HIV, Inflammation, and Cardiovascular Disease

Medical Management of AIDS December 3, 2012
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San Francisco General Hospital
University of California, San Francisco

Many Age-associated Diseases Are More Common in Treated HIV Disease Than in Age-matched Uninfected Persons

- Cardiovascular disease
- Cancer (non-AIDS)
- Bone fractures/osteopenia
- Left ventricular dysfunction
- Liver failure
- Kidney failure
- Cognitive decline
- Frailty
- Immune system

Multiple factors likely explain this increased risk, including co-morbid conditions and antiretroviral drug toxicity

Chronic inflammation is thought to underlie many of these conditions

HIV and Aging

The New York Times
AIDS Patients Face Downside of Living Longer, January 2008

The number of people 50 and older living with HIV in U.S. has increased 77% from 2001 to 2005.

By the year 2015, HIV patients aged 50 and older will account for half of all HIV/AIDS cases in the U.S.

Chronic disease conditions such as cardiovascular disease are an increasing important health issue in this population.

What causes atherosclerosis in HIV patients?

- HAART
  - PI (chronic use)
  - short term HAART is beneficial
  - Abacavir??
  - New classes of HAART?

- Endothelial Dysfunction

- Thrombosis

- HIV infection
  - Inflammation
  - Viral replication
  - LPS (endotoxin)

- PAH
  - Diastolic dysfn
  - Arrhythmias

- Other effects of HIV on the heart

- Traditional Risk Factors
Cases from HIV Cardiology Clinic at SFGH

- Subspecialty clinic focusing on cardiovascular disease and HIV infection

Patient Case
- 44 y.o. male with HIV
  - CD4 280 and VL 50,000
  - Treated with Lopinavir/RTV/ABC/TFV
- Cardiac Risk Factors
  - Blood pressure of 140/90
  - Cigarette smoker
  - HDL of 32 mg/dL, TG 236 mg/dL
  - LDL-C 190 mg/dL, TC 261 mg/dL
  - BMI 30
- Patient referred to Cardiology with dyspnea

What's the pt's 10-year CVD risk?
1. <5%
2. 5-10%
3. 11%-20%
4. >20%

Global CHD risk - Framingham Risk Score
- Age
- LDL-C or TC
- HDL-C
- BP
- DM
- Cigarette smoking

Cardiac Risk Factors:
- 55 year old male
- LDL 190
- HDL of 32
- Blood pressure of 140/90
- Cigarette smoker
- TC 261

NCEP/ATPIII Tool for 10-Year Risk of MI or CHD Death

Risk Assessment Tool for Estimating 10-Year Risk of Developing First CHD (Atherosclerotic and Coronary Atherosclerosis)

Which test should be ordered for initial assessment?

1. Stress echocardiogram
2. Exercise treadmill
3. Exercise with nuclear imaging
4. Cardiac catheterization
5. Carotid ultrasound


Clinical context for exercise testing for patients with suspected ischemic heart disease


Resting EKG on Patient:
Stress echo in HIV:

- 311 HIV-infected individuals with known or suspected CAD.
- 26% with abnormal stress echo
- Abnormal SE provided independent and incremental prognostic value over traditional CV risk factors for CV events.
- Normal SE portends benign prognosis.

*Wever Pinzon, O Circ Cardiovasc Imaging 2011*

**Is the patient’s HIV medication contributing to his risk for CVD?**

1. Yes
2. No
3. Maybe

*but it’s complicated!!!*
**HIV Outpatient Study**

*Incidence of MI in the HOPS Cohort*

- Frequency of MI increased after introduction of PI in 1996 (test for trend, p=0.0125).
- After adjusting for age, sex, smoking, BMI, hyperlipidemia, and HTN, the hazard ratio for PI users compared to non-users was 6.5 (95% CI 0.9-48).

