HIV, Inflammation, and Cardiovascular Disease

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University of California, San Francisco
Patient Case

• 44 y.o. male with HIV
  – CD4 440 and VL UD
  – Treated with
    Lopinavir/RTV/Abacavir/Lamivudine
• Cardiac Risk Factors
  – Blood pressure of 135/90
  – Cigarette smoker
  – HDL of 32 mg/dL (0.83), TG 236 mg/dL (2.66), LDL-C 160 mg/dL (4.14), TC 244 mg/dL (6.31)
  – BMI 30
• Patient referred to Cardiology with dyspnea
Cardiac catheterization
What’s the best way to treat this patient?

• Treat his HIV disease aggressively and treat early

  ART is important and likely early ART initiation (not focus of this talk)

  May have impact on inflammation, but will be covered by others...

• Put him on aspirin and a statin

• Target microbial translocation

• Give him low dose methotrexate

• Consider immune based therapies

• All of the above

Many of those interventions have not worked...
Why study cardiovascular disease and HIV?

• Cardiovascular disease (CVD) is significantly elevated among HIV-infected individuals
• The impact of CVD on the health of HIV patients is profound and will increase as patients grow older
• The increased risk of CVD is independent of traditional risk factors
• Scientific questions in HIV can inform CVD in the general population
• Understanding the mechanisms of CVD in HIV can potentially impact HIV (i.e. cure)
Rates of CVD are Elevated in HIV

Cardiovascular disease is significantly elevated in HIV disease

Includes CAD but also many other cardiovascular conditions are emerging
HIV infection and high rates of CAD

- MI and hospitalizations significantly higher in HIV pts vs. controls
- AMI rates higher in setting of HIV
- Meta analysis: 1.61 RR of CVD for untreated HIV pts vs. controls, RR of 2.00 among treated HIV pts vs. controls

**Limitations:**

*Low rates of events even in large cohorts*

- DAD study: 33,347 pts studied for 5.1 years = 517 MIs = 3/1000PY
- Studies with incomplete data (esp. cigs/FH)

HIV Infection and the Risk of Acute Myocardial Infarction

Matthew S. Freiberg, MD, MSc; Chung-Chou H. Chang, PhD; Lewis H. Kuller, MD, DrPH; Melissa Skanderson, MSW; Elliott Lowy, PhD; Kevin L. Kraemer, MD, MSc; Adeel A. Butt, MD, MS; Matthew Bidwell Goetz, MD; David Leaf, MD, MPH; Kris Ann Oursler, MD, ScM; David Rimland, MD; Maria Rodriguez Barradas, MD; Sheldon Brown, MD; Cynthia Gibert, MD; Kathy McGinnis, MS; Kristina Crothers, MD; Jason Sico, MD; Heidi Crane, MD, MPH; Alberta Warner, MD; Stephen Gottlieb, MD; John Gottdiener, MD; Russell P. Tracy, PhD; Matthew Budoff, MD; Courtney Watson, MPH; Kaku A. Armah, BA; Donna Doehler, DrPH, MS; Kendall Bryant, PhD; Amy C. Justice, MD, PhD

Incident rate ratio for acute MI by age

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Incident Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>2.2</td>
</tr>
<tr>
<td>40-49</td>
<td>1.3</td>
</tr>
<tr>
<td>50-59</td>
<td>1.8</td>
</tr>
<tr>
<td>60-69</td>
<td>1.5</td>
</tr>
<tr>
<td>70-79</td>
<td>1.5</td>
</tr>
</tbody>
</table>

- **HIV associated with a 50% increased AMI risk after adjustment for risk factors**
- **Increased risk remained among those with well-treated HIV**
- **Impact of HIV on risk comparable to traditional risk factors including HTN, DM and hyperlipidemia**
HIV is Strongly linked to Arterial Disease

• HIV infection is independently associated with greater IMT and faster IMT progression.
• Association of HIV is similar in to potent traditional risk factors (DM, smoking, and increased age)
• Higher prevalence of atherosclerosis vs. uninfected men by CT angiography

The impact of CVD among individuals with HIV will increase as this population continues to age.
The number of people 50 and older living with HIV in U.S has increased 77% from 2001 to 2005.¹

Currently in 2015, HIV patients aged 50 and older account for half of all HIV/AIDS cases in the U.S.¹

Chronic disease conditions such as cardiovascular disease are increasingly important health issues in this population.

