Cardiovascular Risk and HIV Infection

Albany Medical College
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Disclosure Information

Research Support: Pfizer (Wyeth pneumococcal vaccine clinical trial)
Overview

- Coronary Heart Disease
  - Role of antiretrovirals
  - Role of HIV
  - Implications for management

Question 1

In general, HIV-infected patients are at increased risk of coronary heart disease compared to age-matched HIV-uninfected patients

1. Strongly Agree
2. Agree
3. Neutral
4. Disagree
5. Strongly Disagree
Rates of MI Appear to be Increased in HIV+ vs. HIV-

- Kaiser N. Calif 1996-2006: age-adjusted admission rate for CHD/MI 3.7 per 1000 person-yr in HIV+ vs. 2.2 in HIV-
- Calif Medicaid: CHD incidence higher in HIV+ men < 34 y.o. (RR 2-7), HIV+ women < 44 y.o. (RR 1.5-2.5)
- French hospitals: Men on PI > 30 mos RR of MI 2.9 vs. general population
- Denmark: 1st hospitalization for MI HIV+ on cART RR 2.1 vs. general population
- Boston hospitals: hospitalization for MI adjusted RR 1.75 for HIV+


How Much CVD is There?

- D:A:D and EuroSIDA -- Non-AIDS events more common than AIDS events and a significant proportion were due to CVD

Case 1

46 y.o. man with HIV (ART naïve) & diabetes mellitus. Labs: CD4 650 cells/mm³, HIV RNA 46,000 copies/ml, HgbA1c 7.2%, TC 280, TG 280, HDL-C 32, LDL 120 mg/dL.

What would you recommend with regard to HIV therapy?

1. Defer ART as it may increase his risk of MI
2. Discuss initiating ART as it may decrease his risk of MI
3. I’m unsure
Incidence of Myocardial Infarction According to cART Exposure


Multifactorial Etiology of Dyslipidemia

Traditional risk factors

HIV-related factors

Antiretroviral-related factors
Effects of Antiretroviral Therapy on Lipids

- Effects of specific drugs may be difficult to determine given their use in combinations
  - Limited data on monotherapy of several agents in healthy volunteers
  - “Return to health” phenomenon*
- Differences between and within classes of antiretrovirals
- Regimens may have beneficial and deleterious effects on different lipid parameters

*Riddler S et al. JAMA. 2003;289:2978-2982

Effects of Antiretroviral Therapy on Lipids

- LDL-C tends to go up modestly with virtually all regimens
- **PIs**: Major effect of most boosted PI regimens is increased TG and non–HDL-C, but HDL-C typically increases as well
  - Unboosted ATV,fAPV have minimal effects on lipids
- **NNRTIs**: Increase HDL-C
  - EFV associated with greater LDL-C and TG increases than NVP (but beneficial effects on HDL-C)
- **NRTIs**: d4T and ZDV associated with ↑ TG, ↑ LDL relative to TDF and ABC
- **New classes**: MVC and RAL do not appear to adversely affect lipids
**Effect of Exposure to PI and NNRTI – before and after Adjusting for Lipids**

- **PI exposure** (per additional year) - Relative Rate of MI (95% CI):
  - RR 1.16
  - RR 1.10

- **NNRTI exposure** (per additional year) - Relative Rate of MI (95% CI):
  - RR 1.05
  - RR 1.00

* Adjusted for sex, age, cohort, calendar year, prior CVD, family history of CVD, smoking, body-mass index, the other drug class

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**D:A:D Study**

- Slight attenuation of IDV, LPV/r RR after adjusting for lipid changes

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D:A:D Study: Increased Risk of MI Associated With Recent ABC or dDI Use Remained After Additional Adjustment for Factors Influenced by ART

No further adjustment
Adjustment also for:
- Latest CD4 cell count
- Latest VL
- Latest lipids
- Latest blood pressure
- Diabetes
- Fat loss/gain
- Latest glucose

*Still using or stopped within last 6 months.
*b All data depicted were also adjusted for demographic factors, calendar year, cohort, CV risk factors that are unlikely to be modified strongly by ART use and cumulative exposure to other antiretroviral drugs.