_Holmberg SD et al Lancet 2002._

**French Hospital Database**

<table>
<thead>
<tr>
<th>Year</th>
<th>Death any cause</th>
<th>Admission for cvd</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-1989</td>
<td>10.0</td>
<td>0.8 (0.5-1.3)</td>
</tr>
<tr>
<td>1990-1999</td>
<td>15.9</td>
<td>1.5 (0.8-2.5)</td>
</tr>
<tr>
<td>2000-2005</td>
<td>33.8</td>
<td>2.0 (1.5-5.0)</td>
</tr>
</tbody>
</table>

_Mary-Krause J et al AIDS 2003._

**VA Study of HIV-Infected Patients**

*Data on Adverse Events of Anti-HIV Drugs (DAD Study)*

- After adjusting for CV risk factors (but not lipids), pts on PI had 16% increase in risk of MI per year vs. 5% per year in pts on NNRTI.

What causes atherosclerosis in HIV patients?

- HAART

What causes atherosclerosis in HIV patients?

- HAART
  - PI (chronic use)

HIV is Independently Associated with IMT

- At baseline, HIV patients had greater IMT compared to controls
- Traditional CAD risk factors (age, LDL-C, and HTN) and advanced immunodeficiency (nadir CD4 <200) were independently associated with IMT in HIV-infected individuals
- Patients with HIV had accelerated progression of IMT compared to non-infected controls
- HIV infection was an independent predictor of higher IMT

HIV and IMT in FRAM

- 433 HIV pts and 5749 controls
- HIV pts had higher internal carotid IMT after adjustment for traditional risk factors (+0.148mm, p=0.0001) vs. controls
- HIV pts had higher common carotid IMT vs. controls (+0.033mm, p=0.005)
- Association of HIV infection to IMT similar to DM, smoking, and a 5-9 increase in age.

Grunfeld C et al AIDS 2009

Hsieh et al Circulation 2004
HIV and MI:

- Database of 1.7 million pts tx'd at MGH and BWH since 1993
- Risk of MI almost doubled in all those with HIV (RR 1.89, P<0.0001), even after adjustment for traditional risk factors
- HIV-infected women had higher rates of MI than HIV-infected men (RR 2.96 compared to 1.4 for men)
- Cigarette smoking data available in 22% of HIV patients only

Triant V et al J Clin Endo Metab 2007

Higher Restenosis in HIV Patients

- HIV patients with acute coronary syndromes are more than a decade younger than HIV-negative patients, more likely to be male (50 vs 61) cigarette smokers and have a low HDL cholesterol
- HIV patients referred for PTCA have significantly higher restenosis rates as compared to HIV-negative
- HIV patients had 30% MACE rate after coronary intervention, but treatment with DES was associated with lower rates.


What causes atherosclerosis in HIV patients?

- HAART
  - PI (chronic use)
- HIV infection

Patient Case

- 44 y.o. male with HIV-1 infection
  - CD4+ count 280 cells/mm³ and VL 50,000 c/mL
  - Treated with LPV/RTV + ABC + TDF
- Cardiac risk factors
  - Blood pressure of 140/90 mm Hg
  - Cigarette smoker
  - HDL of 32 mg/dL, TG 236 mg/dL, LDL-C 190 mg/dL, TC 261 mg/dL
  - BMI 38
- Patient referred to Cardiology with dyspnea

What about traditional risk factors?
CHD Risk Factors Predict Cardiovascular Disease Events in the HOPS Cohort

Traditional Risk Factors in HIV Pts: DAD study

- A prospective study of 23,437 patients followed for a median of 4.5 years per pt.
- 345 MI - which were associated with male sex, FH of CHD, cigarette smoking, prior CVD, DM, HTN, and cholesterol.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR of MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior CVD</td>
<td>4.64 (2.22-9.68)</td>
</tr>
<tr>
<td>Current cigs</td>
<td>2.92 (2.04-4.10)</td>
</tr>
<tr>
<td>DM</td>
<td>1.85 (1.31-2.65)</td>
</tr>
<tr>
<td>HTN</td>
<td>1.30 (1.00-1.72)</td>
</tr>
<tr>
<td>TC</td>
<td>1.28 (1.19-1.35)</td>
</tr>
</tbody>
</table>

Should HIV be considered a CVD risk equivalent?
- After adjustment for other risk factors, HIV infection was associated with subclinical atherosclerosis similar to DM in the FRAM study
- Analysis of HIV-infected individuals from the Veterans Cohort showed that the HR for HIV infection and acute MI was similar to that of DM (1.94, 95% CI 1.58 to 2.37 vs. 2.01, 95% CI 1.68 to 2.53).
- Clinical implications: lower cholesterol targets, lower BP goals

