HIV & Cardiovascular Disease Update

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Massachusetts General Hospital

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September 29, 2017
Disclosures

- None
Learning Objectives

• Outline the impact of non-infectious complications in the management of long-term HIV infection

• Relate postulated mechanisms of cardiovascular disease (CVD) development to features of long-term HIV disease, the aging HIV population and antiretroviral treatment

• Apply best practice guidelines to the optimal management of cardiovascular-related complications in HIV patients
Outline

• Epidemiology of HIV and CVD
• Pathophysiology of HIV and CVD
  – Role of traditional risk factors and ART
  – Role of inflammation/immune activation
• Management of CVD in HIV
  – CVD risk prediction
  – CVD prevention
    • Novel risk factors
    • Traditional risk factors
HIV Patients are Aging

- Projected age distribution of HIV patients on ART 2010-2030
- National Dutch ATHENA cohort with data between 1996 and 2010
- Median age will increase from 43.9 years in 2010 to 56.6 in 2030
- Proportion of HIV patients over 50 will increase from 28% in 2010 to 73% in 2030

HIV Patients will Face Increased Rates of NCDs as they Age

- Predicted burden of non-communicable diseases (NCDs) in HIV patients modeled for 2010-2030
- NCDs include
  - Cardiovascular disease (hypertension, hypercholesterolemia, myocardial infarction, stroke)
  - Diabetes
  - Chronic kidney disease
  - Osteoporosis
  - Non-AIDS malignancies

Aging-associated noncommunicable comorbidities (AANCC) include: HTN, MI, PAD, CVA, angina, DM2, COPD, CKD, non-AIDS cancer, fracture/osteoporosis.
Heart Trouble Early and Often in H.I.V. Patients

By DONALD G. McNEIL, JR.  JUNE 18, 2012

Mike Godfrey was 19 when he found out he had H.I.V.

He was 29 when he began antiretroviral medications.

He was 43 when he had a heart attack.

“I felt fluttery,” he said. “Weird and flush.”

A week later, it came back, and this time I felt something in my chest. I was too stupid to call an ambulance when I went to the hospital.”

Mr. Godfrey’s experience exemplifies why some AIDS specialists have long suspected that heart attacks may occur in people infected with H.I.V. and infected with treatments for the virus.

Co-developed with the American Academy of HIV Medicine

HIV and Your Heart

HIV Medications

Most people take HAART therapy to control the virus and stay healthy. Learn about how these medications work and why cardiovascular risks may change while on HAART therapies.

Your Healthcare Team

Although HIV can be a scary diagnosis, you can look forward to a bright future. Learn how you can actively work with your doctor to manage your health.

HIV and Your Risk for Cardiovascular Disease

By learning about your increased risks, you’ll understand why it’s important to create new healthy habits. Change your future and live a longer and healthier life.

About HIV

Today, HIV is treatable. People living with Human Immunodeficiency Virus (H.I.V.) can plan for a normal lifespan if they stay on treatments and take care of their heart health.

http://www.heart.org/HEARTORG/Conditions/More/HIVandYourHeart/HIV-and-Your-Heart_UCM_313033_SubHomePage.jsp#
## HIV and Risk of Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Population</th>
<th>N (HIV)</th>
<th>Primary Result</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein</td>
<td>2002</td>
<td>Kaiser</td>
<td>4159</td>
<td>↑ MI and CHD in HIV vs. control</td>
<td>1.5 (MI) 1.7 (CHD)</td>
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<tr>
<td>Currier</td>
<td>2003</td>
<td>CA Medicaid</td>
<td>28513</td>
<td>↑ CHD in HIV (age 18-33) vs. control</td>
<td>2.06</td>
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<td>Triant</td>
<td>2007</td>
<td>Partners</td>
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<td>↑ MI in HIV vs. control</td>
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<td>Obel</td>
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<td>Danish cohort</td>
<td>3953</td>
<td>↑ CHD in HIV (on ART) vs. control</td>
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<tr>
<td>Lang</td>
<td>2010</td>
<td>FHDH</td>
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<td>↑ MI in HIV vs. 3 population registries</td>
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<tr>
<td>Durand</td>
<td>2011</td>
<td>Quebec</td>
<td>7053</td>
<td>↑ MI in HIV vs. 4:1 matched control</td>
<td>2.11</td>
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<tr>
<td>Freiberg</td>
<td>2013</td>
<td>VA</td>
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<td>↑ MI in HIV vs. 2:1 matched control</td>
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<tr>
<td>Silverberg</td>
<td>2014</td>
<td>Kaiser</td>
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<td>↑ MI and CHD in HIV vs. 10:1 matched control</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Cardiovascular Outcomes beyond CHD