Conflicting Data on Risk of ABC and CHD

- Studies supporting ABC-MI link:
  - Observational Studies
    - D:A:D Study ¹
    - Viral suppression arm of SMART Trial ²
    - French Hospital Database Study ³
    - Population based study in Denmark ³b
    - ARV Switch Studies
      - STEAL Study (8 CVD events for ABC/3TC vs. 1 for TDF/FTC) ⁴
    - Pathogenic Marker Studies
      - Platelet hyperactivity increased with ABC vs other NRTIs ⁵
      - Increased endothelial dysfunction with ABC vs other NRTIs ⁵
  - Retrospective studies
    - GSK review of clinical trials data ⁷
    - ACTG ALLRT database review ⁹
  - Pathogenic Marker Studies
    - HEAT Trial inflammatory marker substudy ⁸
    - MACS and WIHS inflammation and coagulation marker study ¹⁰

- Studies not supporting ABC-MI link:
  - Retrospective studies
  - GSK review of clinical trials data ⁷
  - ACTG ALLRT database review ⁹
  - Pathogenic Marker Studies
    - HEAT Trial inflammatory marker substudy ⁸
    - MACS and WIHS inflammation and coagulation marker study ¹⁰

Each study has its limitations and as of yet there is no definitive answer to the question of whether ABC causes MI and other CVD.

SMART Study and CV Events

- SMART: 5472 patients (84% on ART) randomized to continuation (viral suppression; VS) or CD4-guided treatment interruption (drug conservation; DC)

<table>
<thead>
<tr>
<th>Events</th>
<th>DC</th>
<th>VS</th>
<th>RH (DC/VS)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical MI, silent MI, CAD requiring invasive procedure or surgery, CVD death</td>
<td>48</td>
<td>31</td>
<td>1.57</td>
<td>1.00–2.46</td>
<td>0.05</td>
</tr>
<tr>
<td>+ Peripheral vascular disease, CHF, CAD requiring medication</td>
<td>76</td>
<td>52</td>
<td>1.49</td>
<td>1.04–2.11</td>
<td>0.03</td>
</tr>
<tr>
<td>+ Unobserved death from unknown cause</td>
<td>84</td>
<td>54</td>
<td>1.58</td>
<td>1.12–2.22</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Conclusion
• Discontinuation strategy associated with higher risk of CV disease


SMART: Intermittent cART Resulted in Worsening of TC-to-HDL Ratio

Baseline:

- On cART
- Off cART

<table>
<thead>
<tr>
<th>DC</th>
<th>VS</th>
<th>Change in Total-to-HDL Cholesterol Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>0.3</td>
<td>P &lt; .0001</td>
</tr>
<tr>
<td>0.2</td>
<td>0.1</td>
<td>P = .02</td>
</tr>
</tbody>
</table>

**SMART: Inflammatory & Coagulation Markers Associated with Mortality**

Subjects in Drug Conservation arm on ART at baseline with HIV-1 RNA ≤ 400 copies/mL (n = 132)


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**Endothelial Dysfunction Improves with Initiation of cART: ACTG A5152s**

Baseline FMD = 3.6% (1.9 – 5.5%)

Kruskal-Wallis Test

ACTG A5095: hsCRP Does Not Decrease with EFV-Based cART

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk 96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>0.2</td>
<td>3</td>
</tr>
<tr>
<td>hs-CRP change from baseline (mg/L)</td>
<td>-20</td>
<td>-20</td>
</tr>
</tbody>
</table>

**Male vs. female:**

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 96</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilcoxon rank sum test</td>
<td>P = 0.13</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Distribution shift by gender</td>
<td>2.5 mg/L [1.0, 5.1]</td>
<td>3.0 mg/L [1.4, 4.9]</td>
<td></td>
</tr>
</tbody>
</table>

Shikuma C, et al. 16th CROI, Montreal, Canada; 2009.

HIV Elite Controllers Have Greater cIMT Than HIV- Controls

- CD8+ CMV-specific T-cell responses correlate with cIMT

2Hsue P et al, AIDS 2006;20:2275-83
T-Cell Activation/Senescence & Subclinical Atherosclerosis

- Carotid intima-medial thickness in WIHS Cohort
  - N = 115 HIV+ (66 on cART; 28 undet VL) and 43 HIV- matched controls (mean age ~46)
  - T-cell activation, senescence associated with carotid lesions and reduced distensibility in HIV+


Pathogenesis Model

Glesby MJ. *HIV and Cardiovascular Risk*. In press, Oxford University Press
Pathogenesis Model

Glesby MJ. *HIV and Cardiovascular Risk*. In press, Oxford University Press
Should We Consider Earlier Initiation of ART to Modify CHD Risk?