Hypertension in Patients with HIV
- Treat to goal <140/90 or <130/80 in pts with DM or CKD
- Majority of pts will require 2 medications

<table>
<thead>
<tr>
<th>BP</th>
<th>SBP</th>
<th>DBP</th>
<th>Lifestyle mod</th>
<th>Drug tx</th>
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<tbody>
<tr>
<td>normal</td>
<td>&lt;120</td>
<td>AND &lt; 80</td>
<td>encourage</td>
<td></td>
</tr>
<tr>
<td>Pre HTN</td>
<td>120-139</td>
<td>Or 80-90</td>
<td>yes</td>
<td>If DM or kidney disease, goal &lt; 130/80</td>
</tr>
<tr>
<td>Stage 1 HTN</td>
<td>140-159</td>
<td>Or 90-90</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Stage 2 HTN</td>
<td>≥ 160</td>
<td>Or ≥ 100</td>
<td>yes</td>
<td>yes</td>
</tr>
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</table>

Freiberg M Abstract #809, CROI 2011.

Compelling indications for BP meds

<table>
<thead>
<tr>
<th>Indication</th>
<th>BP Class</th>
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<tbody>
<tr>
<td>CHF</td>
<td>Thiaz, BB, ACE, ARB, ALDO ANT</td>
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<tr>
<td>2/p MI</td>
<td>BB, ACE, ALDO ANT</td>
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<tr>
<td>High cvd risk</td>
<td>Thiaz, BB, ACE, CCB</td>
</tr>
<tr>
<td>DM</td>
<td>Thiaz, BB, ACE, ARB, CCB</td>
</tr>
<tr>
<td>CKD</td>
<td>ACE, ARB</td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>Thiaz, ACE</td>
</tr>
</tbody>
</table>

Which pts should be on aspirin?

1. Everyone who has had a MI
2. Primary prevention for pts without bleeding issues and 10 year CV risk of 10-20%
3. 1 and 2

Aspirin

- Pts with established CAD: dose 75-162 mg/day
- Primary prevention: “Consider 75mg-160mg per day for pts at higher risk, especially those with 10-y risk of CHD≥10%”

What causes atherosclerosis in HIV patients?

- HAART
- PI (chronic use)
- HIV infection
- Traditional Risk Factors

Smith S AHA/ACC guidelines secondary prevention Circulation 2008
Pearson 14 AHA Guidelines for primary prevention Circulation 2002
Patient Case

- 44 y.o. male with HIV-1 infection
  - CD4+ count 250 cells/mm³ and VL 50,000 c/mL
  - Treated with LPV/RTV + ABC + TDF
- Cardiac risk factors
  - Blood pressure of 140/90 mm Hg
  - Cigarette smoker
  - HDL of 32 mg/dL, TG 236 mg/dL, LDL-C 190 mg/dL, TC 261 mg/dL
  - BMI 30
- Patient referred to Cardiology with dyspnea

What is the goal LDL for this pt?
1. < 70 mg/dL
2. < 100 mg/dL
3. < 130 mg/dL
4. < 160 mg/dL
5. < 190 mg/dL

Assessment of CAD Risk

- Does pt have CHD or risk equivalent?
  - Clinical CHD
  - Symptomatic carotid artery disease
  - Peripheral arterial disease
  - AAA
  - DM
  - Should HIV count as a risk equivalent?
- Count major risk factors
  - Cigarette smoking
  - BP ≥ 140/90 or on BP medication
  - HDL < 40 mg/dL (HDL ≥ 60 mg/dL is a negative risk factor)
  - FH
  - Age
- If ≥ 2 risk factors, determine Framingham risk
  - > 20% – CHD risk equivalent
  - 10-20% - moderately high risk
  - <10% - moderate risk

