HIV and Cardiovascular/Lipid Disorders

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National Jewish Health
Denver, Colorado
Possible risk factors for atherosclerotic cardiovascular events in patients infected with HIV are:

A. Traditional cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, smoking, etc.

B. Some antiretroviral agents

C. HIV infection

D. A and B

E. A and C

F. A, B, and C
According to NCEP guidelines, which of the following lipid measurements are predictive of cardiovascular events?

A. Elevated LDL
B. Elevated non-HDL cholesterol
C. Total cholesterol
D. Elevated triglycerides
E. A, B, and D
F. A and D
G. A and B
H. A and C
Do you calculate the Framingham 10-year cardiovascular risk on your HIV-infected patients?

A. Yes. I use my computer or a portable device
B. No. I use a different calculation
C. No. I don’t know how
D. No. I don’t have time
E. None of the above
Learning Objectives
Upon completion of this presentation, learners should be better able to:

- Recognize that cardiovascular disease in HIV-infected individuals occurs at younger ages and at a higher incidence than the general population.

- Consider traditional, antiretroviral, and inflammatory risk factors when managing cardiovascular disease prevention in patients infected with HIV.

- Manage lipids according to IDSA/AACTG modified National Cholesterol Education Program (NCEP) guidelines.
Faculty and Planning Committee Disclosures
Please consult your program book.

Off-Label Disclosure
There will be no off-label/investigational uses discussed in this presentation.
Cardiovascular Disease in the General Population
Projected Global Deaths (All ages, 2005)

The Magnitude of CAD

- 1 million Americans suffer an acute coronary event each year...over one half million Americans die each year from coronary disease
- 150,000 die from sudden cardiac death
- 63% of women and 50% of men had no known coronary artery disease
- 68% of AMI occur in patients without significant stenosis

American Heart Association/American Stroke Association (2009). Heart and Stroke Statistical Update
Cardiovascular Disease in the HIV-Infected Population
D:A:D
(Data Collection on Adverse Drug Events of Anti-HIV Drugs)
Causes of Death Through October 2007

- HIV-infected patients followed from study entry until death or last follow-up

- There were 2192 deaths in 33,347 people followed for 158,959 person-years (PY); Rate = 1.4/100 PY

- Risk factors for overall death were:
  - Smoking
  - Low BMI (<18 kg/m²)
  - Diabetes
  - HTN
  - HBV/HCV co-infection
  - Low current CD4
  - Higher HIV RNA

Smith C, et al. 16th CROI 2009;Abstract 145.
Overall Mortality and Causes of Death

Overall Mortality*

Years Since Seroconversion*

* N=7680 seroconverters from 22 cohorts, of whom 1938 died (26%; 1424 pre-HAART and 514 during HAART).

Causes of Death†

† No change in the following causes of death: AIDS-related malignancy, other infections, organ failure, and unknown causes.

Risk of MI While Admitted to Either of Two Hospitals in Boston According to HIV Status

A

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>Non-HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>189</td>
<td>26,142</td>
</tr>
<tr>
<td>n</td>
<td>3,851</td>
<td>1,044,589</td>
</tr>
<tr>
<td>RR</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

B

*Adjusted for age, gender, race, hypertension, diabetes and dyslipidaemia.

Triant et al., JCEM, 2007, 92(7):2506-2512.
Contributing Factors to Cardiovascular Disease

• General Population
  – Traditional Cardiovascular Risk Factors
  – The Role of Inflammation

• HIV-infected Population
  – Traditional Cardiovascular Risk Factors
  – Antiretroviral Therapy
  – HIV-associated Inflammation
Traditional Cardiovascular Risk Factors
Management in the General Population
CHD Risk Factors

Gender
Family History
Age

Abdominal Obesity*
Inactivity, Diet
Cigarette Smoking
Hyper-tension*
Hyper-glycemia
Insulin Resistance*