Heart failure
- Increased risk HF in HIV veterans vs. controls
  - Adjusted HR 1.81
  - Higher risk associated with HIV viremia
- Compared with control women, women with HIV have
  - Increased rates cumulative HF hospitalization
  - Increased HF length of stay
  - Increased CV mortality
  - Decreased use of optimal HF pharmacologic therapy

Sudden cardiac death
- In San Francisco HIV cohort sudden cardiac death rate 2.6 per 1,000 PYs
- 4.5-fold higher rate than expected.

Butt Arch Intern Med 2011; Janjua JACC 2016; Tseng JACC 2012.
Hospitalization Rates by Diagnosis

- CVD admissions surpassed AIDS-defining illnesses in 4 U.S. clinics
- In military cohort, higher nadir/recent CD4 count associated with decreased risk all-cause hospitalization

Berry IAC 2010. Abstract TUPE0221; Crum-Cianflone JAIDS 2010;54:2478-257
CVD Mortality in HIV

Underlying cause of Death

<table>
<thead>
<tr>
<th></th>
<th>Mortalité 2000</th>
<th>Mortalité 2005</th>
<th>Mortalité 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$ (%), $N$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>456 (47)</td>
<td>375 (36)</td>
<td>182 (25)</td>
</tr>
<tr>
<td>Non-AIDS-defining nonhepatitis-related malignancy</td>
<td>104 (11)</td>
<td>173 (17)</td>
<td>161 (22)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>122 (13)</td>
<td>154 (15)</td>
<td>77 (11)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>87 (7)</td>
<td>88 (8)</td>
<td>73 (10)</td>
</tr>
<tr>
<td>Unexplained sudden death</td>
<td>215 (22)</td>
<td>252 (24)</td>
<td>235 (32)</td>
</tr>
<tr>
<td>Various causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$p$-value adjusted for age and sex < 0.0001 (multinomial logistic model)

NaNH malignancy: non-AIDS defining and non-viral hepatitis related malignancy

Morlat AIDS 2014.
Outline

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- Pathophysiology of HIV and CVD
  - Role of traditional risk factors and ART
  - Role of inflammation/immune activation
- Management of CVD in HIV
  - CVD risk prediction
  - CVD prevention
    - Novel risk factors
    - Traditional risk factors
Pathophysiology of HIV-Associated CVD

- Early (1990s-early/mid 2000s) understanding of heightened CVD risk
- Traditional CVD risk factors
  - Elevated rates observed in HIV
- ART
  - Select PIs
  - Abacavir (debated)
  - Effects on CVD risk factors versus other effects

Artifacts:
- GENETICS
- DIABETES
- HYPERTENSION
- SMOKING
- DYSLIPIDEMIA
Traditional CVD Risk Factors in HIV

Smoking in HIV
- Heightened rates
  - 56% (D:A:D)
  - 54% (SFGH)
  - 47% (US cohort)
  - 69% (French cohort)
- 85% lifetime history
- Significantly higher than non-HIV patients

Impact of Smoking in HIV

- Treated HIV patients may lose more life years through smoking than HIV
- Excess mortality with smoking increases with age

