HIV, Dyslipidemia, and CVD Risk

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One Case

54-yo man with HIV, diabetes, HTN, and dyslipidemia
No CHD, no family history of CHD, no smoking
HIV: controlled on Atripla 600/200/300 and Isentress 400 mg twice a day
HTN: controlled on HCTZ/ACE-I
T2D: poorly controlled on metformin 1000 plus glipizide 4 (HbA1c 9.3%)
LDL 83 mg/dl, on pravastatin 40 mg
TG 1770 mg/dl on fenofibrate 160 and fish oil supplement 2 g
Also on aspirin 81 mg
One Case

Stress test normal, CAC zero
Amylase and lipase normal
AST 114, ALT 151

Dietary instructions
Omega 3 supplement to 4g
Metformin to 2000 mg
Glipizide to 10 mg

At 3-month follow up, patient has lost 10 pounds
TG 330 mg/dl (LDL 94 mg/dl)
HbA1c 6.3%
AST 60, ALT 75
Another Case

64-yo man with HIV, diabetes, CAD (stent in LAD 8 years prior), and dyslipidemia
HIV: controlled on Truvada 200/300 mg, Isentress 400 mg twice a day, Intelect 100 mg Tab 2 tablets twice a day for 120 days
T2D: poorly controlled on glipizide 5 (HbA1c 9.0%)
Lipids: LDL 97 mg/dl, TG 75 mg/dl, HDL 38 (rosuvastatin 10 mg)
AST 34, ALT 62
Another Case

Dietary instructions
Omega 3 supplement to 4g
Glipizide to 10 mg

At 3-month follow up, patient has lost 7 pounds
LDL 29 mg/dl
HbA1c 6.3%
AST 30, ALT 32
Another Case

Dietary instructions
Omega 3 supplement to 4g
Glipizide to 10 mg

At 3-month follow up, patient has lost 7 pounds
LDL 29 mg/dl
HbA1c 6.3%
AST 30, ALT 32

TG 260, HDL 26
CVD Risk Factors with HIV Infection

- Traditional risk factors
  - Age
  - Dyslipidemia
  - Hypertension
  - Higher smoking rates
  - Impaired glucose tolerance
  - Insulin resistance

- Nontraditional risk factors
  - Subcutaneous fat loss
  - Visceral fat gain
  - Inflammation, CRP increases
  - Direct effects of the virus on the vasculature, increased CIMT
  - Effects of ARV drugs, lipodystrophy

HIV and Dyslipidemia

- Untreated patients with HIV infection commonly show
  - Increased TC
  - Decreased LDL-C
  - Decreased HDL-C
  - Increased TG

- Patients treated with ARV medications commonly show
  - Increased TC
  - Increased LDL-C
  - Decreased HDL-C
  - Increased TG

HIV and CHD Risk

- Increased rates of CHD in HIV-infected patients on anti-retrovirals
  - HIV-positive patients in the Kaiser-Permanente cohort (N = 20,081) had significantly increased CHD risk (p<.001) over HIV-negative control group (N = 215,158)
  - DAD, a large, prospective, multicohort study (N = 23,468) showed association between ARV therapy and risk of MI

The highest prevalence of dyslipidemia was seen in regimens containing drugs from both the PI and NNRTI classes, suggesting a possible additive effect of combinations of drugs from these drug classes.

Dyslipidemia was most strongly correlated with current use of ARV regimens, rather than a history of previous drug regimens.

There was a strong association between elevated total cholesterol level and higher CD4+ cell counts, which was present within each treatment category (PI, NNRTI, NNRTI+PI) except the ARV-therapy-naïve group.

Abnormal Lipid Parameters in HIV Patients

- Abnormalities in lipid parameters can be due to
  - HIV
  - HIV Medications
  - Other Medications
  - Other Diseases
  - Other Factors
  - Genetic predisposition
Can Triglycerides Cause Atherosclerosis?