¹www.cdc.gov
Mortality due to non-AIDS and CVD events increasing in ART era

- Antiretroviral Therapy Cohort Collaboration
- 65,121 HIV pts who started ART followed between 1996-2009
- Non-AIDS deaths accounting for 58% of deaths

Non-AIDS Deaths

- Non-AIDS Malignancy: 22.1%
- Non-AIDS Infection: 15.1%
- Liver disease: 14.5%
- CVD: 14.2%
- Unnatural: 16.8%
- Respiratory: 2.9%
- Other: 10.5%
- Renal: 2%

Antiretroviral Therapy Cohort Collaboration (ART-CC). CID 2014:59282-97
HIV-Infected Individuals compared to uninfected have higher mortality from MI

- MI hospitalizations in US from 1997 to 2006 w/ and w/o HIV
- After adjustment for age, gender, comorbidities, HIV-infected individuals had higher mortality compared to controls (HR 1.38, 95% CI 1.01 to 1.87, p=0.04).
- HIV pts had lower rates of procedures (catheterization, CABG, and anticoagulant tx)

Pearce D et al Am J Cardiol 2012

Hanna DB et al Abstract 729 CROI
CVD as a cause of death in HIV

- United States: 2\textsuperscript{nd} leading non-HIV cause of death (~15%)
- Europe: 3\textsuperscript{rd}, after cancer and liver disease (~8%)
- Deaths to CVD range from 6-15% in different cohorts

As the HIV-infected population continues to age, new cardiovascular issues are developing.
Emerging cardiovascular issues and HIV:

- **Pulmonary HTN**
  Independently associated with HIV
  Prevalence is > 1500 fold higher in HIV
  ART has not altered prevalence

- **Atrial fibrillation**
  Advanced HIV infection associated with higher risk of AF

- **Diastolic Dysfunction**
  HIV patients have > 2.4 higher OR of DD and a higher LV mass compared to controls

All of these conditions are strongly associated with high mortality in patients without HIV
Mechanisms and optimal tx in HIV are largely unknown

Hsue P AIDS 2008
Hsu J JACC 2013
Hsue P Circulation Heart Failure 2010
Sudden Cardiac Death in HIV

HIV pts at SFGH between 2000-2009, 230 deaths
30 (13%) were SCD
Majority of all cardiac deaths were sudden
HIV SCD rate of 2.6/1000 person years ( >4 times general population)

Why is the rate of SCD higher in HIV?
How can we predict at risk individuals?
How do we prevent this?

Tseng Z and Hsue P: JACC 2012
• Traditional risk factors are common in HIV-infected individuals and contribute to CV risk
Traditional Risk Factors in HIV Pts: DAD study

- Prospective study of 23,437 patients median FU 4.5 years
- 345 MI - 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 (3.22-6.69)</td>
</tr>
<tr>
<td>Current cigs</td>
<td>2.92 (2.04-4.18)</td>
</tr>
<tr>
<td>DM</td>
<td>1.86 (1.31-2.65)</td>
</tr>
<tr>
<td>HTN</td>
<td>1.30 (0.99-1.72)</td>
</tr>
<tr>
<td>TC</td>
<td>1.26 (1.19-1.35)</td>
</tr>
</tbody>
</table>

Elevated and pre-HTN SBP and risk of MI

- >81000 individuals from Veterans Aging Cohort study.
  - Matched HIV+ and HIV- Veterans
- Elevated SBP was associated with a higher relative risk of AMI in HIV infected vs. uninfected individuals, even at prehypertensive levels (SBP 120-139)
- 860 MI over 5.9 years
- HIV, preHTN, and HTN associated with increased MI risk

Armah K et al Clin Infect Dis 2014
Should HIV be considered a CVD equivalent?

- Association of HIV to atherosclerosis similar to DM (FRAM study)
- Veterans Cohort: HR for HIV infection and acute MI similar DM
- Mildly elevated BP (SBP 120-139) was associated with a higher risk for MI in HIV

Should we treat HIV like DM, implying different targets for LDL and BP?

Freiberg M JAMA IM 2013.
Armah K CID 2013
While traditional risk factors are important, HIV-related factors play a key role in increased risk of CVD

*Includes impact of HIV medication, inflammation, and immune activation*
Long term ART may increase CV risk

• ART associated with reduction of CVD (VA study)
• DAD Study: ART was associated with a 26% relative increase in MI rate
• Exposure to PI was associated with higher rate of MI per year of exposure
• Abacavir: Some but not all studies demonstrate increased risk of MI with recent use.

What are the optimal ART regimens for individuals at risk for CVD? What is the CV risk associated with newer ART regimens?