- Increased incidence rate ratio for AMI for smokers
- Quitting smoking decreases AMI event rates
  - IRR 3.73 <1 year since quitting
  - IRR 2.07 >3 years since quitting

AMI Incidence Increased with ART/Pis

• D:A:D - prospective observational cohort of 33,347 patients
• Relative risk of AMI 1.16 per year ART exposure
• PIs but not NNRTIs conferred increased risk
• Cumulative exposure to indinavir (RR 1.12 per year) and lopinavir-ritonavir (RR 1.13 per year) associated with increased risk of AMI
• No increased risk observed with atazanavir

AMI Incidence Increased with Abacavir

- MI event rate increases as predicted CHD risk increases
- Within each predicted CHD risk category, MI rates higher with abacavir use
- Relative risk greater at lower predicted CHD risk

### Abacavir and MI Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Design</th>
<th>Effect</th>
<th>Effect Size</th>
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</thead>
<tbody>
<tr>
<td>D:A:D</td>
<td>33347</td>
<td>observational cohort</td>
<td>Yes</td>
<td>RR 1.90</td>
</tr>
<tr>
<td>SMART</td>
<td>2752</td>
<td>observational RCT</td>
<td>Yes</td>
<td>HR 4.3</td>
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<tr>
<td>GSK</td>
<td>14174</td>
<td>pooled RCTs</td>
<td>No</td>
<td>RR 0.81</td>
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<tr>
<td>STEAL</td>
<td>357</td>
<td>RCT</td>
<td>Yes</td>
<td>HR 0.12 (TDF)</td>
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<tr>
<td>Danish</td>
<td>2952</td>
<td>prospective cohort</td>
<td>Yes</td>
<td>RR 2.00</td>
</tr>
<tr>
<td>FHDH</td>
<td>1173</td>
<td>nested case-control</td>
<td>No</td>
<td>OR 1.27</td>
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<tr>
<td>VA (original)</td>
<td>19424</td>
<td>observational cohort</td>
<td>No</td>
<td>HR 1.18/yr</td>
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<tr>
<td>Quebec</td>
<td>7053</td>
<td>nested case-control</td>
<td>Yes</td>
<td>OR 1.79</td>
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<tr>
<td>Meta-analysis</td>
<td>9233</td>
<td>28 RCT meta-analysis</td>
<td>No</td>
<td>RR 0.73</td>
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<td>FDA Meta-analysis</td>
<td>5028</td>
<td>26 RCT meta-analysis</td>
<td>No</td>
<td>OR 1.02</td>
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<tr>
<td>ALLRT</td>
<td>5056</td>
<td>ACTG RCTs</td>
<td>No</td>
<td>HR 0.7</td>
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<tr>
<td>VA</td>
<td>10931</td>
<td>observational cohort</td>
<td>Yes</td>
<td>HR 1.48</td>
</tr>
</tbody>
</table>

Contemporary PIs and CVD Risk

- Increasing CVD risk with cumulative exposure to DRV/r but not ATV/r
- 59% increased risk CVD per 5 years exposure to DRV/r

Ryom et al. Abstract 128LB. CROI 2017
Contemporary PIs and CVD Risk

In multivariate models, cumulative DRV/r use associated with increased CVD risk.

Results unchanged with:
- Allowing factors on causal pathway to CVD to vary over time (vs fixed at baseline)
- Adjustment for bilirubin levels
- Evaluation of MI and stroke individually
- Stratification by high versus low predicted CVD risk

Ryom et al. Abstract 128LB. CROI 2017
Contemporary PIs and CVD Risk

- Cumulative use of DRV/r but not ATV/r associated with increased CVD risk of 59% per 5 years of exposure
- Strength of association similar to that of IDV and LPV/r but not modified by dyslipidemia
- Limitations:
  - Unclear how NRTIs including abacavir accounted for
  - Unmeasured confounding
  - Cannot prove causality
  - No dose data
  - No gender-stratified analyses
- Suggests possible PI class effect
- Clinical implications potentially significant → further studies likely