Lipids*

Brown = Modifiable
Red = Nonmodifiable

*Metabolic syndrome

Diabetes

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Major CHD Risk Factors

Modifiable

• Cigarette smoking
• Diabetes*
• Hypertension:
  – BP ≥140/90 mm Hg or on antihypertensive medication
  (≥130/80 if diabetic or CKD\textsuperscript{∞})
• Low HDL:
  – Male <40 mg/dL
  – Female < 50 mg/dL

Non-Modifiable

• Family history of premature CHD (1st-degree relative):
  – Male relative age <55 yrs
  – Female relative age <65 yrs
• Age
  – Male ≥45 years
  – Female ≥55 years

*Diabetes is regarded as a CHD risk equivalent
\textsuperscript{∞} Chronic Kidney Disease

## 10-Year CHD Risk Framingham Score

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 34</td>
<td>-7</td>
</tr>
<tr>
<td>35 – 39</td>
<td>-3</td>
</tr>
<tr>
<td>40 – 44</td>
<td>0</td>
</tr>
<tr>
<td>45 – 49</td>
<td>3</td>
</tr>
<tr>
<td>50 – 54</td>
<td>6</td>
</tr>
<tr>
<td>55 – 59</td>
<td>8</td>
</tr>
<tr>
<td>60 – 64</td>
<td>10</td>
</tr>
<tr>
<td>65 – 69</td>
<td>12</td>
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<tr>
<td>70 – 74</td>
<td>14</td>
</tr>
<tr>
<td>75 – 79</td>
<td>16</td>
</tr>
</tbody>
</table>

### Total Cholesterol (mg/dL)

<table>
<thead>
<tr>
<th>Age 20 – 39</th>
<th>Age 40 – 49</th>
<th>Age 50 – 59</th>
<th>Age 60 – 69</th>
<th>Age 70 – 79</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;160</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>160 – 199</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>200 – 239</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>240 – 279</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>≥280</td>
<td>13</td>
<td>10</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

### HDL (mg/dL)

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
</tr>
<tr>
<td>50 – 59</td>
</tr>
<tr>
<td>40 – 49</td>
</tr>
<tr>
<td>&lt;40</td>
</tr>
</tbody>
</table>

### Smoking

<table>
<thead>
<tr>
<th>Age 20 – 39</th>
<th>Age 40 – 49</th>
<th>Age 50 – 59</th>
<th>Age 60 – 69</th>
<th>Age 70 – 79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmoker</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smoker</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

### Systolic BP (mm Hg)

<table>
<thead>
<tr>
<th>If Untreated</th>
<th>If Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>0</td>
</tr>
<tr>
<td>120 – 129</td>
<td>1</td>
</tr>
<tr>
<td>130 – 139</td>
<td>2</td>
</tr>
<tr>
<td>140 – 159</td>
<td>3</td>
</tr>
<tr>
<td>≥160</td>
<td>4</td>
</tr>
</tbody>
</table>
## 10-Year CHD Risk Framingham Score

<table>
<thead>
<tr>
<th>Point Total</th>
<th>10-Year Risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
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<td>13</td>
<td>2</td>
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<tr>
<td>14</td>
<td>2</td>
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<td>15</td>
<td>3</td>
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<td>16</td>
<td>4</td>
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<td>6</td>
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<td>8</td>
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<td>14</td>
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<td>22</td>
<td>17</td>
</tr>
<tr>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>≥25</td>
<td>≥30</td>
</tr>
</tbody>
</table>

10-Year Risk: ____%
CHD Risk Prediction

- 2 Risk Factors*

High

Moderately High

Moderate

*If ≤ 1 Risk Factors: 10 Year Risk < 10% and is Low Risk

>20%, CHD, or DM

10%-20%

<10%
## LDL Cholesterol Goals

(Triglycerides <200 mg/dL)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>LDL Level - Initiate TLC*</th>
<th>LDL Level - Consider Drug TX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LR</strong></td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL</td>
</tr>
<tr>
<td>0-1 Risk Factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MR and MHR</strong></td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>10-20%: ≥130 mg/dL &lt;10%: ≥160 mg/dL</td>
</tr>
<tr>
<td>≥2 Risk Factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10 yr risk ≤20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>&lt;100 mg/dL</td>
<td>≥100 mg/dL</td>
<td>≥130 mg/dL Optional &lt;100 mg/dL</td>
</tr>
<tr>
<td>≥2 Risk Factors or CRE</td>
<td>Optional &lt; 70 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10 yr risk &gt;20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Therapeutic lifestyle changes*  
## Non-HDL Cholesterol Goals