However, in the short term, starting ART and starting early likely reduces CV risk by impacting inflammation
SMART: Untreated HIV is associated with increased CVD risk compared to treated disease

Treatment naïve and experienced patients with CD4 cell count >350 cells/mm$^3$

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
Chronic inflammation persists in treated HIV and predicts CV risk and mortality
After adjusting for traditional risk factors, inflammatory biomarkers remain elevated during long-term ART, although the increase is moderate.
## NWCS 329 in treated HIV Infection, pre-Event Soluble Markers relate to Outcome

<table>
<thead>
<tr>
<th>Pre-event Marker</th>
<th>Odds Ratio per 1 IQR increase</th>
<th>P Value</th>
<th>OR for:</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>CA</td>
</tr>
<tr>
<td><strong>IL6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.58 (1.91-3.48)</td>
<td>&lt;.001**</td>
<td>20.9**</td>
<td>3.1**</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>2.48 (1.83-3.35)</td>
<td>&lt;.001**</td>
<td>19.9**</td>
<td>2.9**</td>
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<tr>
<td><strong>IP-10</strong></td>
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<td></td>
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<tr>
<td>Unadjusted</td>
<td>1.49 (1.16-1.91)</td>
<td>0.002**</td>
<td>1.9</td>
<td>1.7*</td>
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<tr>
<td>Adjusted*</td>
<td>1.42 (1.10-1.84)</td>
<td>0.007**</td>
<td>1.8</td>
<td>1.5</td>
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<tr>
<td><strong>sTNFr-I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.99 (1.49-2.66)</td>
<td>&lt;.001**</td>
<td>3.3**</td>
<td>2.3**</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.94 (1.45-2.60)</td>
<td>&lt;.001**</td>
<td>3.3*</td>
<td>2.2**</td>
</tr>
<tr>
<td><strong>sTNFr-II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.88 (1.44-2.46)</td>
<td>&lt;.001**</td>
<td>2.6**</td>
<td>2.1**</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.81 (1.38-2.38)</td>
<td>&lt;.001**</td>
<td>2.9**</td>
<td>1.9*</td>
</tr>
<tr>
<td><strong>Soluble CD14</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.74 (1.29-2.35)</td>
<td>&lt;.001**</td>
<td>2.7*</td>
<td>1.5</td>
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<tr>
<td>Adjusted*</td>
<td>1.67 (1.23-2.27)</td>
<td>&lt;.001**</td>
<td>2.8*</td>
<td>1.4</td>
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<tr>
<td><strong>D-Dimer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.41 (1.78-3.27)</td>
<td>&lt;.001**</td>
<td>8.4**</td>
<td>3.2**</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>2.38 (1.75-3.25)</td>
<td>&lt;.001**</td>
<td>8.1**</td>
<td>3.1**</td>
</tr>
<tr>
<td><strong>CD8+ %DR+38+</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.06 (0.88-1.28)</td>
<td>0.516</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>0.98 (0.80-1.20)</td>
<td>0.863</td>
<td>0.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Adjusted by CD4 count

Slide from Peter Hunt: Tenorio, A et al JID 2014
Emerging biomarkers in HIV:

- sCD14 associated with mortality in SMART
- Fibrinogen and CRP associated with mortality in FRAM
- N-terminal proBNP associated with CV events in HIV
- sCD163 associated with noncalcified coronary plaque/vascular inflammation
- ST2 and GDF15 associated with CV dysfunction and mortality in HIV

What will be the best biomarker to predict CVD in the setting of HIV?

Sandler N JID 2011  
Tien PC JAIDS 2010  
Duprez DA AIDS 2011  
Burdo TH JID 2011  
Subramanian S JAMA 2012  
Secemsky E JACC HF 2015 in press
CV risk persists in treated HIV and inflammation predicts this risk

• Treated suppressed HIV infected individuals have higher vascular disease vs. controls
  – hsCRP is strongly associated with disease
• HIV-infected individuals with well controlled disease had greater arterial inflammation was associated with sCD163
• IL-6, D-dimer, and hsCRP associated with increased risk of CVD (SMART)
• Higher IL-6, D-dimer levels are associated with greater risk of fatal CVD and risk of death after CVD event

Hsue PY AIDS 2009; Hsue PY JAHA 2012; Subramanian S JAMA 2012; Duprez D PlosOne 2012; Nordell A JAHA 2014
• Unclear association between immune perturbations and CVD
Low CD4 count is Associated with CVD:

- Nadir CD4 $\leq 200$ independently associated with carotid IMT
- Proximal CD4 T cell count during therapy associated with incident CVD and AMI
- Kaiser study: HIV+ individuals with higher risk of CHD: seen only in treated individuals with either recent or lowest CD4 $\leq 200$
- Nadir CD4 $< 350$ independently associated with worsened arterial stiffness and endothelial function
- **Will there be a CV benefit in earlier initiation of antiretroviral therapy?**

CD4, Immune depression and CV events in HIV

- Lower CD4 count had higher rates of MI/CHD endpoints but this weakened after adjustment
- Weak linear association with immune depression and MI/CHD
- Association with stroke, may be due to misclassification