Ryom et al. Abstract 128LB. CROI 2017
Traditional Risk Factors Do Not Explain CVD Risk in HIV

• Increased AMI risk persists despite accounting for established CVD risk factors and ART use
  – Traditional risk factors only account for 10-25% of risk in large cohorts
  – Persistent 40-80% increased risk in HIV-infected patients
• Persistently increased risk thought to be driven by HIV-specific inflammation and immune activation, supported by extensive data
  – SMART study
  – Biomarkers of inflammation linked to surrogate markers of CVD
  – Vulnerable plaque and arterial inflammation linked to monocyte activation
  – Low CD4 and high viral load linked to CVD events
• In treated and suppressed HIV patients:
  – Reduced but persistent inflammation/immune activation and CVD risk
SMART, Inflammation and CVD

- SMART study showed increased CVD event rates in drug conservation (episodic treatment) vs. viral suppression (continuous treatment) group
  - HR=1.57, P=0.05
  - Primary endpoint recurrent OI/death

- Inflammatory markers IL-6 and d-dimer increased 1 month after treatment interruption in SMART
- Baseline hsCRP, IL-6, and d-dimer strongly correlated to overall mortality

Arterial Inflammation in HIV

- Arterial inflammation (measured by target to background ratio of FDG uptake in arterial wall) in the aorta was higher in HIV vs non-HIV FRS-matched controls
- sCD163, marker of monocyte activation, higher in HIV group than comparable non-HIV control participants
- Aortic arterial inflammation (TBR) significantly correlated with sCD163 ($P = .04$)

Subramanian JAMA 2012.
Decreased CD4 Count Linked to CVD

- CD4 <500 associated with CVD events independent of CVD risk factors or ART
- CD4 <200 independently associated with AMI with OR of 1.74

Lichtenstein CID 2010; Triant JAIDS 2010.
Increased HIV RNA Linked to CVD

- Increased HIV viral load linked to ischemic stroke events
- Detectable viral load (>50) associated with increased risk myocardial infarction with odds ratio of 1.51

### TABLE 4. HRs for Stroke in HIV-Stratified Models

<table>
<thead>
<tr>
<th></th>
<th>HIV (n = 2255)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.97 (0.50 to 1.89)</td>
<td>0.921</td>
</tr>
<tr>
<td>Age</td>
<td>1.06 (1.03 to 1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 count (cells/mm³)*</td>
<td>0.97 (0.90 to 1.05)</td>
<td>0.477</td>
</tr>
<tr>
<td>HIV RNA (copies/mL)†</td>
<td>1.10 (1.04 to 1.17)</td>
<td>0.001</td>
</tr>
<tr>
<td>CNS infection/malignancy</td>
<td>2.75 (1.26 to 6.03)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Chow JAIDS 2014; Lang CID 2012.
Decreased CD4 Count and HIV Viremia Independently Increase CVD Risk

Table 4. Time-Updated Analyses Assessing the Association of HIV-1 RNA and CD4 Cell Count Values and the Risk of AMI in Separate Models

<table>
<thead>
<tr>
<th>Category</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uninfected</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>≥500</td>
<td>1.75 (1.40-2.18)</td>
<td>.05</td>
</tr>
<tr>
<td>&lt;500</td>
<td>1.39 (1.17-1.66)</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uninfected</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>1.88 (1.46-2.40)</td>
<td>.04</td>
</tr>
<tr>
<td>≥200</td>
<td>1.43 (1.21-1.69)</td>
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</table>

- AMI risk in recent VA study by CD4 and HIV RNA status
- HIV RNA ≥500 and CD4 < 200 associated with increased AMI risk
- AMI risk persists in patients achieving virologic suppression
HIV Elite Controllers: Further Insight into HIV/CVD

