Treatment of Dyslipidemia
To Reduce Cardiovascular Risk in HIV Patients
NLA Spring Clinical Lipid Update
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Disclosures

Research Contracts  IONIS, Amgen
Outline

- Epidemiology of ASCVD in HIV
- Pathogenesis of ASCVD in HIV
- Effects of Newer vs. Older ART on Dyslipidemia
- ASCVD Risk Assessment in HIV
- Lipid Treatment in HIV
- Statin-Anti-Retroviral Drug Interactions
- Diet and Lifestyle Treatment in HIV
Prevalence of HIV in the U.S.
Steady Increases Since the Advent of ART

CDC MMWR, M&M Supplements, June 2012
Incidence of MI in HIV Infection

Higher MI Rates Across the Range of Global Risk

Adjusted AMI Rates in the VA HIV Registry by HIV Status 2003-09, N=81,322

Current Model of ASCVD Risk in HIV

Traditional, Viral, ART and Host Factors Contribute

Modified From: Vachiat, A et al. HIV and Ischemic Heart Disease JACC 2017; 69:73–82.
Molecular Basis of Dyslipidemia in HIV
Experimental Models Show Effects of HIV and ART

### HIV Effects

- **HIV accessory protein Nef** down-regulates ABCA1, inhibiting cholesterol efflux from macrophages and HDL-P formation
- **HIV viral protein vpr** down-regulates PPAR-Y, inhibiting fat cell differentiation and triggering lipolysis and VLDL synthesis

### ART Effects

- **Older Protease Inhibitors (PI’s)** dysregulate SREBP-1c, LPL, LRP, LDLR synthesis, Apo-B degradation, PPAR-Y, and Glucose transporter-4, causing adipocyte dysfunction, insulin resistance, and dyslipidemia
- **Older NRTIs** inhibit mtDNA-polymerase-Y and FA oxidation, triggering lipoatrophy, lipolysis, insulin resistance and dyslipidemia
Blood Lipids in HIV Infection Pre-/Post ART

Pattern of Reduced Lipids Followed by ↑Non-HDL-C

Changes in Blood Lipids in 50 HIV Seroconverters Pre- and Post-ART

Low ‘nadir’ CD4 counts and high HIV titers predict chronically lower HDL-C

Advanced Lipid-Inflammatory Markers in HIV

Increases in LDL-P, Inflammatory Markers Common

- Increased LDL-particle numbers
- Increased small, dense LDL-particle numbers
- Decreased large HDL-particle numbers
- Increased oxidized LDL
- Increased LP-PLA2
- Increased hsCRP
- Increased IL-6
- Increased sCD14, sCD163

Effects of ART on Blood Lipids
Newer Classes/Formulations Are More Lipid Neutral

**Integrase Inhibitors**
- Raltegravir
- Dolutegravir _______ Elvitegravir

**Non-NRTIs**
- Rilpirivine
- Etravirine _______ Efavirenz

**NRTIs**
- Tenofovir _____________ Abacavir

**Newer PIs ________ Older PIs**
- Darunavir/r or cobi
- Atazanavir/r or cobi

**Blood Lipid Effects**

Modified From: from CVD in HIV-infected patients: Predict It and Prevent It @ clinicaloptions.com/hiv
Effects of Modern ART on ASCVD Risk
Newer Data Show Neutral or Favorable Effects

• Randomized Controlled Trials
  – **START Trial** – immediate ART (vs. delayed ART) was associated with a 57% decrease in serious AIDS and non-AIDS related M & M, with *no* significant increase in ASCVD events \(^1\)
  – **SMART Trial** – continuous ART (vs. interrupted ART) was associated with a decrease in AIDS-related M&M, and a 50% decrease in ASCVD events \(^2\)

• Observational Studies and Cohorts
  – Viral suppression with modern ART favorably effects
    • CIMT progression, Flow-Mediated Dilatation
    • ASCVD event rates

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Effects of ART + Lipid-BP Control on MI Risk
Kaiser Cohort Shows Decrease in MI Risk Over Time

MI Incidence and Rate Ratios In the Kaiser Permanente CA HIV Cohort Between 1996-2011, N 24,000 vs. 257,000 Controls