*Sabin CA for DAD, AIDS 2013*
Associations do not prove causation

How can we design clinical studies to demonstrate the role of immunologic/inflammatory factors in HIV patients?
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*
Multiple factors cause persistent inflammation during ART

- HIV production and replication
- Loss of regulatory cells
- ART toxicity, lipodystrophy, and traditional risk factors
- Cytomegalovirus and other copathogens

Inflammation
- ↑ Monocyte activation
- ↑ T-cell activation
- ↑ Endothelium adhesion
- Dyslipidaemia
- Hypercoagulation

Comorbidities
- Cardiovascular disease
- Cancer
- Kidney disease
- Liver disease
- Osteopenia/osteoporosis
- Neurocognitive disease

Deeks, Lewin, Havir; Lancet 2013
Microbial Translocation Decreases with HAART but Persists for Years

Jiang et al, JID, 2009 (also Marchetti, AIDS, 2008)
# Interventions targeting the gut in HIV:

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mechanism</th>
<th>Pt. Type</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifaximin A5286</td>
<td>Nonabsorbable antibiotic decreases LPS in cirrhosis</td>
<td>N=65 CD4&lt; 350 HIV RNA UD on ART</td>
<td>2:1 ratio 4 weeks</td>
<td>Minimal impact on microbial translocation and CD8-T cell activation</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Anti-inflammatory used in UC</td>
<td>N=33 CD4&lt;350 HIV RNA &lt;40 on ART</td>
<td>12 weeks cross over</td>
<td>No impact on T cell activation in blood/gut or inflammatory markers</td>
</tr>
<tr>
<td>Sevelamer A5296</td>
<td>Phosphate lowering medication which binds to LPS</td>
<td>N=36 CD4≥400 HIV RNA &gt; 50 no ART</td>
<td>8 weeks</td>
<td>No impact on microbial translocation or inflammatory markers, decreased in TF, LDL, and ox LDL</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Reduction in intestinal permeability</td>
<td>N=44 HIV RNA&lt;20</td>
<td>12 weeks</td>
<td>Reduction in LPS and IL-6 at week 12 and after 3 months s/p treatment withdrawal</td>
</tr>
</tbody>
</table>

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*Tenorio AR et al JID 2015*
*Somsouk M et al PLoSOne 2014*
*Sandler NG et al JID 2014*
*Villar-Garcia J et al JAIDS 2015*
Can we take cues on how to address inflammation from cardiology?
Inflammatory pathways as targets for atherosclerotic therapies

Robust data linking IL-6 to events

Deposition of cholesterol crystals linked to NLRP3 inflammasome

Statins reduce CRP along with LDL and reduce CV risk

Ridker P and Luscher T. EHJ 2014: 35: 1782-91
**Anti-inflammatory effects of statins**

- Statin tx in pts with low LDL and high inflammation reduces CVD/mortality
- Greatest absolute RR observed among those with highest levels of inflammation
- Greatest risk reduction among those who reduce hsCRP as well as LDL-C

**References**
- Ridker PM et al NEJM 2008
- Ridker PM et al Am J Cardiol 2010
- Ridker PM et al Lancet 2009
- Ridker PM et al NEJM 2005
Rosuvastatin and atorvastatin in HIV did not impact inflammatory markers

- 147 HIV pts on stable ART, with LDL ≤ 130mg/dL and hsCRP> 2mg/L and/or expression of CD38 and HLA-DR antigens on ≥ 19% of CD8+ T cells at screening
- 24 weeks of rosuvastatin 10mg daily reduced Lp-PLA2 and LDL but did not impact inflammatory/coagulation markers (hsCRP, IL-6, D-dimer, fibrinogen).
- Similarly, atorvastatin 40mg daily for 1 year in pts with high fdg-pet and plaque on CTA, decreased Lp-PLA2, but had no impact on IL-6, borderline effect on CRP

Eckard A et al JID 2014
Lo J et al Lancet HIV 2015
Saturn ("Jupiter-HIV") vs. Jupiter

- LDL lowering higher in Jupiter
  - LDL decreased 28% in Saturn vs. 50% in Jupiter
- No impact on inflammatory markers in HIV
  - No impact on hsCRP in Saturn vs. 37% reduction vs. placebo in Jupiter