- Study comparing HIV patients on basis of treatment and virologic suppression status to HIV-negative controls
- Outcome surrogate marker of atherosclerosis
- cIMT increased for all HIV groups versus controls
  - Effect independent of ART exposure, viremia, or immunodeficiency
  - HIV elite controllers had increased cIMT vs. controls

Hsue AIDS 2009.
Pathophysiology of HIV-Associated CVD

ART

Increase risk
Decrease risk

VIRAL REPLICATION
INFLAMMATION
IMMUNE ACTIVATION
MICROBIAL TRANSLOCATION

CVD

DYSLIPIDEMIA
DIABETES
HYPERTENSION
SMOKING

GENETICS
Outline

• Epidemiology of HIV and CVD

• Pathophysiology of HIV and CVD
  – Role of traditional risk factors and ART
  – Role of inflammation/immune activation

• Management of CVD in HIV
  – CVD risk prediction
  – CVD prevention
    • Novel risk factors
    • Traditional risk factors
Challenges in Management of HIV-Associated CVD

- Understanding of mechanism has not yet translated into tailored clinical interventions
  - Area of intensive investigation
- Unclear applicability of general population guidelines
- Limitations of HIV-specific CVD guidelines

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Traditional Risk Factors</th>
<th>Novel Risk Factors</th>
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<tbody>
<tr>
<td>Statins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunomodulatory agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking cessation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN management</td>
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</table>
HIV-Specific CVD Guidelines

Guidelines for the Evaluation and Management of Dyslipidemia in Human Immunodeficiency Virus (HIV)–Infected Adults Receiving Antiretroviral Therapy: Recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group

European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV

Primary Care Guidelines for the Management of Persons Infected With HIV: 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America

ACC/AHA CVD Risk Guidelines Add Complexity to Risk Prediction in HIV

- New ACC/AHA guidelines on CVD risk estimation released in 2013
- New CVD risk prediction equation employed (Pooled cohorts equation)
- Reports of overestimation of risk in the general population
- Release of new longitudinal risk estimator that factors in CVD risk factor treatment

Goff Circulation 2014; Lloyd-Jones JACC 2016.
CVD Risk Prediction in HIV

• FRS shown to underestimate AMI and stroke risk in HIV
• HIV-specific risk prediction algorithm developed by D:A:D group includes traditional CVD risk factors plus:
  – indinavir, lopinavir/ritonavir, and abacavir exposure
  – CD4 count, cumulative PI and NRTI exposure, and current abacavir use (updated model)
• HOPS study of 2283 HIV-infected individuals showed 4 risk scores to be inaccurate in HIV:
  – FRS: moderate discrimination (ability to distinguish patients with and without outcome) and good calibration (agreement between observed and predicted risk)
  – ACC/AHA: good discrimination but poor calibration

CVD Risk Prediction in CNICS

- Pooled Cohorts Equations evaluated in 11288 patients in CNICS cohort
- Discrimination adequate
- Calibration (model fit) moderate but driven by white men
- PCEs predicted lower MI rates (underestimated risk), particularly in low/moderate risk group where clinical decision making uncertain
- HIV-specific factors did not improve risk prediction

Feinstein JAMA Cardiology 2016
CVD Risk Prediction in CNICS

A White men

B Black men

C White women

D Black women
CVD Risk Prediction in Partners: FRS

- FRS and ACC/AHA risk scores validated in 1713 patients in Partners HIV Cohort
- Discrimination suboptimal (c statistics 0.68, 0.65 in men and 0.66, 0.62 in women)
- Calibration poor and reflects inadequate fit of general population functions to HIV
- Observed risk greater than predicted risk in most deciles for men and all deciles with events for women
- Indicates underestimation of risk

Triant, preliminary data.
CVD Risk Prediction in Partners: ACC/AHA

- Observed risk greater than predicted risk in all but 2nd decile for men and all deciles for women
- Indicates underestimation of risk
- Degree of underestimation greater in women and low-moderate CVD risk