<table>
<thead>
<tr>
<th>Calendar Year</th>
<th>Incidence Rate/100,000 py</th>
<th>Rate Ratio$^a$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV-positive</td>
<td>HIV-negative</td>
</tr>
<tr>
<td>1996–2011</td>
<td>268</td>
<td>165</td>
</tr>
<tr>
<td>1996–1999</td>
<td>276</td>
<td>136</td>
</tr>
<tr>
<td>2000–2003</td>
<td>324</td>
<td>162</td>
</tr>
<tr>
<td>2004–2007</td>
<td>270</td>
<td>178</td>
</tr>
<tr>
<td>2008–2009</td>
<td>245</td>
<td>167</td>
</tr>
<tr>
<td>2010–2011</td>
<td>195</td>
<td>165</td>
</tr>
</tbody>
</table>

Basic Lipid Treatment Algorithm in HIV
Similar to General Population

Check fasting lipid panel before cART and within 3-6 mos of starting cART

Count # of CHD risk factors and if > 2 risk factors, Perform 10 – Year Risk Calculation

Modify diet and lifestyle factors, e.g., poor diet, physical inactivity, smoking

If lipids are above threshold for risk group despite lifestyle change, then:

Consider Lipid Lowering Drug

Statin if LDL > target or
If TG > 200 w/ Elevated Non-HDL-C

Consider Lipid Lowering Drug

Fibrate or Omega-3-Fatty Acid
If Serum TG > 500 mg/dl

Consider Altering cART Regimen
<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goals</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
</table>
| Low           | • 0-1 major ASCVD risk factor  
• Consider other risk indicators | Non-HDL and LDL < 130  
< 100 | Non-HDL and LDL > 190  
> 160 |
| Moderate      | • 2 major ASCVD risk factors  
• Consider risk scoring if 2+ RFs  
• Consider other risk indicators | < 130  
< 100 | > 160  
> 130 |
| High          | • > 3 major risk factors  
• DM 1 or 2 with  
  - 0-1 other major risk factor  
  - No target organ damage  
• CKD Stage 3B or 4  
• LDL-C > 190 mg/dl  
• Risk score = High | < 130  
< 100 | > 130  
> 100 |
| Very High     | • ASCVD  
• DM 1 or 2 with  
  - 2+ risk factors or  
  - organ damage | < 100  
< 70 | > 100  
> 70 |

Global Risk Assessment in HIV

Traditional ASCVD Risk Scores Underestimate Risk

Observed vs. Predicted Risk via FRS and ACC/AHA Equation in the Partners HIV Cohort - N=2,270, F/U 6 Years

### Rationale for Statins as 1st Line Drug in HIV

**Statins Best for Lowering Non-HDL-C in Dyslipidemia**

<table>
<thead>
<tr>
<th>Mixed Dyslipidemia</th>
<th>TG</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>Non-HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td>-10 to -37</td>
<td>-26 to -63</td>
<td>+ 5 to + 16</td>
<td>-44 to -60</td>
</tr>
<tr>
<td><strong>Omega-3-fatty acids</strong></td>
<td>-19 to -44</td>
<td>-6 to + 25</td>
<td>-5 to + 7</td>
<td>-1 to -7</td>
</tr>
<tr>
<td><strong>Fibrate</strong></td>
<td>-24 to -36</td>
<td>-5 to -31</td>
<td>+ 10 to + 16</td>
<td>-17</td>
</tr>
<tr>
<td><strong>Niacin</strong></td>
<td>-5 to -38</td>
<td>-3 to -17</td>
<td>+ 10 to + 26</td>
<td>NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Isolated Hypertriglyceridemia</th>
<th>TG</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>Non-HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td>-21 to -52</td>
<td>-27 to -45</td>
<td>+ 3 to + 22</td>
<td>-29 to -52</td>
</tr>
<tr>
<td><strong>Omega-3-fatty acids</strong></td>
<td>-26 to -52</td>
<td>+ 17 to + 49</td>
<td>+ 9 to + 14</td>
<td>-10 to -14</td>
</tr>
<tr>
<td><strong>Fibrate</strong></td>
<td>-46 to -62</td>
<td>+ 3 to + 47</td>
<td>+ 18 to + 23</td>
<td>NR</td>
</tr>
</tbody>
</table>

Rationale for Statins as 1st Line Drug in HIV

Surrogate Endpoint Studies Support Statin Use

- Improved endothelial function
- Reduced markers of immune activation
- Reduced markers of inflammation
- Slowed decline in GFR
- Slowed atherosclerosis progression
Atorvastatin Effects on ASCVD Progression in HIV
Reduced Plaque Progression vs. Placebo