Will statins target the inflammatory pathways of interest in HIV?
Phase III clinical trials of anti-inflammatory therapy in CVD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Trial</th>
<th>Size</th>
<th>Sponsor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Agents impacting on the IL-6 signalling pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canakinumab</td>
<td>IL-1β</td>
<td>CANTOS</td>
<td>10000</td>
<td>Novartis</td>
<td>Enrolling</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>IL-6,TNF</td>
<td>CIRT</td>
<td>7000</td>
<td>NHLBI</td>
<td>Enrolling</td>
</tr>
<tr>
<td>Anakinra</td>
<td>IL-1Ra</td>
<td>IL-HEART</td>
<td>190</td>
<td>UK-MRC</td>
<td>Completed</td>
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<tr>
<td>Colchicine</td>
<td>multiple</td>
<td>LoDoCo</td>
<td>532</td>
<td>HRS, Aus</td>
<td>Positive</td>
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<tr>
<td>Tocilizumab</td>
<td>IL-6</td>
<td>Entrace</td>
<td>3000</td>
<td>Hoffmann</td>
<td>Enrolling</td>
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<tr>
<td>Etanercept</td>
<td>TNF</td>
<td>Entrace</td>
<td>3000</td>
<td>Hoffmann</td>
<td>Enrolling</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Trial</th>
<th>Size</th>
<th>Sponsor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Agents impacting on alternative inflammatory pathways</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinobucol</td>
<td>Ox-LDL</td>
<td>ARISE</td>
<td>6144</td>
<td>AtheroGenics</td>
<td>Negative</td>
</tr>
<tr>
<td>Varespladib</td>
<td>sPLA2</td>
<td>VISTA-16</td>
<td>5000</td>
<td>Anthera</td>
<td>Negative</td>
</tr>
<tr>
<td>Darapladib</td>
<td>Lp-PLA2</td>
<td>STABILITY</td>
<td>15000</td>
<td>GSK</td>
<td>Enrolled</td>
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<tr>
<td>Darapladib</td>
<td>Lp-PLA2</td>
<td>SOLID-TIMI-52</td>
<td>13000</td>
<td>GSK</td>
<td>Enrolled</td>
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<td>Inclacumab</td>
<td>P-Selectin</td>
<td>SELECT-ACS</td>
<td>544</td>
<td>Roche</td>
<td>Completed</td>
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<tr>
<td>Inclacumab</td>
<td>P-Selectin</td>
<td>SELECT-CABG</td>
<td>380</td>
<td>Roche</td>
<td>Enrolled</td>
</tr>
</tbody>
</table>

Ridker P and Luscher T. EHJ 2014: 35: 1782-91
New Strategies for CVD aimed at Inflammation

- CIRT study: Impact of LDMTX on inflammation and CV events
- CANTOS study: IL-1B inhibition using canakinumab dramatically reduces inflammatory markers at 4 months

Both studies were based on observations from individuals with RA

Studies of HIV-associated CVD can also teach us about mechanisms of CVD and identify new targets for treatment

Ridker P Circulation 2012;126: 2739-48
Why methotrexate?

• Low doses of MTX (10-25mg) have been used for almost 20 years among individuals with RA
• ACR provides extensive guidelines on drug monitoring
• Long-term safety of very lose dose methotrexate has been established in RA

Saag KG Arthritis Rheum 2008
LDMTX improves survival and CVD in RA

• LDMTX (10-25mg) used > 20 years in pts with RA with established safety

• Wichita Arthritis Study: MTX use associated with survival benefit, largely by reduction in CV mortality

<table>
<thead>
<tr>
<th></th>
<th>Deaths</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>191</td>
<td>0.4 (0.2–0.8)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>84</td>
<td>0.3 (0.2–0.7)</td>
</tr>
<tr>
<td>Non-cardiovascular mortality</td>
<td>107</td>
<td>0.6 (0.2–1.2)</td>
</tr>
</tbody>
</table>

• Meta-analysis of RA/psoriasis pts showed LDM reduced CV events by 21%

• LDMTX reduces CRP, IL-6, TNF alpha in pts with RA/psoriasis

• Has minimal effects on LDL (in contrast to TNF-inhibitors and IL-6 inhibitors)

A5314 Study Schema: LDMTX and HIV

- Randomized double blinded placebo controlled study in treated and suppressed HIV-infected individuals with CVD or 1 CV risk factor (N=200)
- Occurring simultaneously as the trial in uninfected pts with CVD
- Primary endpoints are safety, impact on inflammatory markers/immune activation, and endothelial function
- 60% enrolled at this time
IL-1 family

- **IL-1α and IL-1β**
  - Exert proinflammatory effects by binding to IL-1 receptor
  - Monocytes and macrophages produce bulk of IL-1β
  - IL-1β is activated by NLRP3 inflamasome which leads to activation of caspase-1 (IL-1β converting enzyme)

- **IL-1R antagonist**
  - Endogenous inhibitor blocks binding of IL-1α and β to IL-1 receptor
IL-1 and atherothrombosis