LDL Cholesterol Goals for Different Risk Categories

<table>
<thead>
<tr>
<th>CHD Risk Categories</th>
<th>LDL-C Goal</th>
<th>Consider drug tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD (10-yr risk ≥ 20%)</td>
<td>&lt; 100 mg/dL</td>
<td>≥ 130 mg/dL</td>
</tr>
<tr>
<td>2+ Risk Factors (10-yr risk ≥ 20%)</td>
<td>&lt; 130 mg/dL</td>
<td>10-yr risk 10%-20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 130 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 year risk &lt; 10%</td>
</tr>
<tr>
<td>0-1 Risk Factor</td>
<td>&lt;160 mg/dL</td>
<td>≥190 mg/dL</td>
</tr>
</tbody>
</table>

NCEP-ATP III: Updated Recommendations

- LDL goal of < 70 mg/dL is a therapeutic option on the basis of clinical trial evidence, especially in very high-risk patients
- In a high-risk person with high triglycerides or low HDL, consider combination treatment using a fibrate or nicotinic acid plus an LDL-lowering drug.


CHD or CHD Risk Equivalents: Very High Risk Category

- Multiple major risk factors (especially diabetes)
- Severe and poorly controlled risk factors (especially cigarette smoking)
- Multiple risk factors of metabolic syndrome (especially high TG > 200 mg/dL plus non-HDL-C > 130 mg/dL with HDL-C < 40 mg/dL)
- Patient with acute coronary syndromes


What lipid-lowering med should you choose?

1. Simvastatin
2. Pravastatin
3. Ezetimibe
4. Atorvastatin
5. Gemfibrozil
6. Rosuvastatin

Dyslipidemia and PI

- Protease inhibitors have been associated with marked increases in cholesterol and triglycerides
- Summary of studies that measured lipid changes in pts during treatment with protease inhibitors (RTV, IDV, NFV)
  - Increase TC + 66%
  - Increase TG + 80%
  - Increase LDL + 37%

Management of PI-Associated Hyperlipidemia

- All current PI inhibit the CYP3A4 isoenzyme.
- Statins + PI can result in rhabdomyolysis.
- May not be effective in controlling high triglycerides, consider fibrates.
- Difficult to reach goal.
- Atazanavir
- Ezetimibe

Overview of Drug Interactions Between Lipid Lowering Agents and HIV Drugs

<table>
<thead>
<tr>
<th>Lipid Lowering Agent</th>
<th>Atorvastatin</th>
<th>Fluvastatin</th>
<th>Simvastatin</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Parfentizol</th>
<th>Cholestyramine</th>
<th>Ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
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<tr>
<td>Lovastatin</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
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<td>R</td>
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<tr>
<td>Rosuvastatin</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
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<tr>
<td>Parfentizol</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
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<tr>
<td>Cholestyramine</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
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<tr>
<td>Ezetimibe</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

Algorithm for Managing Elevated LDL-C in HIV Patients

Pt on PI

- Avoid lovastatin/lovastatin.
- Atorvastatin at lower dose (start at 10mg and titrate up not to exceed 40mg).
- Pravastatin.
- Ezetimibe.

Pt not on PI

- Statin therapy per NCEP guidelines.

If lipids remain high, consider changing PI to Atazanavir.

Atorvastatin associated with reductions in activated T lymphocytes

- 22 patients in a cross over trial
- 80mg atorvastatin or placebo, 4-6 week washout
- No effect on HIV-1 RNA
- Atorvastatin resulted in reductions in CD4+HLA-DR+ (-2.5%, p=0.02)
  reductions in CD8+HLA-DR+(-5%, p=0.006) and CD8+HLA-DR+ T cells (-3%, p=0.03)

Ganesan A et al JID 2011; 203: 756-64.

What do to about the high triglycerides?

1. Treat with statin first
2. Treat with fibrate
3. Will not increase CV risk
4. All of the above
5. Not sure

What about high triglycerides?
- Elevated TG increase CV risk but majority of risk decreases after adjustment for low HDL and other features of the metabolic syndrome
- TG>500 should be treated with fibrate to prevent pancreatitis
- TG<500, guidelines say LDL first then non-HDL-C.
- AIM-HIGH: No benefit in high dose niacin+ statin vs. statin alone in pts with heart disease

Sarwar, N Circulation 2007

What causes atherosclerosis in HIV patients?