*(Triglycerides >200 mg/dL)*

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>N-HDL-C Goal</th>
<th>N-HDL-C Initiate TLC*</th>
<th>N-HDL-C Consider Drug TX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LR</strong> 0-1 Risk Factor</td>
<td>&lt;190 mg/dL</td>
<td>≥190 mg/dL</td>
<td>≥190 mg/dL</td>
</tr>
<tr>
<td><strong>MR and MHR</strong> &gt;2 Risk Factors (10 yr risk ≤20%)</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>&lt;10%: ≤ 190 mg/dL 10-20%: ≥ 160 mg/dL</td>
</tr>
<tr>
<td><strong>HR</strong> &gt;2 Risk Factors or CRE (10 yr risk &gt;20%)</td>
<td>&lt;130 mg/dL Optional &lt; 100 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥ 160 mg/dL Optional &lt; 130 mg/dL</td>
</tr>
</tbody>
</table>

*Therapeutic lifestyle changes

Reduction of LDL-C Decreases Risk of CVD

Lipid Management

• Therapeutic Lifestyle Changes
  – Restriction of saturated fat (<7% of total calories) and cholesterol (<200 mg/day)\textsuperscript{1}
  – Promotion of daily physical activity and weight management\textsuperscript{1}
  – Increase in omega-3 fatty acid consumption\textsuperscript{2}
  – Smoking cessation\textsuperscript{1}

• LDL-C Management\textsuperscript{3}
  – Statin therapy to meet NCEP/ATP III LDL Goals
  – Statins are anti-inflammatory
  – Statins lower LDL-C by increasing expression of LDL receptors
    • Lovastatin and Simvastatin contraindicated
    • Pravastatin contraindicated with darunavir

\textsuperscript{1}NCEP/ATP III. \textit{JAMA}. 2001;285:2486-2497.
\textsuperscript{2}www.americanheart.org/presenter.jhtml?identifier=4632.
\textsuperscript{3}Grundy S. \textit{Circulation}. 2004;110:227-239.
Lipid Management
Triglyceride 200/500 Rule

• If TG level 200-499 mg/dL, adding a fibrate to statins is optional
  – TG < 200 mg/dL: Apolipoprotein B ≈ LDL
  – TG > 200 mg/dL: Apolipoprotein B ≈ non-HDL cholesterol
    • Non-HDL cholesterol goal is 30 mg/dL higher than LDL-C goal

• If TG level ≥500 mg/dL, add a fibrate **before** starting LDL-lowering therapy
  – TG > 500 mg/dL cannot be hydrolyzed off the Apolipoprotein B complex.
  – Failure to hydrolyze TGs traps LDL in the Apo B complex preventing release of LDL into the circulation for processing by LDL receptors (statins increase LDL receptor expression)
  – This results in deposition of LDL into the intima media of the artery.

Traditional Cardiovascular Risk Factors in HIV-Infected
D:A:D: Prevalence of Cardiac Risk Factors in Cohort of HIV-Infected Patients


FHx = family history of CHD; PHx = previous history of CHD; BMI = body mass index; HTN = hypertension; DM = diabetes mellitus; HC = hypercholesterolemia; TG = triglycerides
Modifiable Risk Factors Increased Among HIV vs. General Population

![Bar chart showing modifiable risk factors increased among HIV vs. general population.](chart)

- Smoking: APROCO Cohort (HIV+) vs. MONICA Sample (HIV-)
  - APROCO Cohort (N=223 HIV+ men on PI-containing regimen)
  - MONICA Sample (N=527 HIV- men)
  - P < 0.0001

- Hypertension: APROCO Cohort (HIV+) vs. MONICA Sample (HIV-)
  - P < 0.01

- HDL < 40 mg/dL: APROCO Cohort (HIV+) vs. MONICA Sample (HIV-)
  - P < 0.0001

D:A:D Study: Is the Framingham Risk Estimation Valid in HIV-Infected Patients?