Ridker P et al American Heart Journal 2011
IL-1β inhibition using canakinumab

- Canakinumab is a human monoclonal IL-1β antibody indicated for treatment of IL-1β inflammatory disorders such as CAPS and Muckle-Wells syndrome
- Bind IL-1β and blocks interaction of cytokine with type I and II receptors
- Produces a rapid and sustained inhibition of acute phase response including significant reductions in CRP and IL-6
- Unlike TNF-α inhibitors, has only marginal effects on lipid levels
- Dosing is quarterly subcutaneous injection
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation of hsCRP ($\geq$ 2 mg/L)

Randomized Canakinumab 50 mg SC q 3 months
Randomized Canakinumab 150 mg SC q 3 months
Randomized Canakinumab 300 mg SC q 3 months
Randomized Placebo SC q 3 months

Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death

Secondary Endpoints: Total Mortality, New Onset Diabetes, Other Vascular Events

Exploratory Endpoints: DVT/PE; SVT; hospitalizations for CFH; PCI/CABG; biomarkers
Effects of IL-1β on inflammatory markers and fibrinogen, N=556 pts

Dose response effects at 4 months for crp, il-6 and fibrinogen in PBO subtracted analysis

Ridker PM et al Circulation 2012
Role of IL-1β in HIV Pathogenesis?

- SIV stimulates production of IL-1β from gut-mucosa intestinal Paneth cells leading to breakdown in mucosal integrity, microbial translocation, and inflammation

CD4+ T-cells lost during HIV infection die as a result of caspase-1 dependent pyroptosis which involves release of IL-1β

Chronic cycle of CD4 T-cell death and inflammation

VX-765 caspase-1 inhibitor

Hirao LA et al PLOS Pathogens 2014
Monroe KM et al Science 2014
Doitsch G et al Nature 2014
IL-1β inhibition in HIV:

• Study drug and placebo provided by Novartis
• Pilot Study: N=10 individuals treated all with 150mg canakinumab once, with followup for 12 weeks
  – NHLBI funded: Hsue, Deeks, Ridker, Tawakol
  – To start this summer
• Main study: N=100 individuals randomized 2:1 treated with 150mg canakinumab at baseline and at 12 weeks, followed for 36 weeks
Studies in CVD in HIV can also inform the larger population with CVD
Inflammation underlies CVD in the general population

A. Normal artery
B. Adhesion of leukocytes, maturation of monocytes into macrophages, uptake of lipid resulting in foam cells
C. Migration of SMC, formation of necrotic core
D. Thrombosis

HIV patient population can serve as a model for inflammation – well studied and engaged patients
Studies in this patient population can inform treatment strategies of CVD for all individuals

Will therapies that reduce chronic inflammation in HIV provide insight into the mechanism of HIV disease and be helpful for cure efforts?
HIV-associated inflammation, immune dysfunction and T cell proliferation can cause HIV persistence through several potentially modifiable mechanisms.
Why would inflammation and/or immune dysfunction contribute to HIV persistence?

- Inflammation as a cause for persistence
  - More virus production, more target cells
  - Homeostatic proliferation
  - Upregulation of negative regulators (PD-1)
  - Poor clearance mechanisms
- If inflammation causes persistence, then anti-inflammatory approaches may accelerate cure
- If persistence causes inflammation, then curative strategies will reduce inflammation-associated disease
Sirolimus (rapamycin)—which reduces CCR5 expression, T cell activation and T cell proliferation—is associated with low “reservoir” size post-renal transplant.
Identify and Target Novel Pathways “Probe” Studies from ACTG

- HIV-1 Infection
  - Th17 depletion
  - Immunodeficiency
    - Microbial Translocation
    - Viral Reactivation (eg, CMV)
  - Innate Immune Activation (MØ/DC)
    - ?IDO-1-induced Tryptophan Catabolism
    - ?T Cell Turnover, Activation, Lymphoid Fibrosis
    - T Cell Proliferative Defects
      - Functional T Cell Defects / CD4+ Lymphopenia
    - Infections, Malignancy
  - TLR 7,8 Activation
    - IL-7?
  - IL-1 inhibitors?
  - TNF-α inhibitors?
  - IFN-α Inhibitors?
  - Cardiovascular, Renal, and Liver Disease, Osteoporosis, Frailty, Cognitive Dysfunction

- Novel CMV Drugs?
- Other TLR Inhibitors?
- Chloroquine (A5258)
- LD-Methotrexate (A5314)
- Ruxolitinib (A5336)
- IDO-1 Inhibitors?
- Pro-biotics?
- Pre-biotics?
- Tissue Factor, Clotting
- Thrombosis, CAD/Stroke
- Rifaximin (A5286)
- Sevelamer (A5296)
- Chloroquine
- LD-Methotrexate
- Ruxolitinib

