ACTHIV 2018: A State-of-the-Science Conference for Frontline Health Professionals
How to Comply with ASCVD Guidelines and HIV thrombosis Risk Reduction

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Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Describe the current data on epidemiology and mechanism of CVD in HIV

• Apply best practices for predicting cardiovascular risk in HIV
Faculty and Planning Committee Disclosures
Please consult your program book.

• No disclosures.
• There will be no off-label/investigational uses discussed in this presentation.
Outline

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

• Epidemiology of HIV and CVD

• Pathophysiology of HIV and CVD
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HIV Patients are Aging and Face Increased NCD Rates

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

Non-Communicable Disease Complications in HIV

- Increased NCD rates are not explained by age alone
- For a given age group, HIV patients have higher burden of NCDs
- NCDs include HTN, MI, PAD, CVA, angina, DM2, COPD, CKD, non-AIDS cancer, fracture/osteoporosis

Schouten CID 2014.
Heart disease is increased in HIV and increasingly recognized as a clinical and public health priority.

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 HIV.
He was 29 when he began antiretroviral therapy.
He was 43 when he had a heart attack.

patients whose infection is well suppressed are at higher risk.

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>
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</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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<tr>
<td>Triant</td>
<td>2007</td>
<td>Partners</td>
<td>3851</td>
<td>↑ MI in HIV vs. control</td>
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<tr>
<td>Obel</td>
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<td>Danish cohort</td>
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<td>↑ CHD in HIV (on ART) vs. control</td>
<td>2.12</td>
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<tr>
<td>Lang</td>
<td>2010</td>
<td>FHDH</td>
<td>74958</td>
<td>↑ MI in HIV vs. 3 population registries</td>
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<tr>
<td>Durand</td>
<td>2011</td>
<td>Quebec</td>
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<td>↑ MI in HIV vs. 4:1 matched control</td>
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<td>Freiberg</td>
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<td>Silverberg</td>
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<td>Kaiser</td>
<td>22081</td>
<td>↑ MI and CHD in HIV vs. 10:1 matched control</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Hospitalization Rates by Diagnosis

- Hospitalization data from 2001 to 2008 from 11,645 HIV-infected adults at 4 geographically diverse US HIV clinics within the HIV Research Network
- CVD admissions surpassed AIDS-defining illness admission

Berry IAC 2010 and JAIDS 2012; Crum-Cianflone JAIDS 2010.
CVD-Related Mortality in HIV

- Compared mortality from 2000 to 2010 in French national sample
- AIDS-related mortality markedly declined
- CVD-related mortality increased

Morlat AIDS 2014.
Outline

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  – CVD risk prediction
  – CVD prevention
    • Novel risk factors
    • Traditional risk factors
Pathophysiology of HIV-Associated CVD

- Early 2000s
- Increased CVD risk in HIV initially recognized
- Risk attributed to:
  - Traditional CVD risk factors
Traditional CVD Risk Factors in HIV

Smoking in HIV
- High prevalence
  - 56% (D:A:D)
  - 54% (SFGH)
  - 47% (US cohort)
  - 69% (French cohort)
- 85% lifetime history
- More life years lost through smoking than through HIV

Dyslipidemia in HIV
- Distinctive pattern of low HDL and high TG
- May be impacted by PIs

Pathophysiology of HIV-Associated CVD

- Mid-2000s
- Emerging data on CVD risk with ART drugs and classes
- Risk attributed to:
  - Traditional CVD risk factors
  - Individual ART drug effects

Early 2000s CVD risk data

2006 SMART trial

2007-2008 ART data

2015 START trial

ART DRUGS

DYSLIPIDEMIA
DIABETES
HYPERTENSION
SMOKING
AMI Incidence Increased with 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

Darunavir and CVD Risk

- Increasing CVD risk with cumulative exposure to DRV/r but not ATV/r in multivariate models
- 59% increased risk CVD per 5 years exposure to boosted darunavir
- Strength of association similar to that of IDV and LPV/r but not modified by dyslipidemia
- Multiple sensitivity analyses performed with unchanged results
- Suggests possible PI class effect
  - Atazanavir is exception: hyperbilirubinemia associated with decreased CVD risk
- Clinical implications potentially significant → further studies likely