- HAART (chronic use)
- HIV infection (inflammation?)
- Traditional Risk Factors
Atherosclerotic Lesions: Features

Even treated HIV infection is associated with chronic inflammation

- LPS higher in treated HIV vs. controls
- T cell activation higher in treated HIV vs. controls
- Tissue Factor elevated in treated HIV vs. controls
- hsCRP elevated in elite controllers vs. controls

Brenchley JM Nature Medicine 2006
Hunt PW JD 2003
Funderburg, NT Blood 2010
Hsue PY AIDS 2009

SMART: Untreated HIV is associated with increased CVD risk compared to treated disease

Treatment naive and experienced patients with CD4 cell count >350 cells/mm³

n = 2752
Continuous Strategy: Virologic Suppression (VS)

n = 2720
Intermittent Strategy: Drug Conservation (DC)

Cardiovascular outcomes: 48 events in DC vs. 31 in VS, p<0.05
IL-6 and D-Dimer at study entry were strongly related to all-cause mortality

SMART: Study NEJM 2006
Kuller LH PLOS Medicine 2008

Would you measure hsCRP in this individual
1. Yes
2. No
What does CRP mean in the setting of HIV?

- In absence of HCV, HIV associated with higher CRP in men. HIV/HCV coinfection associated with lower CRP levels
- HIV RNA levels not associated with CRP in contrast to higher IL-6 and fibrinogen
- Elevated CRP and HIV were associated with increased risk for AMI.

Emerging biomarkers:

- sCD14 associated with mortality in SMART
- Fibrinogen and CRP associated with mortality in FRAM
- N-terminal proBNP associated with CV events in HIV

What causes atherosclerosis in HIV patients?

- HAART
  - PI (chronic use)
  - Interruption of HAART is bad
- HIV infection
  - Inflammation
  - Viral replication

Traditional Risk Factors

HIV “Elite” controllers as model to define the role of HIV disease independent of treatment, viremia and immunodeficiency

- Elite Controllers
  - HIV seropositive
  - Antiretroviral untreated
  - No detectable HIV RNA (< 50 copies/mL)
  - Any CD4
Elites had higher IMT vs. Controls

What causes atherosclerosis in HIV patients?

Traditional Risk Factors

Endothelial Dysfunction

Inflammation
Viral replication
LPS (endotoxin)

PI (chronic use)
Interruption of haart is bad

Initiation of combination antiretroviral therapy rapidly improves vascular function

Brachial Artery Flow-Mediated Dilation

Endothelial Stimulus:
Reactive hyperemia after five minute cuff occlusion.
Stimulates functioning endothelial cells to release NO. NO diffuses into vascular smooth muscle. Muscle relaxes.

Control stimulus:
Nitroglycerin, an endothelium-independent vasodilator

Quantity measured:
Diameter of artery, using B-mode ultrasound

•Treatment naïve HIV pts – randomized to 3 different regimens
•Regardless of regimen, FMD improvement was similar in each arm
•FMD increased by 1.48% (P < .001), but does not restore FMD to normal

Torriani JACC 2008

Elite controllers had 0.14mm higher mean IMT compared to controls after adjusting for traditional risk factors (P<0.003)

This difference remained significant when stratifying by smoking, HTN, age, or when restricting analysis to pts with CD4> 500 cells/mm³

H Vine AIDS 2009

TORRINI 2008
What causes atherosclerosis in HIV patients?

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- Short term HAART is beneficial
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- Inflammation
- Viral replication

Traditional Risk Factors

Patient Case

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  - Cigarette smoker
  - HDL of 32 mg/dL, TG 236 mg/dL
  - LDL-C 190 mg/dL, TC 261 mg/dL
- BMI 30
- Patient referred to Cardiology with dyspnea

Would you discontinue ABC in this patient?

1. Yes
2. No
3. Maybe

Abacavir and Increased Risk of MI

- A total of 33,347 patients studied for a median of 5.1 years
- 517 MIs were identified
- Recent use of abacavir was associated with increased MI rate (RR 1.90, 95% CI 1.47-2.45, P = .0001) as was recent use of ddl (RR 1.49, 95% CI 1.14-1.95, P = .003).
- No association seen with recent or cumulative use of ZDV, d4T, or 3TC.

