td>
<td>310,138</td>
<td>1.28</td>
<td>1.16, 1.42</td>
</tr>
<tr>
<td>HIV+</td>
<td>291</td>
<td>143,844</td>
<td>2.02</td>
<td>1.80, 2.27</td>
</tr>
</tbody>
</table>


Is the Framingham Risk Estimation Valid in HIV-Infected Patients?

Observed and Predicted MI Rates According to ART Exposure (D:A:D Study)

Agenda

- Facing the problem
- HIV and CVD: pathological mechanisms
- Unique risks by HIV on overall CV risk
  - Lipodystrophy in HIV – therapy
  - Lipids and HIV – lipid lowering therapy
  - HIV & CVD prevention – scientific gaps

Lipodystrophy in HIV – therapy?
HIV-Associated Lipodystrophy

CT abdomen in a young healthy male subject

Moderate amount of subcutaneous adipose tissue (SAT) and very little visceral adipose tissue (VAT)

CT abdomen in a patient with HIV-associated lipodystrophy

Virtual absence of subcutaneous adipose tissue (SAT) and the large amount of visceral adipose tissue (VAT)

Epidemiological Factors Affecting the Development of Lipodystrophy

- **Disease**
  - Duration
  - Severity of immune deficiency
  - Magnitude of immune reconstitution

- **Host**
  - Age, sex, race, family history, BMI
  - Diet, exercise
  - Tobacco use

- **Antiretroviral Therapy**
  - Specific agent
  - Duration of therapy
Therapeutic Options in the Development of Lipodystrophy

1. Do nothing
2. Stop HAART
3. Switch HAART
4. Treat individual abnormalities

Lipoatrophy is not reversible to any significant extent.

Therapy Lipodystrophy in HIV

• Approach the metabolic complications as they would in non-HIV infected individuals, with some extra attention of possible drug-drug interactions.

• Complementary therapies (eg, weight control, smoking cessation) should be stressed in all cases, as they likely have a greater influence on the outcome than the individual antiretroviral agent.

• Diet and Resistance training.

• Fibrates/Statins

• Diabetes: diet and oral agents
Metabolic Effects of a Growth Hormone–Releasing Factor in Patients with HIV

- The measure of visceral adipose tissue decreased by 15.2% in the tesamorelin group and increased by 5.0% in the placebo group.

- The levels of triglycerides decreased by 50 mg/dl and increased by 9 mg/dl respectively (P < 0.001).

- Cholesterol/HDL cholesterol ratio decreased by 0.31 and increased by 0.21, respectively (P < 0.001).


Agenda

- Facing the problem
- HIV and CVD: pathological mechanisms
- Unique risks by HIV on overall CV risk
- Lipodystrophy in HIV – therapy
  - Lipids and HIV – lipid lowering therapy
  - HIV & CVD prevention – scientific gaps
MACS: 10-Year Prospective Assessment of Lipid Levels

- Multicenter AIDS Cohort Study
  - 50 HIV-negative men who seroconverted
- Prior to seroconversion
  - Lipid levels were within normal range and similar to NHANES III
- After seroconversion
  - Prior to HAART (n = 50)
    - Notable reductions in lipid levels
  - 3 years after HAART (n = 38)
    - For most, lipid levels returned to baseline values (but not HDL), with expected increase due to aging


Protease Inhibitors Modify Lipoprotein Metabolism through Multiple Mechanisms

Kelesidis T & Curier JS. Endocrinol Metab Clin N Am 2014;43:665-84
Dyslipidemic effects of NRTIs

- NRTIs have been associated with metabolic alterations, particularly changes in serum triglyceride concentrations.
- Replacement of NRTIs such as stavudine with tenofovir is a strategy to reduce the cardiovascular risk and improve the lipid profile of patients with dyslipidemia.
- The association between abacavir and excess CVD risk remains controversial.
- Switching from multidrug class-suppressive regimens to triple therapy containing 2 NRTIs showed increases in plasma lipids.
- Tenofovir and lamivudine/emtricitabine seem to be the drugs that are not associated with dyslipidemia.