↑ HDL
Reduce inflammation, immune activation?
Improve endothelial function

↑ LDL, TGs
↑ Visceral fat
↓ Insulin sensitivity

Evaluation of Dyslipidemia

- Obtain fasting (min 8 hrs) lipid panel (total cholesterol, HDL-C, LDL-C, triglycerides):
  - Before initiating ART
  - 3 to 6 months after starting or switching therapy
    - Consider 1-2 months later if TGs > 200 mg/dL at baseline
  - Annually during stable therapy (with fasting glucose)
- Base interventions on prognosis of HIV disease and assessment of cardiovascular risk using NCEP ATP III guidelines
  - Framingham risk equations if 2 or more major risk factors

Risk Stratification

- Intensity of risk-reduction therapy should be adjusted to patient’s risk of a CHD event
- CHD risk is assessed by three steps
  - Evaluating for the presence of CHD or CHD risk equivalent conditions
  - Counting risk factors
  - Framingham risk assessment in selected patients
- CHD risk is used to set LDL-C and non-HDL-C goals


Case 2

- 37 y.o. man on tenofovir/FTC/lopinavir/ritonavir for 3 years (1st regimen)
- Current CD4 560, HIV RNA < 50
- BMI 32 kg/m²
Fasting Lipids

- Total cholesterol 290 mg/dL
- HDL-C 36 mg/dL
- LDL-C 190 mg/dL
- TGs 320 mg/dL

- No prior lipid panel available

Coronary Heart Disease Risk Factors

- No family h/o premature CHD
- Blood pressure 130/82
- Smoker
- Age < 45
- HDL < 40 mg/dL
- (Obesity)
Risk Stratification

Framingham Point Scores
Estimate of 10-year Risk

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The risk assessment tool below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age:
Gender:
Total Cholesterol
HDL Cholesterol
Smoker
Systolic Blood Pressure
Currently on any medication to treat high blood pressure

Calculate 10-Year Risk

Total cholesterol: Total cholesterol values should be the average of at least two measurements obtained from lipoprotein analysis.

HDL cholesterol: HDL cholesterol values should be the average of at least two measurements obtained from lipoprotein analysis.

Risk score results:
Age: 37
Gender: male
Total Cholesterol: 256 mg/dL
HDL Cholesterol: 36 mg/dL
Smoker: Yes
Systolic Blood Pressure: 130 mmHg
Currently on medication for HBP: No

Risk Score: 15%

*The risk score shown was derived on the basis of an equation. Other NCEP materials, such as ATP III print products, use a point-based system to calculate a risk score that approximates the equation-based one.

To interpret the risk score and for specific information about CHD risk assessment as part of detection, evaluation, and treatment of high blood cholesterol, see ATP III Executive Summary and ATP III At a Glance.
**NCEP Indications for Intervention: Hypercholesterolemia**

<table>
<thead>
<tr>
<th></th>
<th>Initiate dietary intervention</th>
<th>Consider drug therapy</th>
<th>LDL-C goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without CHD and less than 2 risk factors*</td>
<td>≥ 160 mg/dL</td>
<td>≥ 190 mg/dL</td>
<td>&lt; 160 mg/dL</td>
</tr>
<tr>
<td>Without CHD and with 2 or more risk factors</td>
<td>≥ 130 mg/dL</td>
<td>≥ 160 mg/dL</td>
<td>&lt; 130 mg/dL (optional &lt; 100)</td>
</tr>
<tr>
<td>With CHD/risk equivalent</td>
<td>≥ 100 mg/dL</td>
<td>≥ 130 mg/dL</td>
<td>&lt; 100 mg/dL (optional &lt; 70)</td>
</tr>
</tbody>
</table>

* Risk factors include age (men ≥ 45 years, women ≥ 55 years or premature menopause without estrogen replacement therapy), family history of CHD (first-degree male relative with CHD before 55 years of age or first-degree female relative before 65 years of age), current cigarette smoking, hypertension, low HDL cholesterol (< 35 mg/dL), diabetes mellitus. In the presence of high HDL cholesterol (> 60 mg/dL), subtract 1 risk factor.