Observed and predicted MI rates according to ART exposure (D:A:D Study; n=23,468)

Incidence of MIs is low: 345 over 94,469 patient-years’ follow-up (3.7/1,000 patient-years)

- Observed rates
- Best estimate of predicted rates

CHD Risk Factors in HIV-Infected Population

- Gender
- Family History
- Age
- Lipids*
- Inactivity, Diet
- Abdominal Obesity*
- Cigarette Smoking
- Hypertension*
- Insulin Resistance*
- Hyperglycemia

HIV Infection

Brown = Modifiable
Red = Nonmodifiable

ART

ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals
Antiretroviral Therapy and Cardiovascular Disease
D:A:D

PIs and Incidence of MI

An increase in incident CVD is associated with duration of PI-containing combination antiretroviral therapy

D:A:D Study: NRTI Use and Risk of MI

- D:A:D study
  - 33,347 HIV patients on HAART
- 517 patients developed MI over 157,912 person-years of follow-up
  - Recent didanosine use (n=124)
  - Recent abacavir use (n=192)
  - Recent other NRTI use (n=237)
- Recent use of abacavir and didanosine (but not cumulative or past use) associated with increased risk of MI
  - Risk persists regardless of length of use
  - Risk was reversible with discontinuation of drugs
  - Most MIs occurred in patients with existing cardiovascular risk factors

<table>
<thead>
<tr>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine 0.97 (0.76-1.25)</td>
<td>0.82</td>
</tr>
<tr>
<td>Stavudine 1.00 (0.76-1.32)</td>
<td>0.93</td>
</tr>
<tr>
<td>Lamivudine 1.25 (0.96-1.62)</td>
<td>0.10</td>
</tr>
<tr>
<td>Abacavir 1.90 (1.47-2.45)</td>
<td>0.001</td>
</tr>
<tr>
<td>Didanosine 1.49 (1.14-1.95)</td>
<td>0.003</td>
</tr>
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Implications:
Use caution in the interpretation of these preliminary findings and await further studies

D:A:D Study: NRTI Use and Risk of MI

- **D:A:D study**
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<td>0.003</td>
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</tbody>
</table>

**Implications:**
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SMART Study Design

- Randomized, controlled study of treatment interruption
- Primary endpoint: development of OI or death from any cause
- Secondary endpoint: development of major CV, renal, or hepatic disease

Patients with CD4+ >350 cells/mm$^3$ (n=5472)

Virologic Suppression (VS) Strategy

Immediate or Continued ART

Drug Conservation (DC) Strategy

Deferred ART*
(until CD4+ <250 cells/mm$^3$)

* Patients in the deferred ART arm initiated therapy when CD4+ count decreased to <250 cells/mm$^3$, until CD4+ count increased to >350 cells/mm$^3$ with repeated interruptions and re-initiation at CD4+ cell counts of >350 and <250 cells/mm$^3$, respectively.

SMART Study Results: HIV and Clinical Events

**Opportunistic Disease or Death from Any Cause**
- Hazard ratio, 2.6; 95% CI, 1.9-3.7; P<0.001
- Drug Conservation Group
- Viral Suppression Group

**Major Cardiovascular, Renal or Hepatic Disease**
- Hazard ratio, 1.7; 95% CI, 1.1-2.5; P=0.009
- Drug Conservation Group
- Viral Suppression Group

**No. at Risk**
- Drug conservation: 2720 2074 1666 1301 1040 870 689 540 444 372 280 162
- Viral suppression: 2752 2081 1695 1310 1077 906 724 572 474 388 288 173

SMART Study Group NEJM 2006;355:2283-2296
XXX Study: Drug A + Versus Drug B in HAART Regimen:

- Open-label, non-inferiority study: ART-naïve, HIV+ patients randomized to Drug A or Drug B
- Primary end points: proportion of patients achieving HIV-1 RNA <400 c/mL at Week 48 and treatment discontinuations because of an adverse event
MACS Cohort: Mean Lipid Values Before and After HIV Infection (Treated and Untreated)


[Graph showing mean lipid values before and after HAART treatment, with data points for TC, LDL, and HDL over non-fasting values and years.]
Incidence of CVD events by select factors at baseline* and during observation among 2,005 HOPS patients, January 2002- September 2009.