Change in Non-Calcified Plaque Volume over 12 Months in 40 HIV+ Subjects with ASCVD by Cardiac CTA and LDL-C \( \leq 130 \) Randomized to Atorvastatin 40mg vs. Placebo

Lo et al. Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis The Lancet HIV, Volume 2, Issue 2, 2015, e52–e63
Rosuvastatin Effects on CCA-CIMT in HIV
Reduced CIMT Progression vs. Placebo-SATURN Trial

Change in CCA-CIMT over 96 Weeks in 128 HIV+ Subjects with LDL < 130 + Markers of Inflammation or Immune Activation Randomized to Rosuvastatin v. Placebo

Rosuvastatin slows progression of subclinical atherosclerosis in patients with treated HIV infection.
Longenecker, Chris; Sattar, Abdus; Gilkeson, Robert; McComsey, Grace
Statins for Reducing MACE in Low Risk HIV
REPRIEVE to Test Statins in HIV with ASCVD Risk < 10%

• **Subjects**
  – 6,500 HIV infected individuals age 40-75 years
  – On stable ART for 6+ months with CD4 > 100 cells/mm³
  – 10 Yr ASCVD risk < 7.5% and No ASCVD, DM, or LDL > 190

• **Intervention**
  – Pitavastatin 4mg daily vs. Placebo
  – Follow up 6 Years

• **Endpoints**
  – Primary: Major adverse cardiovascular events (MACE)
  – Secondary: All-cause mortality, AIDS-related diagnoses
  – Sub-Study: Plaque volume / morphology by CCTA
    Inflammatory biomarkers

Reprievetrial.org
Statin Efficacy-Safety Trials in HIV
Potent Statins More Efficacious, Combinations Safe

- **INTREPID Study** – showed Pitavastatin 4mg is superior to Pravastatin 40mg at 52 weeks, decreasing LDL 30%-32%, Non-HDL-C 27-29%

- **ANRS Study** – showed Rosuvastatin __mg is safe in patients taking PI’s boosted with ritonivir, and more efficacious than Pravastatin __mg

- **ACTG 5087 Trial** – showed Pravastatin plus Fenofibrate is safe at 48 weeks, though % of subjects achieving LDL-C goal was low at 10%
**Statin Safety in HIV Patients on ART**

**Statin AUC Is Increased by Some Protease Inhibitors**

<table>
<thead>
<tr>
<th>CYP</th>
<th>Statin</th>
<th>Protease Inhibitor Effects on Statin AUC</th>
<th>Restrictions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3A4</td>
<td>Lovastatin</td>
<td>Large increases in AUC</td>
<td>Do not use</td>
</tr>
<tr>
<td>3A4</td>
<td>Simvastatin</td>
<td>Large increases in AUC</td>
<td>Do not use</td>
</tr>
<tr>
<td>3A4</td>
<td>Atorvastatin</td>
<td>Large increase in AUC with - Tipranavir - Lopinavir</td>
<td>Do not use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Modest increase in AUC with - Darunavir - Fosamprenavir - Saquinavir</td>
<td>Restrict Dose &lt;20mg</td>
</tr>
<tr>
<td>2C9</td>
<td>Rosuvastatin</td>
<td>Possible large increase in AUC with - Tipranavir</td>
<td>Do not use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Modest increase in AUC with - Lopinavir - Atazanavir</td>
<td>Restrict Dose &lt;10mg</td>
</tr>
<tr>
<td>2C9</td>
<td>Fluvastatin</td>
<td>Increase in AUC with - Nelfinav</td>
<td>Restrict Dose</td>
</tr>
<tr>
<td>Min</td>
<td>Pravastatin</td>
<td>Large increase in AUC with - Darunavir - Lopinavir</td>
<td>Restrict Dose</td>
</tr>
<tr>
<td>Min</td>
<td>Pitavastatin</td>
<td>Small increases or decrease in AUC</td>
<td>Any Dose OK</td>
</tr>
<tr>
<td>Drug</td>
<td>Safety</td>
<td>Precautions</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------------------</td>
<td>---------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Generally safe</td>
<td>Same as general</td>
<td></td>
</tr>
<tr>
<td>Omega-3-FA</td>
<td>Generally safe</td>
<td>Same as general</td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td>Generally safe</td>
<td><strong>Use with caution</strong></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Generally safe</td>
<td>Same as general</td>
<td></td>
</tr>
<tr>
<td>Bile Acid Sequestrants</td>
<td>Contraindicated with elevated TG, Risk of malabsorption of HIV drugs</td>
<td><strong>Avoid Use</strong></td>
<td></td>
</tr>
</tbody>
</table>
## Other Causes of High TGs-Non-HDL-C

