The Heart of the Matter: HIV Cardiology Update

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Learning Objectives

- Cite three sources of reversible risk of cardiovascular (CV) disease in people with HIV
- Review Reprieve and other studies with clinical CV endpoints
- Optimize ART to minimize additional CV risk
- Discuss heart disease, aging, and mobility with patients

This talk will include off-label and investigational uses of antiretroviral drugs.
Outline

• Introduction
• Epidemiology: HIV and CV risk
• Pathogenesis
• Prevention and Treatment: 2 cases
• How to talk to PWHIV about aging, mobility, and CV disease
DSMB closed study of HIV+ low-mod CV risk age >50 after 5.1 years due to efficacy
-35% decrease in Major Adverse Cardiovascular Events (MACE)
-21% decrease in MACE or all-cause mortality
ARS #1

Which of the following statements best characterizes the use of statins in people living with HIV?

1. All patients with HIV should be treated with a statin
2. Some patients with HIV should be treated with a statin
3. The evidence is not conclusive that any PWHIV should be treated with a statin
4. I am not sure
ARS #1

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3. The evidence is not conclusive that any PWHIV should be treated with a statin
4. I am not sure
Overlapping Epidemics: HIV, Obesity, Diabetes Mellitus, and Cardiovascular Disease in the US

Koethe. CROI 2019
HIV History: SMART Study 2006

Lower incidence of CVD in pts on ART vs no ART

Elevated D-dimer & CRP Associated w/ 3.8x increase risk of mortality in PWHIV in START, SMART, & ESPRIT Studies

Boulware D et al. JID 2011;203:1637–46 DOI:10.1093/infdis/jir134

Jupiter trial shows that Rosuvastatin reduces CV Dx By 44% in people with no HIV and high CRP and chronic Inflammation
Ridker PM. NEJM 2008;359:
### HIV History: Statin Use Associated with a 77% Lower Mortality at the Moore Clinic, JHU, 2011

<table>
<thead>
<tr>
<th>Category, Subcategory</th>
<th>Relative Hazard (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin Use, Age (median years)</td>
<td>0.33 (0.14, 0.76)</td>
<td>0.009</td>
</tr>
<tr>
<td>Statin Use, Race</td>
<td>Black: 0.82 (0.47, 1.46), P=0.51</td>
<td>Others: 1.0 (reference)</td>
</tr>
<tr>
<td>Statin Use, HIV Risk Group</td>
<td>IDU: 2.30 (1.30, 4.07), P=0.004</td>
<td>Heterosexual: 1.50 (0.96, 2.35), P=0.08</td>
</tr>
<tr>
<td>CD4+ at HAART start (per 100 cell/mm² higher increments)</td>
<td>0.96 (0.84, 1.09), P=0.52</td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA at HAART start (per log₁₀ higher increments)</td>
<td>0.96 (0.79, 1.18), P=0.16</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin at HAART start (per g/dL higher increments)</td>
<td>0.80 (0.71, 0.90), P=0.0003</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol at HAART start (per 10 mg/dL higher increments)</td>
<td>0.98 (0.93, 1.03), P=0.36</td>
<td></td>
</tr>
<tr>
<td>Year HAART started, &lt; = 2004</td>
<td>1.20 (0.74, 2.06), P=0.50</td>
<td></td>
</tr>
<tr>
<td>Year HAART started, &gt; 2004</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>HAART Drug, NNRTI</td>
<td>1.23 (0.59, 2.52), P=0.42</td>
<td></td>
</tr>
<tr>
<td>HAART Drug, Others</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Prior ART</td>
<td>1.37 (0.82, 2.31), P=0.23</td>
<td></td>
</tr>
<tr>
<td>Prior ADI</td>
<td>2.24 (1.39, 3.60), P=0.001</td>
<td></td>
</tr>
<tr>
<td>Viral Hepatitis C Co-Infection</td>
<td>1.07 (0.62, 1.84), P=0.81</td>
<td></td>
</tr>
</tbody>
</table>

*Male vs. female sex could not be analyzed independently because of collinearity with the MSM risk group.
(Multivariate adjusted association of Statin use and each of the other variables) I categories are 0 mg/dL increase/g/dL increase.
doi:10.1371/journal.pone.0021843.t002

Other mortality predictors:
- low hgb
- older age
- injection drug use
- prior AIDS