<table>
<thead>
<tr>
<th>Cumulative antiretroviral exposures since HIV diagnosis</th>
<th># of persons</th>
<th>CVD incidence per 100 py</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to NRTI</td>
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<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>1,941</td>
<td>1.36</td>
<td>0.029</td>
</tr>
<tr>
<td>No</td>
<td>64</td>
<td>3.39</td>
<td>referent</td>
</tr>
<tr>
<td>Exposure to NNRTI</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,470</td>
<td>1.24</td>
<td>0.023</td>
</tr>
<tr>
<td>No</td>
<td>535</td>
<td>1.89</td>
<td>referent</td>
</tr>
<tr>
<td>Exposure to PI</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,602</td>
<td>1.38</td>
<td>0.88</td>
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<tr>
<td>No</td>
<td>403</td>
<td>1.46</td>
<td>referent</td>
</tr>
<tr>
<td>Exposure to zidovudine</td>
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</tr>
<tr>
<td>Yes</td>
<td>1,309</td>
<td>1.38</td>
<td>0.93</td>
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<tr>
<td>No</td>
<td>696</td>
<td>1.43</td>
<td>referent</td>
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</table>

Incidence of CVD events by select factors at baseline* and during observation among 2,005 HOPS patients, January 2002 - September 2009.

<table>
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<th>CVD incidence per 100 py</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to &quot;d-drug&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,222</td>
<td>1.37</td>
<td>0.78</td>
</tr>
<tr>
<td>No</td>
<td>783</td>
<td>1.46</td>
<td>referent</td>
</tr>
<tr>
<td>Exposure to abacavir</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>909</td>
<td>1.29</td>
<td>0.44</td>
</tr>
<tr>
<td>No</td>
<td>1,096</td>
<td>1.49</td>
<td>referent</td>
</tr>
<tr>
<td>Exposure to tenofovir</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,363</td>
<td>0.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>642</td>
<td>2.65</td>
<td>referent</td>
</tr>
<tr>
<td>Exposure to HAART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,931</td>
<td>1.36</td>
<td>0.10</td>
</tr>
<tr>
<td>No</td>
<td>74</td>
<td>2.72</td>
<td>referent</td>
</tr>
</tbody>
</table>

## Inconsistent Results: From major studies on CVD risk in HIV-infected and HAART-treated patients

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study</th>
<th>Event</th>
<th>ARV</th>
<th>Effect</th>
<th>Traditional risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA</td>
<td>36,766</td>
<td>R</td>
<td>1,207 CHD</td>
<td>HAART or PI</td>
<td>No</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>HOPS</td>
<td>1807</td>
<td>P</td>
<td>84 CV events</td>
<td>specific ARVs</td>
<td>No</td>
<td>Age &gt;40 y, diabetes, HTN</td>
</tr>
<tr>
<td>SMART</td>
<td>5472</td>
<td>p</td>
<td>63 CHD</td>
<td>intermittent HAART</td>
<td>No – stopping therapy led to complication</td>
<td>Age</td>
</tr>
<tr>
<td>Kaiser</td>
<td>4408</td>
<td>R</td>
<td>86 MI</td>
<td>PIs</td>
<td>Risk of HIV+ vs. HIV- No risk on PI</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Medi-Cal</td>
<td>28,513</td>
<td>R</td>
<td>NA</td>
<td>ART</td>
<td>Risk with ART in 18–33 year olds</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>DAD</td>
<td>23,490</td>
<td>P</td>
<td>345 MI</td>
<td>cART and PI</td>
<td>Yes</td>
<td>Smoking, age, gender, HTN, DM</td>
</tr>
<tr>
<td>French</td>
<td>34,976</td>
<td>R</td>
<td>49 MI</td>
<td>PI</td>
<td>Yes</td>
<td>Age</td>
</tr>
<tr>
<td>Johns Hopkins</td>
<td>2671</td>
<td>Case control</td>
<td>43 CHD</td>
<td>HIV+ vs. HIV-</td>
<td>Yes</td>
<td>Age, HTN, DM</td>
</tr>
<tr>
<td>Frankfurt</td>
<td>4993</td>
<td>R</td>
<td>29 MI</td>
<td>HAART</td>
<td>Yes</td>
<td>Age &gt;40</td>
</tr>
</tbody>
</table>