Slide from Peter Hunt
• Newer cholesterol lowering agents on the horizon?
PCSK9 Regulates LDL-C via LDL-R

- Serine protease synthesized in the liver
- Regulates LDL-C via LDL-R recycling
- PCSK9 antibody inhibitors reduce LDL-C by 30 – 80%.
- Predicts adverse CV outcomes and event-free survival
- PCSK9 antibody inhibitors reduce CV events

9Leander et al. Moderated Poster ESC 2014.
10Werener al. Moderated Poster ESC 2014.
11Robinson et al NEJM 2015
12Sabatine et al NEJM 2015
PCSK9 is Elevated in HIV+ vs. HIV- Subjects in Unadjusted Analysis

P=0.07

HIV-
Median (IQR): 374.5 (296-451)
Range 125-820 ng/mL
N=72

HIV+
Median (IQR): 403.0 (304-517)
Range: 99-1130 ng/mL
N=495
PCSK9 is Elevated in HIV+ vs. HIV- Subjects After Adjustment

- Unadjusted: 11% higher PCSK9
- Demographic-adjusted*: 12% higher PCSK9
- Adjusted for demographics and statins*: 10% higher PCSK9

*age, male, transgender, race
Dramatic LDL-C lowering in HIV+ subjects treated with Evolocumab (n=6)

Mean Baseline: 140 mg/dL
Mean Post-dose: 55 mg/dL
Mean % Reduction: -59%

Kohli P et al submitted 2015
Reduction in Lp(a) in HIV+ subjects treated with Evolocumab (n=6)

Mean Baseline: 169 mg/dL
Mean Post-dose: 133 mg/dL
Mean % Reduction: -30%

-28%
-31%
-18%
-36%
-67%
+2%

Kohli P et al submitted 2015
Why study cardiovascular disease and HIV?

- Cardiovascular disease is significantly elevated in HIV disease
- The impact of CVD on the health of HIV patients is profound and will increase as patients grow older
- This increased risk of CVD is independent of traditional risk factors
- Scientific questions in HIV can inform CVD in the general population
- Understanding the mechanisms of CVD in HIV can potentially impact HIV (i.e. cure)

NHLBI working group convened Sept 2012: identifying need for more cardiologists to become engaged in HIV

Shah MR et al JACC 2015
Persistent Gaps

• What’s the best marker for chronic inflammation in HIV?
  – how does this marker predict CV risk?

• What is the best treatment to lower HIV-associated inflammation?
  – Will it be HIV-related therapy or a more generalized approach?

• Are newer ART regimens such as CCR5 inhibitors or integrase inhibitors associated with specific CVD profiles?

• For HIV-infected individuals with CVD or at high risk for CVD, when is the optimal time to start ART and what is the optimal ART regimen?

• Should treated HIV infection be considered a CVD equivalent (similar to DM)?
  – Implies aggressive risk factor intervention to secondary prevention targets (LDL<70)
Acknowledgements

SFGH Positive Health
SCOPE: Steve Deeks, Peter Hunt
Jeff Martin, Hiroyu Hatano, Becky Hoh
Options: Rick Hecht
Pulm: Laurence Huang

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What is responsible for the excess CV risk in HIV?
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.

MACS: Non-Calcified Coronary Plaque in HIV+

- HIV+ indep. associated with non-calcified plaque score (p=0.03), along with HTN, DM, dyslipidemia
- Indep. associations with stenosis \( \geq 50\% \) for HAART >10 yrs, CD4 nadir, and detectable HIV RNA

Growing recognition of role of monocytes/macrophages HIV-associated CVD

• Circulating monocytes associated with increased CAC progression (SUN)
• Monocyte profile of untreated HIV mirrors individuals with ACS
• sCD163 associated with arterial inflammation in HIV

Baker JV et al AIDS 2013
Funderberg N et al Blood 2012
Subramanian S et al JAMA 2012
Conversely, studies in CVD and HIV can also inform HIV-related issues, including cure efforts.
Management of PI-Associated Hyperlipidemia

• Most statins metabolized by cytochrome P450 system (CYP3A4) and all protease inhibitor downregulate the activity of CYP3A4
• Thus coadministration of statin and PIs can lead to increased AUC for statin and rhabdomyolysis
• For patients on PIs:
  – Simvastatin and lovastatin are contraindicated
  – Atorvastatin can be used at low doses with monitoring
  – Pitavastatin/fluvastatin probably ok
• Rosuvastatin – not metabolized by CYP3A4 system but using low dose is suggested