**CONFOUNDERS**

**Higher CV risk factors**
- older age
- more prior AIDS
- higher cholesterol
- 2x use of BP Rx

**Lower CV risk factors**
- Lower HCV
- Higher CD4

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Statin guidelines are confusing!
HIV is a CV Dx “RISK ENHANCER”

Grundy SM. Circulation. 2018;139:25. DOI: (10.1161/CIR.0000000000000625)
Introduction: HIV and Cardiovascular Disease (CVD)
How to talk to patients about aging, mobility, CV risk #1

• People with HIV have 2x higher rates of CVD
  – Includes CVA, peripheral vascular disease; effect comparable to DM
• 50% of PWHIV are age > 50 years. CVD risk increases w/ age
  – Life-long prevention is useful; increasing imperative in aging PWHIVs
• Older PWIHV have more comorbidities
  – DM, CV, CA, CKD, lipids, liver, coag’pathy, MH, CNS, frailty, polypharm
  – Additional rationale for prevention, recognition and management
  – Mobility and exercise are key elements of CV disease reduction
Risk of MI in PWH compared to HIV negative controls

Incidence of MI by Age in D:A:D


Events: 2, 11, 36, 48, 55, 48, 31, 15, 16, 14

PYFU: 3634, 10801, 20075, 16900, 9741, 6687, 3699, 2093, 989, 641

Comparative Risk of MI by Risk Factor

- **Hypertension**: OR (99% CI)\(^a\) = 2.48 (2.30-2.68), PAR = 23.4%
- **Diabetes**: OR (99% CI)\(^a\) = 3.08 (2.77-3.42), PAR = 12.3%
- **Lipids\(^c\)**: OR (99% CI)\(^a\) = 3.87 (3.39-4.42), PAR = 54.1%
- **Smoking\(^d\)**: OR (99% CI)\(^a\) = 2.95 (2.72-3.20), PAR = 36.4%
- **Shah, et al.**
  - HIV\(^e\)**: RR (95% CI)\(^b\) = 2.16 (1.68-2.77), PAR = 0.92%

**References**

Risk Factor Management for CV Disease in PWHIV
How to talk to patients about aging, mobility, & CV disease #2

• Exercise, smoking cessation, BP control, healthy lifestyle, DM control, ART selection, lipid control, and other CV risk reduction are key elements
  — Some recent evidence of improvement in management in past decade in the US*

Risk Factor Management for CV Disease in PWHIV

How to talk to patients about aging, mobility, & CV risk #3

- Exercise, smoking cessation, BP control, healthy lifestyle, DM control, ART selection, lipid control, and other CV risk reduction are key elements
  - Some recent evidence of improvement in management in past decade in the US

- Increasing weight gain, insulin resistance, & DM in PWHIV are contributing to increased risk of CV disease
  - No proven new strategies or ART switches to date
Respond Cohort: New Onset DM by BMI and INSTI Use

Predicted risk of DM by current INSTI use and BMI

Note: Figure 1 shows the predicted risk per 1000 person years of DM for BMI (antilog of logBMI) among INSTI and non-INSTITI users when adjusted for sex, natural log of Age, HIV risk group, ethnicity, CD4, current TDF/TAF use. Among INSTI users, raltegravir (RAL) 12%, dolutegravir (DTG) 60%, other INSTIs (elvitegravir (EVG), bictegravir (BIC), cabotegravir (CBG)) 28%.

Rupasinghe D, et al. IAS 2023; Brisbane, Australia; July 23-26, 2023. Abst. OAB0402.
D:A:D: BMI Increase is Associated With Risk of DM2, but Not Risk of CVD