2. Friis-Møller N, *13th CROI*, Denver 2006, #144

**ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals**
IDSA Recommendations for Dyslipidemia Management in HIV-Infected Patients

- Obtain fasting lipid profile, prior to starting ARVS and within 3 to 6 months of starting new regimen

- Count number of cardiovascular disease (CVD) risk factors and determine level of risk. If ≥2 risk factors, perform a 10-year risk calculation, based on Framingham

- Intervene for modifiable nonlipid risk factors such as diet and smoking

- If lipids remain above threshold based on risk group despite vigorous lifestyle interventions, consider altering ARV therapy or using lipid-lowering drugs

LIPID-LOWERING DRUG THERAPY IS NECESSARY IF:

- Serum LDL cholesterol above threshold, or TG 200-500 mg/dL with elevated non-HDL cholesterol: STATIN

OR

- Serum TG >500 mg/dL: FIBRATE

Adapted with permission from Dube MP, et al. Clin Infect Dis. 2003;37:613-627. Figure 1. Publisher: University of Chicago Press. © 2003 The Infectious Diseases Society of America. All rights reserved.
Inflammation and Cardiovascular Disease in the General Population
Early Appearance of Atherosclerosis

Prevalence of Fibrous Plaque Lesions in Coronary Arteries

P = 0.001 for trend toward increasing prevalence with age in coronary arteries.

Endothelial Dysfunction in Atherosclerosis

NEJM.1999;340:115-126
Fatty-Streak Formation in Atherosclerosis

NEJM.1999;340:115-126
Formation of an Advanced, Complicated Lesion of Atherosclerosis

NEJM.1999;340:115-126
Evolution of the Atherosclerotic Plaque

Increased States of Inflammation Weaken the Fibrous Cap

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Increased States of Inflammation Weaken the Fibrous Cap

"In states characterized by heightened inflammation, the fibrous cap is under double attack"
Unstable Fibrous Plaques in Atherosclerosis

NEJM.1999;340:115-126

ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals
Molecular Factors Involved in Plaque Evolution


ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals
It's the doughnut, not the hole
Inflammation and Cardiovascular Disease in the HIV-Infected Population
D:A:D Study: Risk Factors for CHD in an HIV+ Population

Drug class: not sufficient # of events to examine yet
Adjusted for BMI, HIV risk, cohort, calendar year and race

Relative Rate of Myocardial Infarction (95% CI)

Better ↔ Worse

- cART Therapy
- Age per 5 years older
- Male gender
- Previous CVD
- Smoking
- Family history
- Diabetes mellitus (yes versus no)
- Hypertension (yes versus no)

RR 1.17 (1.08-1.26)


ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals
HIV Outpatient Study (HOPS)


Relative Rate of Cardiovascular Event (95% CI)