Effect of ARTs and Changes in Lipids

Lake JE & Currier JS. Lancet 2013;13:964-75
A Systematic Review of the Usefulness of Statin Therapy in HIV-Infected Patients

• Given the increased CVD risk in HIV patients and the proven benefit of statins reducing CVD events across numerous patient groups, statin therapy might be particularly beneficial for patients with HIV.

• Safety concerns and limited quality trial data evaluating clinical outcomes in HIV-infected patients on simultaneous ART and statin therapy have likely limited statin use in HIV-infected patients chronically taking ART.


Statin Metabolism, Pharmacokinetics and Antiretroviral Drug-drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism</th>
<th>Bioavailability and Absorption (%, respectively)</th>
<th>Lipophilic?</th>
<th>Potential Antiretroviral Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>CYP3A4</td>
<td>&lt;5, 30</td>
<td>Yes</td>
<td>PI, NNRTI</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>CYP3A4, CYP3A4</td>
<td>&lt;5, 60-80</td>
<td>Yes</td>
<td>PI, NNRTI</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Partial Hepatic (OATP1B1), Partial biliary/renal excretion</td>
<td>18, 24</td>
<td>No</td>
<td>PI</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>CYP2C9, CYP3A4 (minor)</td>
<td>25, 98</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>CYP3A4</td>
<td>12, 30</td>
<td>Yes</td>
<td>PI</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>CYP2C9 (&lt;10%)</td>
<td>20, rapid</td>
<td>No</td>
<td>PI</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Glucuronidation, CYP2C9</td>
<td>51, 50</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Feinstein MJ et al. Am J Cardiol 2015;115:1760-6
### Results of Search Strategy

**Question:** What is the safety and efficacy of statins in patients with HIV on antiretroviral therapy (ART)?

**Search:** 1) "HIV" and "Antiretroviral" and "Statin"
2) Add filter: "Clinical trial"

- 33 Results (initial search)
- 18 Studies included for systematic review

### Results

<table>
<thead>
<tr>
<th>N</th>
<th>Population</th>
<th>ART Intervention (R=Randomized; NR=Non-Randomized)</th>
<th>Follow-Up (Wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Viral load ≤ 500 copies/ml Total chol &gt;240 mg/dl</td>
<td>PI R: Diet/Pravastatin vs Diet</td>
<td>24</td>
</tr>
<tr>
<td>25</td>
<td>Refractory hyperlipidemia</td>
<td>Any NR: Pravastatin or Fluvastatin</td>
<td>12</td>
</tr>
<tr>
<td>174</td>
<td>Combined dyslipidemia (LDL ≥ 130 or triglyceride ≥ 200)</td>
<td>Any R: Pravastatin vs. fenofibrate</td>
<td>48</td>
</tr>
<tr>
<td>137</td>
<td>Mixed hyperlipidemia On first PI-based regimen</td>
<td>Any PI R: NNRTI instead of PI vs. pravastatin with PI</td>
<td>52</td>
</tr>
<tr>
<td>135</td>
<td>Combined hyperlipidemia</td>
<td>On first PI-based regimen PI I R: NNRTI instead of PI vs. pravastatin vs. placebo</td>
<td>52</td>
</tr>
<tr>
<td>12</td>
<td>Viral load &gt;1000 Discontinued ART</td>
<td>Any NR: Simvastatin</td>
<td>12</td>
</tr>
<tr>
<td>20</td>
<td>Elevated LDL</td>
<td>Any PI R: Fluvastatin vs. Ezetimibe</td>
<td>12</td>
</tr>
<tr>
<td>29</td>
<td>Hyperlipidemia</td>
<td>Any PI R: Pravastatin vs. placebo</td>
<td>8</td>
</tr>
<tr>
<td>33</td>
<td>Hyperlipidemia</td>
<td>Any PI R: Pravastatin vs. placebo</td>
<td>16</td>
</tr>
<tr>
<td>301</td>
<td>Hyperlipidemia On ART ≥12 months</td>
<td>Any NR: Pravastatin vs. fibrates vs. diet/exercise</td>
<td>104</td>
</tr>
<tr>
<td>41</td>
<td>On ART</td>
<td>Any PI R: ART interruption → atorvastatin vs. placebo</td>
<td>12</td>
</tr>
<tr>
<td>32</td>
<td>Dyslipidemia due to ART</td>
<td>Any NR: Atorvastatin and diet</td>
<td>26</td>
</tr>
<tr>
<td>94</td>
<td>Total cholesterol &gt;250 despite diet/exercise</td>
<td>PI R: Rosuvastatin vs. pravastatin&lt;comma&gt; atorvastatin</td>
<td>52</td>
</tr>
<tr>
<td>88</td>
<td>Dyslipidemia</td>
<td>PI R: Rosuvastatin vs. pravastatin</td>
<td>6.5</td>
</tr>
<tr>
<td>45</td>
<td>Lipoatrophic patients on ritonavir-boosted lopinavir</td>
<td>PI R: Uridine vs. pravastatin</td>
<td>24</td>
</tr>
<tr>
<td>74</td>
<td>Combined dyslipidemia</td>
<td>Any R: Pravastatin vs. fenofibrate</td>
<td>48</td>
</tr>
<tr>
<td>37</td>
<td>LDL ≥ 3% 10 yr FRS&lt;comma&gt; no other statin or ACE-i indication</td>
<td>Any R (2x2): Lisinopril vs. pravastatin vs. placebo</td>
<td>16</td>
</tr>
<tr>
<td>36</td>
<td>Hypercholesterolemia and carotid atherosclerosis</td>
<td>Any NR: Rosuvastatin</td>
<td>104</td>
</tr>
<tr>
<td>147</td>
<td>LDL ≤ 130 mg/dl Elevated Lp-PLA2</td>
<td>Any R: Rosuvastatin vs. placebo</td>
<td>48</td>
</tr>
</tbody>
</table>