*Dube MP CID 2003
Hare B CID 2002
Hsue P Circulation 2005
Currier JS et al UptoDate 2015*
Statin Choices: a review

<table>
<thead>
<tr>
<th>Statin</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Atorvastatin</strong></td>
<td>can use, just reduce dose to 10 or 20mg</td>
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<tr>
<td><strong>Lovastatin</strong></td>
<td>X</td>
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<tr>
<td><strong>Pravastatin</strong></td>
<td>can use, just less potent; use at lower doses (particular caution with DRV)</td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>X</td>
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<tr>
<td><strong>Fluvastatin</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rosuvastatin</strong></td>
<td>can use at 5 or 10mg dose, infrequently used b/c less accumulated data in HIV</td>
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<table>
<thead>
<tr>
<th>PL's</th>
<th>NNRTI's</th>
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<tbody>
<tr>
<td>Statins are metabolized by CYP3A4 system</td>
<td>All protease inhibitors downregulate CYP3A4</td>
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<td>EFV: raises CYP3A4 activity</td>
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<td></td>
<td>Pl's -&gt; can boost statin levels to dangerous levels and trigger rhabdomyolysis</td>
</tr>
</tbody>
</table>
# Overview of Drug Interactions Between Lipid Lowering Agents and HIV Drugs

<table>
<thead>
<tr>
<th>Lipid Lowering Agents</th>
<th>Atazanavir</th>
<th>Darunavir</th>
<th>Fosamprenavir</th>
<th>Indinavir</th>
<th>Lopinavir</th>
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<th>Saquinavir</th>
<th>Efavirenz</th>
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<th>Nevirapine</th>
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<th>Raltegravir</th>
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<td>Atorvastatin</td>
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[www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
Differential Effect of ART on Lipids

Slide from Dr. Vivek Jain UCSF

Green: No effect on lipids

Red: Worsening of lipid profile
Switching HIV regimens and lipids?

• Must weigh change in lipids vs. loss of virologic control
• If on PI associated with dyslipidemia, consider change to integrase inhibitor or NNRTI (rilpivirine)
• Change from lopinavir to atazanavir may be beneficial to lipids
• Change from boosted PI to raltegravir may benefit lipids

Mallolas J et al JAIDS 2009
Martinez E et al AIDS 2010
Eron JJ et al Lancet 2010
Acknowledgements

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Algorithm for Managing Elevated LDL-C in HIV Patients

Pt on PI
- Avoid lovastatin/simvastatin
- Atorvastatin at lower dose (start at 10mg and titrate up not to exceed 40 mg)
- Rosuvastatin at lower dose
- Pravastatin interacts with darunavir
- Pitavastatin/Fluvastatin?
- Ezetimibe

If lipids remain high, consider changing PI to integrase inhibitor (raltegravir)
Or a more lipid friendly PI atazanavir

Pt not on PI
- Statin therapy per NCEP guidelines

How will the new guidelines impact HIV-infected individuals?

Saturn ("Jupiter-HIV") vs. Jupiter

- LDL lowering higher in Jupiter
  - LDL decreased 28% in Saturn vs. 50% in Jupiter
- No impact on inflammatory markers in HIV
  - No impact on hsCRP in Saturn vs. 37% reduction vs. placebo in Jupiter

Will statins target the inflammatory pathways of interest in HIV?
Rosuvastatin in HIV did not impact inflammatory markers

- 147 HIV pts on stable ART, with LDL ≤ 130mg/dL and hsCRP > 2mg/L and/or expression of CD38 and HLA-DR antigens on ≥ 19% of CD8+ T cells at screening
- 24 weeks of rosuvastatin 10mg daily reduced Lp-PLA2 and LDL but did not impact inflammatory/coagulation markers (hsCRP, IL-6, D-dimer, fibrinogen).

Eckard A et al JID 2014
Role of Chronic Inflammation in the Pathogenesis of HIV-Associated Coronary Artery Disease during Antiretroviral Therapy

Deeks et al., NEJM 2012
Statin Use and DM in HIV:

• Retrospective study of statin use and risk of DM (abstract 766): pts with no statin at ART initiation
  – 5380 pts followed for 9.8 years, nadir CD4 214, 162 developed DM,
  – Statin use associated with 77% reduction in risk of DM (95% CI 0.08 to 0.63, p=0.004)
  – BMI > 30, TG, BL glucose, and use of D4T and DDI also associated.

• HIV Outpatient Study (Abstract 767)
  – 4962 pts followed for 49 months.
  – Statin use associated with incident DM (HR 1.1 per year, 95%CI 1.01-1.2, Hispanic race, and BMI ≥ 30.

Spagnuolo V et al Abstract 766 CROI 2013
Lichtenstein K et al Abstract 767 CROI 2013