## 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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<td>D:A:D</td>
<td>33347</td>
<td>observational cohort</td>
<td>Yes</td>
<td>RR 1.90</td>
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<td>observational RCT</td>
<td>Yes</td>
<td>HR 4.3</td>
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<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>
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<td>prospective cohort</td>
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<td>RR 2.00</td>
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<td>nested case-control</td>
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<td>OR 1.27</td>
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<tr>
<td>VA (original)</td>
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<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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<td>Meta-analysis</td>
<td>9233</td>
<td>28 RCT meta-analysis</td>
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<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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<td>ALLRT</td>
<td>5056</td>
<td>ACTG RCTs</td>
<td>No</td>
<td>HR 0.7</td>
</tr>
<tr>
<td>VA</td>
<td>10931</td>
<td>observational cohort</td>
<td>Yes</td>
<td>HR 1.48</td>
</tr>
</tbody>
</table>

Abacavir and MI Risk in the NA-ACCORD

- N=8265 NA-ACCORD participants
- Recent abacavir use in prior 6 months associated with increased risk of MI after adjustment for known CVD risk factors
  - Adjusted HR 1.84

Kaplan Meier estimates for time from ART initiation to first myocardial infarction, by recent (within the last 6 months) abacavir use

Elion et al. JAIDS 2018:epub.
Abacavir and CVD Risk

- Several studies at CROI 2018 add to abacavir story
- Platelet function
  - Mallon (80) – increased platelet reactivity
  - Taylor (673) – studies of platelet dysfunction with abacavir (reversal of NO’s inhibitory effect on platelet aggregation, enhanced granule secretion and platelet activation)
  - Collado-Diaz (674) – pro-thrombotic effect of abacavir depends on leukocytes
- Increased coronary plaque with abacavir (692)
- Modelling study of abacavir replacement on CVD risk (692)

CVD Risk Persists...

- Persistently increased risk after accounting for traditional CVD risk factors and ART drugs
  - Traditional risk factors only account for 10-25% of risk in large cohorts
  - Persistent 40-80% increased risk in HIV-infected patients
- What is additional component driving risk?
Pathophysiology of HIV-Associated CVD

- Risk attributed to:
  - Traditional CVD risk factors
  - Individual ART drug effects
  - Inflammation and immune activation

ART DRUGS

INFLAMMATION

IMMUNE ACTIVATION

DYSLIPIDEMIA

DIABETES

HYPERTENSION

SMOKING

Early 2000s CVD risk data

2007-2008 ART data

2006 SMART trial

2015 START trial
SMART, Inflammation and CVD

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

- 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
- Suggests role for inflammation

Inflammation and CVD

• Extensive data support a role for inflammation in HIV-associated CVD risk
  – SMART study
  – Biomarkers of inflammation linked to surrogate markers of CVD
  – Vulnerable plaque and arterial inflammation linked to monocyte activation
  – Clinical surrogates of inflammation (viral load) and immune activation (CD4) linked to CVD events
  – START study

• Aortic arterial inflammation (measured by target to background ratio of FDG uptake in arterial wall) higher in HIV vs non-HIV
• sCD163, marker of monocyte activation, higher in HIV group than comparable non-HIV control participants
• Aortic arterial inflammation (TBR) significantly correlated with sCD163
Decreased CD4 Count Linked to CVD

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

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

- Increased HIV viral load associated with increased ischemic stroke risk
- Detectable viral load (>50) associated with increased AMI risk (OR 1.51)

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

- AMI risk in VA study by CD4 and HIV RNA status
- HIV RNA\(\geq 500\) and CD4\(<200\) each associated with increased AMI risk
- **AMI risk persists in patients achieving viral suppression**
  - Risk attributed to persistent inflammation

**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\(^a\)**

<table>
<thead>
<tr>
<th>Category</th>
<th>HR (95% CI)</th>
<th>P Value(^b)</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>(\geq 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>(\geq 200)</td>
<td>1.43 (1.21-169)</td>
<td></td>
</tr>
</tbody>
</table>

Freiberg JAMA IM 2013.
START Study

- Strategic Timing of AntiRetroviral Treatment (START) study
- First RCT to assess rates of events including non-AIDS by early (>500) versus deferred (<350) ART initiation
- Kaplan–Meier estimates of the cumulative percentages of patients with the composite primary end point (serious AIDS-related or serious non-AIDS-related event)
- Early treatment reduced serious illness/death by 53%
  - 70% risk reduction for AIDS events
  - 33% risk reduction for non-AIDS events

- Reinforced net benefit of early ART from CVD perspective

Insight Start Study Group NEJM 2015
Pathophysiology of HIV-Associated CVD

- Risk attributed to:
  - Traditional CVD risk factors
  - Individual ART drug effects
  - Inflammation and immune activation
  - Untreated HIV