Feinstein MJ et al. Am J Cardiol 2015;115:1760-6
Conclusions from Meta-Analysis

- Based on available data, rosuvastatin has a favorable combination of efficacy and safety for patients on ART, particularly PIs.

- If a generic statin is preferred in a patient on PI-based ART, simvastatin should be avoided and atorvastatin (at a dose of 10 mg or 20 mg daily) or pravastatin should be chosen.

- Atorvastatin tends to be more efficacious at lipid lowering, and pravastatin has somewhat less interaction with boosted PI-based ART regimens.

- Less data exist regarding interactions between statins and non–PI-based ART regimens; although if a generic is preferred, it is probably reasonable to choose atorvastatin or pravastatin.


REPRIEVE Trial

- Pitavastatin appears to have a particularly favorable pharmacokinetic profile even in the setting of PI co-administration.

- The REPRIEVE trial:
  - a randomized double-blind trial of pitavastatin 4 mg versus placebo (ACTG A5332)
  - in 6,500 HIV-infected patients for primary CVD prevention
### Lipoprotein Particle Subclasses, Cardiovascular Disease and HIV Infection
SMART Substudy


<table>
<thead>
<tr>
<th>HDL Particle (μmol/L)</th>
<th>Un-adjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (4th/1st)</td>
<td>P-value</td>
</tr>
<tr>
<td>Total</td>
<td>0.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Large</td>
<td>0.69</td>
<td>0.09</td>
</tr>
<tr>
<td>Medium</td>
<td>0.91</td>
<td>0.67</td>
</tr>
<tr>
<td>Small</td>
<td>0.53</td>
<td>0.007</td>
</tr>
</tbody>
</table>

### Management of Other Comorbidities Contributing to CVD in HIV Patient

- RAS-blockers should be the first therapy in hypertension because of their protective effects.
- Antiplatelet drugs should be given according to the guidelines for the general population.
- Diabetes and insulin resistance should be managed according to the guidelines for the general population and HIV-infected subjects.
Conclusions

• As the population with HIV on effective ART ages, the burden of comorbid cardio-metabolic disease will continue to increase.

• Improved screening algorithms to detect cardio-metabolic disease in people with HIV are needed.

• Additional research is needed to determine the efficacy of traditional and novel strategies to treat cardio-metabolic disease in people with HIV.

• The contribution of inflammation to the development of cardiovascular disease is not fully understood.
CVD Prevention and Treatment in HIV Scientific Gaps

• Potential differences in the prevention and treatment of HIV-related CVD

• Efficacy and effectiveness of evidence-based CV therapies in HIV patients

• Novel therapies to address unique pathophysiology of HIV-related CVD