Many Are More Common in HIV+ Individuals

<table>
<thead>
<tr>
<th>Diet/Lifestyle</th>
<th>Conditions</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette Smoking †‡</td>
<td>Type 2 DM / Metabolic Syndrome †‡</td>
<td>Oral estrogens, Tamoxifen</td>
</tr>
<tr>
<td>Physical Inactivity ‡</td>
<td>Polycystic Ovarian Syndrome</td>
<td>Beta-Blockers, Thiazides</td>
</tr>
<tr>
<td>Alcohol Excess ‡</td>
<td>Hypothyroidism</td>
<td>Retinoic Acid, L-Asparaginase</td>
</tr>
<tr>
<td>Calorie Excess ‡</td>
<td>Cushing Syndrome</td>
<td>Anti-psychotics</td>
</tr>
<tr>
<td>High Glycemic / High CHO Diet</td>
<td>Nephrotic Syndrome ‡</td>
<td>Anti-retroviral therapy †‡</td>
</tr>
<tr>
<td></td>
<td>Renal Failure</td>
<td>Cyclosporine, Sirolimus, Interferon</td>
</tr>
</tbody>
</table>

RR of CVD with increasing age in the D:A:D Cohort and the effects of stopping smoking, reducing cholesterol (by 1 mmol/L) or reducing systolic BP (by 10 mmHg) at age 50 years. If smoking cessation occurs at age 50, the RR of CVD at age 65 drops from almost 6-fold to 3-fold.
Diet Change for Dyslipidemia in HIV

Benefits, But Greater Barriers

• **Benefits of Diet Change in HIV**
  – 2012 Systematic Review – Aggregate of 4 clinical trials
  – Significant reductions in serum TG’s of -0.46 mmol/L (95% CI -0.85 - -0.07)

• **Barriers to Diet Change in HIV**
  – **Psychological** - overeating to prevent / reverse wasting
  – **Financial** - high cost of fish, fresh produce
  – **Cultural** – family eating and cooking patterns
  – **Environmental** – unstable living situations, food deserts

• **Facilitators of Diet Change in HIV**
  – Frequent provider contact and feedback
  – Support groups
  – Experiential learning

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Exercise for Dyslipidemia in HIV
Improved Body Composition, Fat Mass

• **Qualitative Review 2014**
  – 19 RCTs of aerobic +/- resistance training
  – Favorable effects on **cardiorespiratory fitness and body composition (fat mass, waist circumference)**
  – Inconsistent effects on **blood lipids, markers of immune function**
  – Functional aerobic impairment (FAI) noted

• **Cochrane Review and Meta-Analysis 2016**
  – 24 RCTs of aerobic +/- resistance training
  – Significant improvements in **cardiorespiratory fitness, body composition, muscle strength, psychiatric score and QOL**
  – Insufficient study of **blood lipids**

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1. Jaggers, JR. Health benefits of exercise for people living with HIV. Amer Jour Lifestyle 2014 vol. 10 no. 3 184-192
Summary

- **CVD risk** is increased in HIV due to traditional, viral and ART factors
- **Newer ARTs** reduce AIDS M&M, and may not alter lipids or raise ASCVD risk
- **Lipid screening and risk assessment** are required in all with HIV, which can be considered an additional risk factor, especially since traditional risk scores underestimate risk
- **Statins are the drugs of first choice** in HIV infection, and ezetimibe, fenofibrate, omega-3-FA’s and niacin are safe for add-on therapy
- **Statin-ART interactions** exist but are less with newer ARTs, and can be avoided with Pitavastatin or carefully dosed Atorvastatin, Rosuvastatin or Pravastatin
- **Smoking cessation** has the most potential for reducing CVD in HIV
- **Diet Change** improves non-HDL-C in HIV, though unique barriers exist, and **Exercise** improves related measures