Multivariable Poisson regression model

<table>
<thead>
<tr>
<th>Factor</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>cART Therapy</td>
<td>1.00</td>
<td>(0.53-1.34)</td>
</tr>
<tr>
<td>Age per 5 years older</td>
<td>1.07</td>
<td>(1.05-1.10)</td>
</tr>
<tr>
<td>LDL/non-HDL-C &gt; Goal</td>
<td>1.63</td>
<td>(1.08-2.46)</td>
</tr>
<tr>
<td>HDL &lt;40 mg/dL</td>
<td>1.56</td>
<td>(1.02-2.39)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.99</td>
<td>(1.32-3.01)</td>
</tr>
<tr>
<td>Baseline CD4 &lt;350 cells/mm³</td>
<td>1.78</td>
<td>(1.22-2.58)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.95</td>
<td>(1.27-2.98)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.29</td>
<td>(1.18-2.13)</td>
</tr>
</tbody>
</table>

ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals
HIV Outpatient Study (HOPS)

Multivariable Poisson regression model


ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals
Attributable Risk for CVD


ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals
Attributable Risk for CVD

- High Risk: 57.7%
- Moderately High Risk: 47.1%
- Moderate Risk: 26.4%
- CD4 < 500: 25.6%


ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals
Improved immune function decreases the risk of non–HIV-related death

- n=23,000+
- 1,248 (5.3%) deaths 2000 - 2004 (1.6/100 person-years)
  - Of these, 82% on ART
- Incidence of CV-related mortality lower than other non–HIV-related deaths


**D:A:D Study: Relative Risk of Death According to Immune Function and Specific Cause**

<table>
<thead>
<tr>
<th>Latest CD4+ count (cells/mm³)</th>
<th>Relative Risk of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>1.0</td>
</tr>
<tr>
<td>50–99</td>
<td>10</td>
</tr>
<tr>
<td>100–199</td>
<td>100</td>
</tr>
<tr>
<td>200–349</td>
<td>1000</td>
</tr>
<tr>
<td>350–499</td>
<td>10000</td>
</tr>
<tr>
<td>&gt;500</td>
<td>100000</td>
</tr>
</tbody>
</table>

- **HIV**
- **Liver**
- **Malignancy**
- **Heart**

**ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals**
FRAM: The Effects of HIV on CHD/Death Results

• Comparing mortality risk in 468 HIV-infected vs 278 controls, ages 33-45: 7X higher death risk in the HIV group ($P<0.0001$)

• After adjusting for traditional CV risk factors: the death risk remained 3.4X higher in people with HIV ($P = 0.009$)

• Current smoking (but not past smoking) nearly tripled the death risk ($HR = 2.73$, $P = 0.0001$)

• Every added 10 years of age raised the risk more than 60% ($HR = 1.61$, $P<0.0001$)

• Every doubling of the baseline CD4 cell count lowered the risk 35% ($HR = 0.65$, $P<0.0001$)

FRAM = Fat Redistribution and Metabolic Change in HIV Infection Study

FRAM: Fat Redistribution and Metabolic Change in HIV Infection Study

- HIV itself emerged as a mortality risk factor as potent as:
  - Age
  - Male gender
  - Smoking
  - Diabetes

Modrich L, et al. 16th CROI 2009;Abstract 146.
Summary
Contributors to CVD Risk

Traditional CVD Risk Factors
- ICAM
- VCAM
- IL-6
- RANTES
- CCR2
- CCR5
- HDL
- TGs
- TNF-alpha
- Fibroblasts
- Metalloproteinases
- Collagenases
- Oxidized LDL
- IL-1
- CD4 Cells
- Glycated LDL
- MCP-1
- Interferon-gamma
- IL-2
- Foam Cells
- Smooth Muscle Cells

HIV Infection

Antiretroviral Therapy
Summary
Goal: Reduction of CHD Risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated HIV</td>
<td>Initiate HAART</td>
</tr>
<tr>
<td>Traditional risk factors</td>
<td>Lifestyle modifications (TLC) ± pharmacologic therapy (NCEP Guidelines)</td>
</tr>
<tr>
<td>Lipid effects of HAART</td>
<td>Avoid specific anti-retrovirals if lipid-lowering therapy and TLCs are ineffective</td>
</tr>
</tbody>
</table>

ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals
Mate, doesn’t HIV infection add at least some additional risk for cardiovascular disease? Questions?