- Association between TG and CHD in populations is weaker than that between LDL and CHD
- Trials with TG-lowering drugs have not produced definitive evidence
- Severe hyperTG does not commonly cause CVD
- TG accumulation is not a hallmark of atherosclerosis
Foam-cell Formation: Cholesterol entry

Li and Glass. Nat Med 2002
Lipid Profile in Patients With Premature Coronary Artery Disease

**Men**

<table>
<thead>
<tr>
<th>Plasma Lipid Concentration (mg/dL)</th>
<th>Control</th>
<th>CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>138</td>
<td>139</td>
</tr>
<tr>
<td>TG</td>
<td>141</td>
<td>177</td>
</tr>
<tr>
<td>HDL-C</td>
<td>45</td>
<td>35</td>
</tr>
</tbody>
</table>

**Women**

<table>
<thead>
<tr>
<th>Plasma Lipid Concentration (mg/dL)</th>
<th>Control</th>
<th>CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>134</td>
<td>152</td>
</tr>
<tr>
<td>TG</td>
<td>110</td>
<td>219</td>
</tr>
<tr>
<td>HDL-C</td>
<td>57</td>
<td>47</td>
</tr>
</tbody>
</table>

*P* < 0.005 as compared with control.

†*P* < 0.05 as compared with control.

TG Levels and CHD Risk: Meta-analysis of 29 Studies

N=262,525.
*Individuals in top versus bottom third of usual log-TG values, adjusted for at least age, sex, smoking status, lipid concentrations, and (in most studies) blood pressure.
Kuopio Study: Metabolic Syndrome and Mortality

CVD Mortality

RR (95% CI), 3.55 (1.96-6.43)

All-Cause Mortality

RR (95% CI), 2.43 (1.64-3.61)

Follow-up, y

Follow-up, y

Metabolic Syndrome: Yes

Metabolic Syndrome: No

RR = relative risk.

CV Risk Assessment

Advanced lipid testing
hsCRP and Lp-PLA2
cIMT
CAC
Long-Term Prognosis Associated with Absolute Coronary Calcification and CAC Progression

n= 25,257


Budoff M and Raggi P, submitted for pubblication
Lifestyle Changes

Diet (calories, nutrients, alcohol, supplements)
Weight management
Exercise
Smoking cessation
Central Adiposity in HIV is Associated with Increased 5-year Mortality


<table>
<thead>
<tr>
<th>Tertile</th>
<th>VAT:</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terile 1</td>
<td>VAT:</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Tertile 2</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Tertile 3</td>
<td></td>
<td>10.00</td>
<td></td>
</tr>
</tbody>
</table>

Reference:
- Tertile 1: 1.77 (1.03, 3.03) P = 0.039
- Tertile 2: 2.12 (1.13, 3.98) P = 0.019
Effects of a 6-month Lifestyle Modification Program in HIV Pts

Lipid-lowering Management Strategies

- Lifestyle changes
- Statins (plus ezetimibe)
- Fibrates
- Omega 3 supplementation
- Niacin
Benefits of Intensive LDL-C Lowering

# Coadministration of Statins with Protease Inhibitors

<table>
<thead>
<tr>
<th>Statins</th>
<th>Protease Inhibitors</th>
<th>Drug-Drug Interaction</th>
<th>Dosing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>Darunavir; Saquinavir, Fosamprenavir, Lopinavir, Tipranavir Atazanavir Atazanavir + Ritonavir Lopinavir + Ritonavir</td>
<td>Possible increase in rosuvastatin concentration Inc. Rosuv. AUC 213% &amp; Cmax by 6-fold Inc. Rosuv. AUC 3-fold &amp; Cmax 7-fold Inc. Rosuv. AUC 2-fold &amp; Cmax 5-fold</td>
<td>Start 5 mg; Use lowest possible dose Limit dose to 10 mg Limit dose to 10 mg Limit dose to 10 mg</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>All Protease Inhibitors Nelfinavir Fosamprenavir+/-Ritonavir Darunavir or Saquinvir + Tipranavir+ Ritonavir Telaprevir</td>
<td>Increase atorvastatin concentration Ritonavir</td>
<td>Use lowest possible dose Limit dose to 40 mg Limit dose to 20mg Limit dose to 20 mg AVOID AVOID</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Darunavir Lopinavir+-/Ritonavir Saquinavir Darunavir/Ritonavir</td>
<td>Increases prava-concentration Increases pravastatin -concentration May decrease prava-concentration (~50%) Inc. pravastatin AUC 81% &amp; Cmax 63%</td>
<td>Use lowest possible dose No dose adjustment (FDA) No dose adjustment (FDA)</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Atazanavir Atazanavir+ Ritonavir Darunavir+Ritanavir Lopinavir+Ritonavir</td>
<td>31% increase in pitavastatin AUC 20-26% decrease in pitavastatin AUC 20-26% decrease in pitavastatin AUC</td>
<td>No dosage adjustments.</td>
</tr>
<tr>
<td>Simvastatin or Lovastatin</td>
<td>All Protease Inhibitors inc. Boceprevir or Telaprevir</td>
<td>Significant increases in simvastatin or lovastatin concentrations</td>
<td>ALL Contraindicated</td>
</tr>
</tbody>
</table>