Results – CVD and DM Risk

<table>
<thead>
<tr>
<th>Baseline BMI</th>
<th>CVD events</th>
<th>Rate/1000 yrs</th>
<th>DM events</th>
<th>Rate/1000 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline BMI &lt;20</td>
<td>24</td>
<td>17.52</td>
<td>2</td>
<td>1.44</td>
</tr>
<tr>
<td>BMI decrease &gt;2</td>
<td>27</td>
<td>7.62</td>
<td>12</td>
<td>3.04</td>
</tr>
<tr>
<td>BMI decrease 1-2</td>
<td>166</td>
<td>6.08</td>
<td>48</td>
<td>1.76</td>
</tr>
<tr>
<td>BMI stable 1</td>
<td>32</td>
<td>3.99</td>
<td>16</td>
<td>1.99</td>
</tr>
<tr>
<td>BMI increase 1-2</td>
<td>58</td>
<td>4.72</td>
<td>38</td>
<td>3.11</td>
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<tr>
<td>BMI increase &gt;2</td>
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<td></td>
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<tr>
<td>Baseline BMI 20-25</td>
<td>97</td>
<td>7.77</td>
<td>35</td>
<td>2.82</td>
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<tr>
<td>BMI decrease &gt;2</td>
<td>144</td>
<td>7.24</td>
<td>48</td>
<td>2.43</td>
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<tr>
<td>BMI decrease 1-2</td>
<td>606</td>
<td>5.21</td>
<td>324</td>
<td>2.82</td>
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<tr>
<td>BMI stable 1</td>
<td>133</td>
<td>4.60</td>
<td>93</td>
<td>3.26</td>
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<tr>
<td>BMI increase 1-2</td>
<td>163</td>
<td>4.85</td>
<td>162</td>
<td>4.93</td>
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<tr>
<td>BMI increase &gt;2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline BMI 25-30</td>
<td>84</td>
<td>8.46</td>
<td>60</td>
<td>6.43</td>
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<tr>
<td>BMI decrease &gt;2</td>
<td>71</td>
<td>7.34</td>
<td>65</td>
<td>7.14</td>
</tr>
<tr>
<td>BMI decrease 1-2</td>
<td>250</td>
<td>6.06</td>
<td>266</td>
<td>6.81</td>
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<tr>
<td>BMI stable 1</td>
<td>56</td>
<td>5.83</td>
<td>80</td>
<td>8.88</td>
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<tr>
<td>BMI increase 1-2</td>
<td>65</td>
<td>5.01</td>
<td>131</td>
<td>11.08</td>
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<tr>
<td>BMI increase &gt;2</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline BMI 30+</td>
<td>29</td>
<td>7.91</td>
<td>29</td>
<td>9.65</td>
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<tr>
<td>BMI decrease &gt;2</td>
<td>14</td>
<td>7.95</td>
<td>16</td>
<td>10.32</td>
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<tr>
<td>BMI decrease 1-2</td>
<td>61</td>
<td>7.88</td>
<td>86</td>
<td>12.69</td>
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<tr>
<td>BMI stable 1</td>
<td>5</td>
<td>3.09</td>
<td>22</td>
<td>15.68</td>
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<tr>
<td>BMI increase 1-2</td>
<td>19</td>
<td>5.70</td>
<td>50</td>
<td>17.35</td>
</tr>
<tr>
<td>BMI increase &gt;2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EACS Nov 2023: BMI is a superior predictor of incident DM and metabolic syndrome compared to DEXA scan

CVD: Adjusted for age, race, mode of transmission, sex, recent abacavir and other NRTI use, cumulative protease inhibitor use, CD4 count, family history of CVD, smoking status

DM: Adjusted for age, race, mode of transmission, sex, stavudine use, triglycerides, CD4 count, smoking status and HDL (high-density lipoprotein)


Taramasso L, et al. EACS 2023; Warsaw, Poland; October 18-21, 2023. Abst. 1004.
TDF and EFV are weight suppressive
  - Weight gain following d/c of either drug

20-30% of weight gain on ART is return to health in advanced HIV disease

INSTIs do not independently cause weight increase
  - Social norms and obesogenic lifestyles are contributors

No evidence to date that ART switch leads to weight reduction

Metabolic risk: risk of DM and metabolic syndrome with weight gain

Diet and exercise can mitigate weight gain associated w/ INSTIs & TAF
  - GLP-1 inhibitors are effective in PWHIV in early trials
A 12-Week Multicomponent Exercise Program Reverses Frailty in Older Adults With HIV

Frailty (Frailty Phenotype), physical function (Senior Fitness Test (SFT), hand grip strength, SPPB), mood (HADS, GDS-SF), and quality of life (WHOQOL-HIV-BREF)

Use of GLP-1 Agonists in HIV: Retrospective cohort

- Retrospective cohort study (2/2021 - 2/2023) at UCSD
- Inclusion criteria
  - Age ≥ 18 years old
  - Prescribed GLP-1 RA during study period
- Exclusion criteria
  - PWH with no weight data available after GLP-1 RAs initiation
- BMI 34.1 kg/m²
- 49% white, 38% Hispanic, 17% female
- 52% Semaglutide, 31% dulaglutide
- Only 41% reached maximal dose
- Mean 15.4 month FU