Triant, preliminary data.
CVD Risk Prediction in HIV: Strategies

- Established CVD risk prediction functions underestimate risk in HIV
- Optimizing CVD risk prediction in HIV will likely require incorporating novel risk factors that reflect the mechanism of HIV-associated CVD into established algorithms
- New ACC/AHA risk score overestimates risk in general population but may underestimate risk in HIV

Clinical strategy
- Consider using ACC/AHA risk score as lower estimate of risk
- Patients in high-risk category by at least one score (>10% for FRS and >7.5% for ACC/AHA) merit:
  - Suppressive ART if not already treated
  - Strong consideration of statin
  - Aggressive CVD risk factor reduction
ART and CVD Risk

• **Paradigm shift in role of ART in relation to CVD risk in HIV**

• **2010 IAS-USA HIV treatment guidelines**
  – Recommended initiation of ART specifically for patients with high cardiovascular risk regardless of CD4 count
  – Endorse aggressive management of modifiable CVD risk factors

• **2012 DHHS HIV treatment guidelines**
  – Recommend antiretroviral therapy for all HIV-infected individuals
  – *The recommendation to initiate therapy at CD4 count >500 cells/mm3 (BIII) is based on growing awareness that untreated HIV infection or uncontrolled viremia may be associated with development of many non-AIDS defining diseases, including cardiovascular disease (CVD), kidney disease, liver disease, neurologic complications, and malignancy*

• Strategic Timing of AntiRetroviral Treatment (START) study

• First RCT to assess rates of events including non-AIDS/CVD by early (>500) versus deferred (<350) ART initiation

• Kaplan–Meier estimates of the cumulative percentages of patients with the composite primary end point (a serious AIDS-related or serious non–AIDS-related event, including death) in the two study groups.

• Early treatment reduced serious illness/death by 53%
  – Greater risk reduction for AIDS events (70%) vs non-AIDS events (33%)

Insight Start Study Group NEJM 2015
START: Early ART Does Not Improve Vascular Function

- Early ART does not improve vascular function among younger patients with preserved immunity
  - No improvement (increase) in arterial elasticity comparing immediate vs deferred ART
- Explanations
  - CVD risk may not be reflected in this outcome
  - Follow up may not be adequate
  - START patient group may have decreased CVD risk at baseline (young pts with preserved CD4)
  - Preliminary CVD events in START: 12 in immediate arm vs 14 in deferred arm

ART and CVD Risk: Strategies

• Treat HIV to reduce CVD risk

• CVD-related benefit from virologic suppression and immune reconstitution achieved by treating HIV thought to outweigh possible proatherogenic effects of individual medications

• START trial was first RCT to assess rates of comorbidities including CVD by early versus deferred ART initiation

Clinical strategy

• Treat HIV to reduce inflammation, immune activation, and associated cardiovascular risk

• Consider underlying CVD risk when selecting specific drugs, as individual ART medications may have varying risk

Thompson JAMA 2010; clinicaltrials.gov NCT00867048.
Statins in HIV

- **Dyslipidemia in HIV:**
  - Prevalent, with higher rates than control patients
  - Distinctive pattern of low HDL and high TG
  - May be more difficult to treat with statins
  - Drug interactions with ARVs important

- **Statins are mainstay of treatment and may reduce both traditional and non-traditional risk factors**

- **Statins in HIV:**
  - Effectively lower LDL
  - Decrease immune activation (T cell and monocyte)
  - Contribute to immune reconstitution independent of ART
  - Decreased mortality in HIV observational cohort

Paradigm Shift in Cholesterol Treatment for General Population

- New cholesterol/statin guidelines released November 2013
- Replaced NCEP ATP-III
- Controversial new approach to treating cholesterol

Stone Circulation 2014.
2013 ACC/AHA
Cholesterol Treatment Guidelines

• Statin initiation: 4 major benefit groups
  – Clinical ASCVD
  – LDL ≥ 190 mg/dL
  – DM age 40-75
  – Estimated 10-year ASCVD risk ≥ 7.5%