**Observed MI Rates Track with Predicted Rates by Framingham Risk Equation in D:A:D Cohort**

![Graph showing observed vs predicted MI rates](image)

Case: Therapeutic Lifestyle Change

- Won’t quit smoking due to concern about weight gain
- Already exercises 3-5 times/week
- Referred to dietician
- After 6 weeks of dietary intervention, TGs went down modestly but rest of lipid profile is essentially unchanged (LDL-C = 154 mg/dL)

Lifestyle Intervention: What works

<table>
<thead>
<tr>
<th>Triglycerides</th>
<th>Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very responsive</td>
<td>Can be similar to low dose statin</td>
</tr>
<tr>
<td>Restrict saturated and trans fats, alcohol</td>
<td>Reduce intake of cholesterol-raising nutrients</td>
</tr>
<tr>
<td>Emphasize omega-3 and monounsaturated fats</td>
<td></td>
</tr>
<tr>
<td>Limit simple carbohydrates</td>
<td></td>
</tr>
<tr>
<td>Exercise, weight loss, ? treat insulin resistance</td>
<td>Plant stanols/sterols: 2 g/day</td>
</tr>
<tr>
<td></td>
<td>Soluble fiber: 10-25 g/day</td>
</tr>
<tr>
<td></td>
<td>Supplement with almonds, soy</td>
</tr>
</tbody>
</table>
Question

In addition to ongoing discussion about smoking cessation, which of the following would you recommend next?

1. Start lipid-lowering therapy
2. Change his antiretroviral regimen
3. Do nothing

Diet & Exercise x 4-8 weeks
If not at goal, consider pharmacologic lipid-lowering therapy vs. switching

TC 245
LDL-C 154
HDL-C 37
TGs 270

33% 33% 33%

Tenofovir/FTC/lopinavir/ritonavir
Types of Antiretroviral Switches

- Randomized, controlled trials in virologically suppressed patients show efficacy
  - PI to NNRTI, ABC, or alternative PI (ATV)
  - d4T or ZDV to ABC or TDF
  - EFV to NVP
- Switching LPV/r to RAL improved lipids but resulted in more virologic failures (likely due to lack of fully active NRTI backbones in some subjects)
- Stopping antiretroviral therapy not an option


Switching Antiretrovirals vs Starting Lipid-Lowering Therapy

- Pros
  - May avoid lipid-lowering medications
    - Costs
    - Adverse effects
    - Drug interactions
  - Modest effect in many patients
- Cons
  - Possible loss of viral suppression, emergence of resistance
  - Adverse effects of new antiretrovirals
  - Greater improvements in TC and LDL-C with lipid-lowering therapy
  - No evidence for CHD risk reduction (pleiotropic effects?)
Dyslipidemia: Comparing Switching to Lipid-Lowering Therapy

- 130 NNRTI-naïve patients on PI-based HAART ≥12 m
- Diet-resistant hyperlipidemia
  - Chol > 250, TG > 200
- Randomized to replace PI with NVP or EFV, or to add pravastatin 20 mg or bezafibrate 400 mg
- Adding a lipid-lowering agent more effective than switching to NNRTI


Statins Interact with Protease Inhibitors

Sekar VJ, 8th Intl Workshop Pharm HIV Therapy, 2007; Kiser JJ, JAIDS 2008;47:570-578.
Efavirenz Lowers Exposure to Statins


Prevalence of Cardiac Risk Factors in a Cohort of HIV-Infected Individuals

D:A:D Cohort Study: Smoking and MIs

33,308 HIV-positive pts in 212 clinics in Europe, the US and Australia

432 myocardial infarctions

IRR

5 -

1 -

Never smoked

Baseline status

Stopped smoking during follow-up

Previous

Current

< 1 yr

1-2 yrs

2-3 yrs

3+ yrs

1.73

3.40

3.73

3.00

2.62

2.07

Adjusted for: age, sex, cohort, calendar year, ART, FH of CVD, DM, and time-updated lipids and BP assessments. No start/stop dates, pack-yr data, other lifestyle factors

Petoumenos CROI 2010 #124

Summary

- HIV-infected patients appear to be at increased risk of CHD
  - Direct/indirect effects of antiretroviral therapy; HIV itself
  - Increasing recognition of role of inflammation, immune activation
    - Initiating cART earlier has the potential to reduce CHD risk
- Monitor fasting lipids, glucose
- Switching antiretrovirals (e.g. PI to NNRTI) and lipid-lowering therapy are options for treating dyslipidemia
- Keep drug-drug interactions in mind