Pitavastatin and Lopinavir/Ritonavir PK Study

Pitavastatin Plasma PK Profile

- Mean plasma Concentration vs time profile of pitavastatin administered and measured alone vs coadministered with lopinavir/ritonavir
- Lopinavir/Ritonavir 800mg/200mg, Pitavastatin 4mg
- Pharmacokinetics data obtained from 23 healthy subjects that completed the study
- ng/mL=nanograms per milliliter; PK=pharmacokinetic

Change in AUC $\downarrow$ 20%
Change in Cmax $\downarrow$ 4%

LIV-MT-0372, PS78181.
Pitavastatin and Lopinavir/Ritonavir PK Study

Lopinavir Plasma PK Profile

- Mean plasma Concentration vs time profile of pitavastatin administered and measured alone vs coadministered with lopinavir/ritonavir
- Lopinavir/Ritonavir 800mg/200mg, Pitavastatin 4mg
- Pharmacokinetics data obtained from 23 healthy subjects that completed the study
- ng/mL=nanograms per milliliter; PK=pharmacokinetic

LIV-MT-0372, PS78181

Change in AUC$_{0-T}$ ↓ 9%
Change in Cmax ↓ 7%
• Mean plasma Concentration vs time profile of pitavastatin administered and measured alone vs coadministered with lopinavir/ritonavir
• Lopinavir/Ritonavir 800mg/200mg, Pitavastatin 4mg
• Pharmacokinetics data obtained from 23 healthy subjects that completed the study
• ng/mL=nanograms per milliliter; PK=pharmacokinetic

Change in AUC$_{0-T}$ ↓ 11%
Change in Cmax ↓ 11%

LIV-MT-0372, PS78181
Pitavastatin and Darunavir/Ritonavir PK Study
Pitavastatin Plasma PK Profile

- Mean plasma Concentration vs time profile of pitavastatin administered and measured alone vs coadministered with darunavir/ritonavir
- Darunavir/Ritonavir 800mg/100mg, Pitavastatin 4mg
- Pharmacokinetics data obtained from 27 healthy subjects that completed the study
- ng/mL=nanograms per milliliter; PK=pharmacokinetic

Data on file:04/26/2012:
Pitavastatin and Darunavir/Ritonavir PK Study
Darunavir Plasma PK Profile

Mean plasma Concentration vs time profile of pitavastatin administered and measured alone vs coadministered with darunavir/ritonavir
- Darunavir/Ritonavir 800mg/100mg, Pitavastatin 4mg
- Pharmacokinetics data obtained from 27 healthy subjects that completed the study
- ng/mL=nanograms per milliliter; PK=pharmacokinetic

Data on file: 04/26/2012
Pitavastatin and Darunavir/Ritonavir PK Study
Ritonavir Plasma PK Profile

Change in AUC$_{0-T}$ ↑ 8%
Change in Cmax ↑ 2%

- Mean plasma Concentration vs time profile of pitavastatin administered and measured alone vs coadministered with darunavir/ritonavir
- Darunavir/Ritonavir 800mg/100mg, Pitavastatin 4mg
- Pharmacokinetics data obtained from 27 healthy subjects that completed the study
- ng/mL=nanograms per milliliter; PK=pharmacokinetic

Data on file: 04/26/2012:
Lipid-lowering Management Strategies: Fish Oils and Fibrates