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up on GLP-1 RA</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Weight, kg (± Std. dev)</td>
<td>103.4 (83.5 – 123.4)</td>
<td>98 (78.5 – 117.9)</td>
<td>-5.4 kg</td>
</tr>
<tr>
<td>Mean BMI, kg/m², (± Std. dev)</td>
<td>34.1 (28.5 – 39.8)</td>
<td>32.3 (26.6 – 38.2)</td>
<td>-1.8 kg/m²</td>
</tr>
<tr>
<td>Mean Hgb A1C, (± Std. dev)</td>
<td>7.0 (5.0 – 8.9)</td>
<td>6.4 (4.9 – 8.0)</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

- 53 patients (23.5%) had >5% weight loss
- 41 patients (18.2%) changed from obese to overweight
- Factors associated with >5% weight loss (multivariable analysis)
  - Higher baseline BMI [OR 1.07 (1.02-1.3)]
  - Longer duration of treatment (months) [OR 1.04 (1.01-1.07)]
- The use of dulaglutide was associated with decreased odds of achieving
- >5% weight loss [OR 0.33 (0.17-0.66)] as compared to the other GLP-1 RAs
First RCT of Semaglutide in HIV+ subjects

Week -4 to Week -1
Lead-In Phase (4 Weeks)
To assess stability and lifestyle habits of patients
Randomize
Semaglutide N=54
Placebo N=54

Week 0 (Entry) to Week 8
Interventional Titration Phase (8 Weeks)
0.25 mg dose weekly for 4 weeks, then 0.5 mg dose weekly for 4 weeks

Week 9 to Week 32
Full-Dose Interventional Phase (24 Weeks)
1.0 mg dose weekly

Weeks 33 to Week 56
Post-Interventional Phase (24 Weeks)
Post-treatment observational phase

Changes in Weight and BMI
Weight ↓ 8.3% vs ↑0.2%
65% on semaglutide vs. 4% on placebo lost ≥5% weight

DXA Changes in Body Composition
Total fat ↓ 15% vs ↑0.2%
Total lean mass ↓ 5.4% vs ↓0.6%

NB: No changes in liver, pericardial fat

Outline

- Introduction
- Epidemiology: HIV and CV risk
- Pathogenesis
- Prevention and Treatment
- How to talk to PWHIV about aging, mobility, and heart disease
Multifactorial etiology of CVD in HIV

Non-modifiable
- Age
- Gender
- Family hx

Behavior
- Tobacco
- Stimulants
- Diet
- Inactivity

CVD Risk

Chronic Inflammation

Dyslipidemia

Visceral adiposity

Insulin resistance/Hyperglycemia

Endothelial dysfunction
- CMV
- HIV directly
- Platelets

Leaky Gut

HTN

ART

Slide from J. Aberg, ACTHIV 2019.
Immune activation

Circulating CD4+ T-cells

Viremia

Mucosal CD4+ T-cells

4–8 weeks Acute

5–15 years Chronic

2–3 years AIDS
Impact of Chronic Immune Activation and Inflammation

• Premature aging
• Cardiovascular disease
• Chronic liver disease
• Osteopenia, osteoporosis
• Chronic kidney disease
• Non-AIDS-associated cancer
• Thrombo-embolism, DVT & PE
• Neurocognitive deficits

Elevated D-dimer & CRP Associated w/ 3.8x increase risk of mortality in PWHIV in START, SMART, & ESPRIT Studies

.....rationale for earlier ART initiation
Early ART reduces but does not eliminate excess risk of CV Dx
**HIV Infection**

- Loss of immunoregulatory cells
- Thymic dysfunction and loss of regenerative potential
- Co-Infections
- HIV replication
- Loss of gut mucosal integrity and microbial translocation

**ART**

- Defects in T cell regenerative potential
- Loss of immunoregulatory function
- CMV and other copathogen levels
- Microbial translocation
- Inflammatory Lipids

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**Innate Immune Activation**

- Increased cell turnover and lymphoid fibrosis
- Increased TF expression and clotting
- Cytokine secretion (eg, IL-6, TNFL)

- Immune exhaustion
- CAD/stroke, thrombosis
- “Inflam-Aging” (atherosclerosis, osteoporosis)

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Outline

• Introduction
• Epidemiology: HIV and CV risk
• Pathogenesis
• Prevention and Treatment
• How to talk to PWHIV about aging, mobility, and heart disease
Prevention and Treatment of CV Disease

Reversible risks
• Smoking cessation
• Mobility & exercise
• Sensible eating
• BP control
• Insulin resistance & DM control
• ART selection
• Lipid management

Irreversible risks
• Older age
• Gender
• Genetics

Possible reversible risks
• Dental & gingival health
A 12-Week Multicomponent Exercise Program Reverses Frailty in Older Adults With HIV

Frailty (Frailty Phenotype), physical function (Senior Fitness Test (SFT), hand grip strength, SPPB), mood (HADS, GDS-SF), and quality of life (WHOQOL-HIV-BREF)

ARS #2

Which of the following is known about pitavastatin relative to other statins?