• No LDL treatment targets
• No non-statin therapies
• New risk calculator to estimate 10-yr ASCVD risk
• Recommend increased statin treatment in general population
Limitations of New Cholesterol Guidelines in HIV

Future Updates to the Blood Cholesterol Guideline

CQs for future guidelines could examine:

1. the treatment of hypertriglyceridemia;
2. use of non-HDL-C in treatment decision-making;
3. whether on-treatment markers such as Apo B, Lp(a), or LDL particles are useful for guiding treatment decisions;
4. the best approaches to using noninvasive imaging for refining risk estimates to guide treatment decisions;
5. how lifetime ASCVD risk should be used to inform treatment decisions and the optimal age for initiating statin therapy to reduce lifetime risk of ASCVD;
6. subgroups of individuals with heart failure or undergoing hemodialysis that might benefit from statin therapy;
7. long-term effects of statin-associated new onset diabetes and management;
8. efficacy and safety of statins in patient groups excluded from RCTs to date (e.g., HIV positive or solid organ transplant); and
9. role of pharmacogenetic testing.

8. Limitations

Exceeding the risk of adverse events or drug-drug interactions. Clinician judgment is especially important for several patient groups for whom the RCT evidence is insufficient for guiding clinical recommendations. These patient groups include younger adults (<40 years of age) who have a low estimated 10-year ASCVD risk, but a high lifetime ASCVD risk based on single strong factors or multiple risk factors. Other groups include those with serious comorbidities and increased ASCVD risk (e.g., individuals with HIV, rheumatologic or inflammatory diseases, or who have undergone a solid organ transplant). This guideline encourages clinicians to use clinical judgment in these situations weighing potential benefits, adverse effects, drug-drug interactions and patient preferences.

Stone Circulation 2014.
Further Challenges in Applying New Cholesterol Guidelines to HIV

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin (40 mg)–80 mg</td>
<td>Atorvastatin 10 (20) mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Kosuvasatin 20 (40) mg</td>
<td>Rosuvastatin (3) 10 mg</td>
<td>Pravastatin 10–20 mg</td>
</tr>
<tr>
<td>Simvastatin 20–40 mg</td>
<td>Pravastatin 40 (80) mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin 20–40 mg</td>
</tr>
<tr>
<td>Fluvastatin 40 mg bid</td>
<td>Pitavastatin 2–4 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

Dose-adjustment in HIV (with PIs)
Contraindicated in HIV (with PIs)
Awaiting further study in HIV

Stone Circulation 2014.
The REPRIEVE trial is the first large-scale randomized clinical trial to test a strategy for preventing heart-related disease among people living with HIV.

Hypothesis: Statins will prevent cardiovascular disease in HIV-infected patients, particularly among the large group with minimal traditional risk and not meeting current guidelines for clinical use of statins but at risk for CVD based on unique pathophysiology of vulnerable plaque morphology and inflammation.

Personal communication, Grinspoon 2014.
**REPRIEVE Study Design**

- **Screening and Consent**
  - Asymptomatic HIV+ patients with no history of CVD

- **Randomization**
  - Placebo
  - Pitavastatin 4mg/day

- **Intervention**
  - Mechanistic Study
    - Coronary plaque, vascular inflammation, immune activation

- **Mechanistic Primary Endpoint**
  - CV Death
  - MI
  - Unstable Angina
  - Stroke
  - Arterial Revasc

- **Clinical Primary Endpoint**
  - Individual components of primary endpoint
    - All cause death
    - Incidence/Progression of noncalcified plaque; High-risk plaque
    - Inflammatory, immunological, metabolic biomarkers
    - Predictors of statin effects
    - Statin safety and non AIDS comorbidities: DM, Infections, Cancer

- **Secondary Endpoints**

- **Eligibility**
  - Age >40
  - No CVD
  - Not on statin
  - Stable ART
  - Not recommended for statin by 2013 ACC/AHA guidelines