♦ Fish oils
  • Known to decrease triglycerides in HIV-infected patients\textsuperscript{1}
  • Well tolerated and have few side effects\textsuperscript{1}
  • Cardiovascular benefit is unclear\textsuperscript{1}

♦ Fibrates
  • Appear to have no pharmacologic interactions with ARVs\textsuperscript{1}
  • Reduce triglycerides by 40\%-50\% in HIV-infected patients; are well tolerated\textsuperscript{1}
  • Most clinical studies report that 1\%-40\% of patients achieved a target of TG ≤200 mg/dL\textsuperscript{1}
  • Less effective than statins for reducing LDL-C\textsuperscript{2}
  • Cardiovascular benefit is unclear\textsuperscript{1}

\textbullet\ HIV=human immunodeficiency virus; ARVs=antiretrovirals; TG=triglyceride; LDL-C=low-density lipoprotein cholesterol

Lipid Changes on Atorvastatin in the TNT Study

PROVE IT-TIMI 22 Trial Subanalysis: Relationship Between LDL-C, TG, and CHD

Estimates of Death, MI, and Recurrent ACS Between 30 days and 2 years of Follow-Up

According to Achieved LDL-C <70 mg/dL

According to Achieved TG <150 mg/dL

19%

27%

HR: hazard ratio

Subanalysis of the PROVE IT-TIMI 22 study in 4162 patients hospitalized for ACS and randomized to atorvastatin 80 mg or pravastatin 40 mg, with follow-up through 2 years.
Fibrate Efficacy Overview: CHD Risk Reduced 35% in Patients with Dyslipidemia

Overview of fibrate efficacy in clinical trials

CHD events significantly reduced in patients with dyslipidemia

- Helsinki Heart Study, TG 204 mg/dl HDL-C <42 mg/dl; b The Veterans Affairs Cooperative Studies Program High Density Lipoprotein Cholesterol Intervention Trial, TG>180; c Bezafibrate Infarction Prevention, TG>200; d Fibrate Intervention and Event Lowering in Diabetes, TG>204; HDL-C<40; e Action to Control Cardiovascular Risk in Diabetes, TG>204; HDL-C<34.

Patient Subgroup – TG >150mg/dL and HDL <40mg/dL: JELIS

Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS)

Fig. 3. Effects of EPA on the incidence of MCE for the high TG/low HDL-C group. Hazard ratio and P value adjusted for age, gender, smoking, diabetes, and hypertension. HR, hazard ratio; CI, confidence interval.

Lipid-lowering Management Strategies: Niacin

- Increases HDL-C
- Commonly causes flushing
- Can cause insulin resistance
- Affects glycemic control in patients with diabetes
- Should be used with caution in HIV patients who exhibit insulin resistance or lipodystrophy
- Short-term use of niacin has shown to improve endothelial function in HIV-infected patients with low HDL-C


• HDL-C=high-density lipoprotein cholesterol; HIV=human immunodeficiency virus
AIM HIGH: No Measurable Effects of Niacin Added to Simvastatin

- 3414 Subjects with CAD
- Simvastatin alone or with ezetimibe ± ER niacin
- On niacin TG 120 mg/dL, HDL 44 mg/dL, LDL 65 mg/dL
- Controls TG 152 mg/dL, HDL 38 mg/dL, LDL 67 mg/dL
- 282 subjects on niacin had primary endpoint (16.4%)
- 274 controls had primary endpoint (16.2%)

NEJM, 2011; 365: 2255-2267
AIM-HIGH—Results

1st Endpoint: CHD Death, nonfatal MI, ischemic stroke, high-risk ACS, hospitalization for coronary or cerebrovascular revascularization

HR 1.02, 95% CI 0.87, 1.21
Log-rank P value = 0.79

N at risk
Monotherapy: 1696, Combination Therapy: 1718

Time (years)
0 1 2 3 4

Cumulative % with Primary Outcome
0 10 20 30 40 50

Conclusions

- The dyslipidemia of HIV patients may have different causes and proper diagnosis will help management
- CV risk assessment as in other patient types
- Lifestyle changes (weight loss) very effective in adjusting glucose and TG/HDL levels
- Statins to be used according to FDA restrictions
- Fibrates, niacins, and omega 3 fats have not provided definitive evidence of CV benefits yet