### ABC controversy continues:
- **Data from 26 RCT from 1996-2010**
  - 16 trials from drug manufacturer
  - 5 from actg
  - 5 academic centers
  - 9832 subjects included
  - 25 (0.5%) abc and 22 (0.46%) non abc
- **VA study: recent abacavir use independently associated with increased risk for CV events, also an association between recent TFV exposure and CHF**

*Ding X et al CROI 2011 Poster 808
Choi A et al AIDS 2011*

### Increased Risk of MI or CV Events and Association with ABC or TDF

<table>
<thead>
<tr>
<th>Design</th>
<th>N/Total Pop</th>
<th>Age</th>
<th>Increased MI Risk?</th>
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<tbody>
<tr>
<td>LASTART</td>
<td>33,308</td>
<td>47</td>
<td>Yes (RR: 1.68)</td>
</tr>
<tr>
<td>SMART</td>
<td>115,998</td>
<td>47</td>
<td>Yes (RR: 1.14)</td>
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<td>SMART post-hoc</td>
<td>4,072</td>
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<td>Yes (RR: 0.92)</td>
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<tr>
<td>SMART post-hoc</td>
<td>19,968</td>
<td>45</td>
<td>No (RR: 1.55)</td>
</tr>
</tbody>
</table>

**What causes atherosclerosis in HIV patients?**

- **HAART**
  - PI (chronic use)
  - Interruption of haart is bad
  - Short term HAART is beneficial
- **Endothelial Dysfunction**
- Starting tx late vs. early?
- **HIV infection**
  - Inflammation
  - Viral replication
  - LPS (endotoxin)

**Traditional Risk Factors**
Clinical guidelines recommend starting HAART when CD4+ T cell count <350. Would earlier initiation of HAART alter risk of cardiovascular disease?

1. Yes
2. No
3. Maybe

Hypothesis

- Earlier initiation of HAART at higher CD4+ T-cell count thresholds is associated with improved CV risk as measured by FMD and arterial stiffness as compared to delayed initiation at lower CD4+ T-cell counts

Ho, J AIDS 2010

Nadir CD4+ count Independently Associated with Impaired FMD

- OPTIONS/SCOPE
  - After adjustment for traditional and HIV-related factors, nadir CD4 count < 350 cells/ul was independently associated with lower FMD
  - Individuals with CD4 nadir <350 had 1.22% lower FMD (95% CI 0.19 - 2.20, p=0.02) compared to those with a nadir ≥ 350.
  - Proximal CD4 count not associated with FMD

Ho J et al in submission 2011

START Study

- HIV-infected individuals, ART naïve, with CD4> 500 cells/mm³
- Randomized trial looking at early ART (immediately after randomization) vs. deferred ART (CD4 <350 cells/mm³ or AIDS)
- Primary endpoint: Development of AIDS event, non-AIDS event or death from any cause

http://insight.ccbr.umn.edu/start/
What causes atherosclerosis in HIV patients?

**Traditional Risk Factors**
- Inflammation
- Viral replication
- LPS (endotoxin)

**HAART**
- PI (chronic use)
- Intermittent use of HAART is bad
- Short term HAART is beneficial
- Abacavir??
- Starting tx late vs. early?

**HIV infection**
- Inflammation
- Viral replication
- LPS (endotoxin)

Effect of intensification of HIV therapy?

Mechanistic Trials in HIV to Address HIV therapy in progress:

- Intensification of existing HIV therapy using:
  - Maraviroc with Peter Hunt (CCR5 inhibitor):
    - placebo controlled study of 50 patients treated for 6 months. Completed.
    - Increase in T cell activation, but decrease in LPS
    - FMD results being analyzed
  - Raltegravir with Hiroyu Hatano (integrase inhibitor): last patient completes FMD in November 2011.

Will intensification of HIV medication be able to reduce CV risk?