*Personal communication, Grinspoon 2014.*
Statins in HIV: Strategies

- HIV patients excluded from RCTs
- Different mechanism of CVD
- Different typical cholesterol profile
- Unclear role of new ACC/AHA risk calculator
- Statin intensity definition not directly applicable

Clinical strategy
- In HIV, still likely that statins will be effective in risk groups outlined by guidelines
  - Traditional risk factors remain important in HIV
  - Risk scores may underestimate risk in HIV
- Await REPRIEVE results

Clinical strategy based on expert opinion.
Dyslipidemia in HIV: Strategies

Clinical strategy

- Check fasting lipids
  - At HIV diagnosis
  - Prior to and within 1-3 months after starting or changing ART
  - Every 6-12 months
- Consider starting statin based on ACC/AHA cholesterol guidelines
- Consider therapy with:
  - Statin if LDL above ATPIII goal or TG 200-500 with elevated non-HDL
  - Fibrate if TG>500
- 2013 HIV primary care guidelines includes detailed statin-ARV interaction chart

<table>
<thead>
<tr>
<th>Statin</th>
<th>Level w/ PI</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>--</td>
<td>Can use safely</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>↑</td>
<td>Use with caution/low dose</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↑↑</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Lovastatin</td>
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</tr>
<tr>
<td>Pitavastatin</td>
<td>?</td>
<td>Accruing data</td>
</tr>
</tbody>
</table>

Novel Interventions Targeting Inflammation and Immune Activation

- ART treatment intensification
- Methotrexate
- CCR5 antagonists
- Rifaximin
- Sevelamer
- Mesalamine
- Pentoxifylline
- Hydroxychloroquine
- IL-1β inhibition with canakinumab

Smoking Cessation in HIV: Strategies

• Priority for all HIV-infected patients
• HIV patients cited as priority in 2008 clinical practice guideline *Treating Tobacco Use and Dependence*
• HIV-specific smoking cessation interventions differ in efficacy

Clinical strategy
• Apply guidelines for general population to all HIV smokers
  – Routine screening integrated into HIV primary care
  – Strong, brief, intensive repeated counseling
  – Pharmacologic interventions (varenicline safe and effective in HIV)
• Consider systematic approaches to identify HIV smokers and ensure smoking cessation interventions applied

DM and HTN Management in HIV: Strategies

- Check fasting glucose or HbA1C at HIV diagnosis, 1-3 months after starting or changing ART, and every 6-12 months
- HbA1C may be used for screening
  - Consider cutoff 5.8%
  - HbA1C may underestimate glycemia in HIV
- Check HbA1C every 6 months in DM
- Lifestyle intervention recommended
  - Shown to decrease HbA1C for HIV patients

- Check blood pressure annually
- Follow existing JNC8 (2014 Hypertension Guideline) for general population
  - No HIV-specific guidelines
- Consider drug interactions
  - Use of some calcium-channel blockers contraindicated with protease inhibitors

Prevention of HIV-Associated CVD

- ART
- Prevenir CVD
- ART

- Anti-inflammatories and Immune Modulators
- Statins

- Traditional Risk Factor Modification
  - Statins
  - Smoking Cessation
  - Lifestyle

Counsel
Implications and Future Questions

• Significant impact of CVD in HIV populations related to inflammation
• Current treatment paradigms do not reflect this pathophysiology
• Recommended strategies
  – Build CVD risk assessment into practice
  – Manage traditional CVD risk factors aggressively (e.g. smoking)
  – Start appropriate statin if candidate by general population guidelines
  – Low threshold for diagnostic workup in traditionally low-risk groups
  – Treat HIV to reduce CVD risk
• Future questions
  – How is CVD risk most accurately assessed in HIV?
  – What is the role for statins and immunomodulatory agents in reducing CVD risk in HIV?
  – Should HIV be considered a cardiovascular risk equivalent?
• Intensity and consistency of HIV care provide opportunity to prevent and manage chronic disease complications