- Early 2000s CVD risk data
- 2006 SMART trial
- 2007-2008 ART data
- 2015 START trial

- UNTREATED HIV
- ART DRUGS
- DYSLIPIDEMIA
- DIABETES
- HYPERTENSION
- SMOKING
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    - 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
- Current guidelines may be inadequate
  - Unclear applicability of general population guidelines
  - Limitations of HIV-specific guidelines with respect to CVD

<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>
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<tr>
<td>ASA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART</td>
<td></td>
<td></td>
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<tr>
<td>Immunomodulatory agents</td>
<td></td>
<td></td>
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<tr>
<td>Smoking cessation</td>
<td></td>
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<tr>
<td>Diabetes management</td>
<td></td>
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<tr>
<td>HTN management</td>
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</table>
Disconnect of Mechanism and Prevention in HIV-Associated CVD

Inflammation
Immune Activation
CVD
Untreated HIV
ART Drugs

Current CVD Prevention Strategies Only Target Traditional CVD Risk Factors

Early 2000s CVD risk data
2006 SMART trial
2007-2008 ART data
2015 START trial
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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

• Risk prediction algorithms predict 10-year risk of developing CVD for the general population
  – Framingham Risk Score
  – ACC/AHA

• Accuracy of CVD risk prediction algorithms in HIV is unclear

• Hypothesized that existing CVD risk prediction algorithms **underestimate** risk
  – Incorporate only traditional CVD risk factors
  – Do not incorporate novel, HIV-related factors

• In 2013 ACC/AHA released new CVD risk prediction algorithm (Pooled Cohorts Equations) designed to be applicable to a more general U.S. population.
  – Initial reports demonstrated possible **overestimation** of risk

CVD Risk Prediction 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)
  – Not widespread clinical adoption in U.S.

• Emerging data suggest traditional CVD risk algorithms are inaccurate in HIV
  • HOPS cohort
    – Evaluated 4 risk scores in 2283 HIV-infected individuals
    – No model performed well for both common metrics:
      • Discrimination (ability to distinguish patients with and without outcome)
      • Calibration (agreement between observed and predicted risk)
    – FRS: good calibration but moderate discrimination
    – ACC/AHA PCE and D:A:D: good discrimination but moderate calibration
    – SCORE: poor discrimination and calibration

• CNICS cohort
• Partners HIV cohort

CVD Risk Prediction in CNICS

• ACC/AHA Pooled Cohorts Equations validated in 11288 patients in CNICS
• Discrimination (ability to distinguish patients with and without outcome) adequate
• Calibration (agreement between observed and predicted risk) moderate but driven by white men
• **Underestimation** of risk demonstrated:
  – Among black women and men
  – Among low/moderate predicted CVD risk groups where clinical decision making uncertain
• HIV-specific factors did not improve risk prediction
CVD Risk Prediction in Partners

- FRS and ACC/AHA risk scores validated in 1272 patients in Partners HIV Cohort
- Discrimination (ability to distinguish patients with and without outcome) moderate
  - c statistics 0.68, 0.65 in men and 0.66, 0.62 in women for FRS and ACC/AHA
- Calibration (agreement between observed and predicted risk) poor
  - Reflects inadequate fit of general population functions to HIV
- Observed risk greater than predicted risk for ACC/AHA in all but 2nd decile for men and all deciles for women
- Underestimation of risk demonstrated, with degree of underestimation greater:
  - Among women
  - Among low/moderate CVD risk groups where clinical decision making uncertain

Triant, CROI 2015; Triant, Circulation 2018.
CVD Risk Prediction in HIV: Strategies

• Established CVD risk prediction algorithms appear to 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

Clinical strategy
• Consider using ACC/AHA risk score as lower estimate of risk
  – Current algorithms do not account for HIV-related factors
• Patients in high-risk category by at least one score (>7.5% for ACC/AHA or >10% for FRS) merit:
  – Suppressive ART if not already treated
  – Strong consideration of statin
  – Aggressive CVD risk factor reduction
    • Role for entire clinical team (non-prescribers)
    • Promotion of lifestyle modification

Based on expert opinion.
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    • Traditional risk factors
Statins in HIV