1. Yes
2. No
3. Maybe
Case 2: HIV and Acute MI

- 37 year old Latino gentleman, HIV positive since 1996, with CD4 nadir of 4, DM, hyperlipidemia, present with chest pain

Cardiac Catheterization

- Pt treated with TNK, however had continued chest pain
- Referred for PTCA
- PTCA unsuccessful, refer for CABG

Thrombotic complications in pts with HIV

- Prospective study of 100 medical clinics in U.S.\(^1\)
  - 42,935 HIV patients observed for 2.4 years
  - Incidence of thrombosis was 2.6/1000 PY
  - Associated with age, CMV, GI, hospitalization, megestrol, IDV
- Johns Hopkins HIV Clinical Cohort - identified 160 cases, incidence of 5.1/100 person yrs fu.\(^2\)
- VTE associated with lower CD4 count, higher HIV VL, prior hospitalization, and elevated WBC.

\(^1\)Sullivan PS et al AIDS 2000
\(^2\)Ahonkhal A, Retrovirus 2007
Coagulation system in HIV

ATIII, an inhibitor of thrombin is elevated in HIV infection

ETP, a measure of thrombin generation in vivo is decreased in HIV

Collaboration with Ethan Weiss: findings suggest that the model of coagulation, inflammation, and thrombosis is complex. *Hsue P et CID in press*

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Other Cardiovascular issues and HIV:

**Pulmonary HTN**
- Independently associated with HIV infection
- Prevalence of 0.46% (similar to pre-HAART era)
- HAART does not alter hemodynamic parameters
- Independent predictors of survival were CD4 count and cardiac index

**Diastolic Dysfunction**
- HIV infected individuals had a 2.4 higher OR of having diastolic dysfunction and a higher LV mass index compared to controls which were independently associated with HIV infection.

**Arrhythmias** – in collaboration with Zian Tseng and Greg Marcus

*Hsue P AIDS 2008*
*Sitbon O AMRCCM 2008*
*Degano B AIDS 2010*
*Hsue P Circulation Heart Failure 2010*

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What causes atherosclerosis in HIV patients?

**HAART**
- PI (chronic use)
- short term HAART is beneficial
- Abacavir??
- New classes of HAART?

**HIV infection**
- Inflammation
- Viral replication
- LPS (endotoxin)
- Effect of intensification of HIV therapy?

**Endothelial Dysfunction**

**Thrombosis**

**PAH**

**Diastolic dysfn**

**Arrhythmias**

**Traditional Risk Factors**

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Next steps: identifying therapies for HIV-associated inflammation
Model for HIV, inflammation, and non-AIDS conditions

Other methods to lower inflammation in HIV:
- Chemokine receptor inhibitors
- Intensification of therapy with integrase inhibition
- Targeting CMV co-infection
- Microbial translocation
- Enhancement of T cell renewal

Other therapeutic options:
- NSAIDS
- ACE-I/ARBs
- Statins
- Prednisone, hydroxyurea, cyclosporine
- Lp-PLA2 inhibition
- Biologics:
  - TNF inhibitors, IL-6 inhibitors, IL-1 inhibitors

Conclusions
- HIV infection is independently associated with CVD
- Antiretroviral therapy partially reverses the risk associated with HIV infection
- Certain antiretroviral drugs are associated with increased risk; this effect may be mediated via inflammatory changes (abacavir)
- HIV-associated inflammation persists in absence of viremia (HAART, elite controllers) and this inflammatory process predicts CVD
HIV as a model to study other inflammatory conditions and cvd?

Rituxan therapy in RA pts improves FMD

Cardiac Surgery in Patients with HIV
- Retrospective review of 37 patients from 1994-2000\(^1\)
  - Median age of 41 years, 34/37 male
  - In the CABG group, 81% were free from recurrent angina, CHF, death, and repeat revascularization after 3 years.
  - No opportunistic infections developed
- Retrospective review of HIV patients from Kaiser undergoing surgery 1997-2002\(^2\)
  - Cardiothoracic surgery had fewer complications compared to HIV negative (5.3% vs. 26.3%, \(P = .07\))

Typical Anginal Symptoms in HIV patients?
- 42 year old gentleman with HIV, CD4 of 8 cells/mm\(^3\), hospitalized with PCP
- Dyspnea on day of discharge

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Cardiac Catheterization

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Patients at SFGH

Patients at SFGH