• Statins are an intervention that may reduce both traditional and novel CVD risk factors in HIV; pleiotropic effects include:
  – Lipid-lowering effects
  – Anti-inflammatory effects
• In HIV, statins have been shown to:
  – Effectively lower LDL
    • May be less effective in HIV vs non-HIV
  – Decrease immune activation (T cell and monocyte)
  – Contribute to immune reconstitution independent of ART
  – Reduce non-calcified plaque volume and high-risk coronary plaque features
  – Slow progression of CCA-IMT
  – Reduce risk of virologic failure after viral suppression on ART
  – Decrease mortality in an HIV observational cohort
• Yet it remains unknown whether statins prevent CVD in HIV
  – Ongoing REPRIEVE trial is addressing this critical question

2013 ACC/AHA Cholesterol Guidelines

- Recommended new approach to determine statin eligibility (replaced NCEP ATP-III)
- Statin initiation recommended for 4 major benefit groups
  - Clinical ASCVD
  - LDL ≥ 190 mg/dL
  - DM age 40-75
  - Estimated 10-year ASCVD risk ≥ 7.5%
- New ACC/AHA CVD risk algorithm used to estimate 10-yr ASCVD risk
- Unclear applicability in HIV
  - HIV patients excluded from RCTs on which guidelines based
  - ACC/AHA risk score may be inaccurate in HIV
  - Statin-ART drug interactions are not accounted for in statin intensity recommendations which are fixed dose
- Guidelines failed to recommend statins in majority of HIV patients with high-risk morphology coronary plaque or with carotid plaque

Limitations of ACC/AHA 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.
Further Challenges in Applying New Cholesterol Guidelines to HIV

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
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<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>
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<tr>
<td><strong>Atorvastatin (40†)–80 mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg</strong></td>
<td><strong>Simvastatin 10 mg</strong></td>
</tr>
<tr>
<td><strong>Kosuvastatin 20 (40) mg</strong></td>
<td><strong>Kosuvastatin (3) 10 mg</strong></td>
<td><strong>Pravastatin 10–20 mg</strong></td>
</tr>
<tr>
<td><strong>Simvastatin 20–40 mg†</strong></td>
<td><strong>Pravastatin 40 (80) mg</strong></td>
<td><strong>Lovastatin 20 mg</strong></td>
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<tr>
<td><strong>Lovastatin 40 mg</strong></td>
<td><strong>Fluvastatin XL 80 mg</strong></td>
<td><strong>Fluvastatin 20–40 mg</strong></td>
</tr>
<tr>
<td><strong>Fluvastatin 40 mg bid</strong></td>
<td><strong>Pitavastatin 2–4 mg</strong></td>
<td><strong>Pitavastatin 1 mg</strong></td>
</tr>
</tbody>
</table>

Dose-adjustment in HIV (with PIs)

Contraindicated in HIV (with PIs)

Awaiting further study in HIV

Stone Circulation 2014.
REPRIEVE

• To address gaps in knowledge on statins in HIV, the REPRIEVE trial was designed to address:
  • Whether statins prevent CVD in HIV
  • Which patients with HIV should receive a statin
• REPRIEVE is the first large-scale randomized clinical trial to test a strategy for preventing heart-related disease among people living with HIV
• REPRIEVE specifically targets patients at low traditional CVD risk who would not be recommended for a statin to assess whether statins impact HIV-related risk factors beyond lipids

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

- 6500 patients
  - 4552 enrolled
- 100+ sites
  - US/international
- Eligibility
  - Age >40
  - No CVD
  - Not on statin
  - Stable ART
  - Not recommended for statin by 2013 ACC/AHA guidelines
- To be completed mid-2018

Personal communication: Grinspoon and Fitch 2017.
Novel Interventions Targeting Residual Inflammation and Immune Activation

- **ART treatment intensification**
  - Addition of raltegravir did not improve endothelial function or markers of T cell activation

- **CCR5 antagonists** - block HIV co-receptor CCR5
  - Maraviroc reduced progression of atherosclerosis in mouse model

- **Rifaximin** – antibiotic with anti-inflammatory properties
  - Minimally affected microbial translocation and T-cell activation in ART immune nonresponders

- **Sevelamer** – phosphate-binding drug
  - Did not reduce microbial translocation/immune activation but did improve lipid indices

- **Mesalamine** (5-aminosalicylic acid) – decreases mucosal inflammation in UC
  - Did not reduce T cell activation or increase CD4 count

Novel Interventions Targeting Residual Inflammation and Immune Activation

- **Pentoxifylline** - phosphodiesterase inhibitor
  - Did not improve endothelial function and *unexpectedly* increased inflammatory biomarker sTNFRI in untreated HIV
  - Did not improve endothelial function and unexpectedly attenuated reductions in proatherogenic inflammatory biomarkers in patients initiating ART

- **Hydroxychloroquine** – immunomodulatory/anti-inflammatory used in SLE and GFVD
  - Did not reduce T cell activation and *unexpectedly* resulted in greater CD4 decline and increased viral replication

- **Low-dose methotrexate**
  - Recent trial of 176 patients – A5314
  - No difference in endothelial function (assessed by FMD), inflammatory or coagulation markers (hsCRP, IL-10, sCD163, d-dimer, fibrinogen, VCAM, IL-6)
  - Decrease in CD4 and CD8 T cell activation with low-dose methotrexate
  - Decrease in arterial inflammation by FDG-PET with low-dose methotrexate

- **IL-1β inhibition with canakinumab** – monoclonal antibody that binds IL-1β and inhibits IL-6 production
  - Ongoing trial assessing endothelial function (assessed by brachial artery FMD), vascular inflammation (assessed by FDG-PET/CT scanning), inflammatory markers (hsCRP, IL-6, sCD163), D-dimer, T-cell/monocyte activation, HIV reservoir size

Traditional CVD Risk Factors: Strategies

**SMOKING**
- Prioritize cessation for all HIV-infected smokers

**DYSLIPIDEMIA**
- Use current guidelines as lower threshold for statin prescription
- Check fasting lipids as per HIV Primary Care Guidelines
- Be aware of statin-ART drug interactions
- Await REPRIEVE results

**DIABETES**
- Check fasting glucose or HbA1C as per HIV Primary Care Guidelines
- HbA1C may underestimate glycemia in HIV
  - Consider cutoff 5.8%

**HTN**
- Follow existing JNC8 (2014 Hypertension Guideline) for general population

Lifestyle Modification Strategies: Role of the Clinical Team

- Intensive lifestyle modification improves CVD risk indices in HIV-infected patients with metabolic syndrome
- Quitting smoking decreases AMI event rates in HIV
  - IRR 3.73 <1 year since quitting
  - IRR 2.07 >3 years since quitting

- Apply guidelines for general population to all HIV smokers
  - Routine screening integrated into HIV primary care
  - Strong, brief, intensive repeated counseling
  - Unclear whether HIV-specific smoking cessation interventions indicated
  - Role for all members of clinical team

- Consider systematic approaches to identify HIV-infected patients who might benefit from lifestyle modification
  - Counseling and education
  - Linking to community resources

ART and CVD Prevention

- Shift over time in overall role of ART in relation to CVD risk in HIV
- Benefit of ART with viral suppression and immune reconstitution thought to outweigh potential pro-atherogenic effects of individual medications
  - Can be considered CVD intervention for novel risk factors

- Role of ART as beneficial from CVD standpoint supported by clinical trials
  - SMART trial: continuous treatment superior to interrupted treatment
  - START trial: early treatment superior to deferred treatment

- Role of ART as beneficial from CVD standpoint reflected in HIV treatment guidelines
  - 2010 IAS-USA HIV treatment guidelines recommended initiation of ART specifically for patients with high cardiovascular risk regardless of CD4 count
  - 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*

Prevention of HIV-Associated CVD

TREAT HIV

SELECT ART BASED ON CVD RISK

PREVENT CVD

STATINS
NOVEL ANTI-INFLAMMATORIES

TRADITIONAL RISK FACTOR MODIFICATION:
STATINS
SMOKING CESSATION
TREAT DM/HTN
LIFESTYLE

Early 2000s
CVD risk data

2006
SMART trial

2007-2008
ART data

2015
START trial
Implications and Future Questions

• Significant impact of CVD in HIV populations related to inflammation
• Current treatment and prevention paradigms do not reflect mechanism
• Clinically relevant questions
  – How is CVD risk most accurately assessed in HIV?
  – What is the role for statins and anti-inflammatory/immunomodulatory agents in reducing CVD risk in HIV?
  – How does CVD differ in HIV patients in resource-limited settings?
  – Should HIV be considered a cardiovascular risk equivalent?
• Recommended strategies
  – Treat HIV to reduce inflammation, immune activation and associated CVD risk
  – Build CVD risk assessment into practice
  – Consider underlying CVD risk when selecting specific ART drugs
  – Manage traditional CVD risk factors aggressively (e.g. smoking)
  – Engage entire clinical team including nonprescribers
• Intensity and consistency of HIV care and patient engagement in care provide opportunity to prevent and manage chronic disease complications
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