1. It is the strongest statin for lowering LDL
2. It is the strongest statin for reducing inflammation
3. It is the statin with the least amount of drug-drug interactions
4. It is the statin with the lowest incidence of muscle-related symptoms
5. None of the above, it is similar to other statins
ARS #2

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1. It is the strongest statin for lowering LDL
2. It is the strongest statin for reducing inflammation
3. It is the statin with the least amount of drug-drug interactions
4. It is the statin with the lowest incidence of muscle-related symptoms
5. None of the above, it is similar to other statins
**REPRIEVE: Pitavastatin Calcium 4mg vs Placebo in PLWH age > 50 yrs and Low/Moderate CV Risk:**

Schema and Baseline Characteristics

Grinspoon S, et al. IAS 2023; Brisbane, Australia; July 23-26, 2023. Abst. SY06.

**ASCVD RISK & LIPID ENROLLMENT CRITERIA**

- Fasting LDL cholesterol as follows:
  - If ASCVD risk score <7.5%, LDL cholesterol must be <190 mg/dL
  - If ASCVD risk score ≥7.5% and ≤10%, LDL must be <160 mg/dL
  - If ASCVD risk score >10% and ≤15%, LDL must be <130 mg/dL

NOTE: If LDL <70 mg/dL, participant is eligible regardless of 10-year ASCVD risk score in line with the ACC/AHA 2013 Prevention Guidelines.

- Fasting triglycerides <500 mg/dL
**REPRIEVE Trial: Primary Endpoints**

- **First Primary MACE (Major Adverse CV Event)**
  - **Cumulative incidence of event**
    - **Pitavastatin**
      - 0% 0.6% 1.0% 1.4% 1.9% 2.4% 2.7%
    - **Placebo**
      - 0% 0.7% 1.4% 2.1% 2.7% 3.4% 4.4%
  - **Number at risk**
    - **Pitavastatin**
      - 3888 3647 3475 3364 2997 1947 1052
    - **Placebo**
      - 3881 3693 3506 3356 2997 2182 959

- **First MACE or Death**
  - **Cumulative incidence of event**
    - **Placebo**
      - 0% 0.8% 1.6% 2.4% 3.4% 4.5% 5.5%
    - **Pitavastatin**
      - 0% 0.8% 2.0% 3.3% 4.4% 5.3% 7.1%
  - **Number at risk**
    - **Pitavastatin**
      - 3888 3647 3475 3364 2998 1948 1027
    - **Placebo**
      - 3881 3693 3506 3356 2997 1975 919

Grinspoon S, et al. IAS 2023; Brisbane, Australia; July 23-26, 2023. Abst. SY06.
REPRIEVE Trial: Event Risk by Baseline ASCVD and Number Needed to Treat (NNT)

Increasing MACE events with increasing ASCVD risk score

Decreasing NNT with increasing ASCVD risk score

NNT = number needed to treat   MACE = major adverse cardiovascular event

Grinspoon S, et al. IAS 2023; Brisbane, Australia; July 23-26, 2023. Abst. SY06.
## REPRIEVE Trial:

### Consistent Effects Across Sub-groups

<table>
<thead>
<tr>
<th>Category</th>
<th>N (Overall)</th>
<th>Hazard Ratio (95% CI)</th>
<th>N (Placebo)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>3888</td>
<td>0.65 (0.48, 0.90)</td>
<td>3881</td>
<td>0.70 (0.51, 0.95)</td>
</tr>
<tr>
<td>ASCVD Risk Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-&lt;2.5</td>
<td>1096</td>
<td>0.65 (0.48, 0.90)</td>
<td>1060</td>
<td>0.79 (0.54, 1.16)</td>
</tr>
<tr>
<td>2.5-&lt;5</td>
<td>1030</td>
<td>0.50 (0.33, 0.76)</td>
<td>1025</td>
<td>0.72 (0.47, 1.08)</td>
</tr>
<tr>
<td>5-10</td>
<td>1474</td>
<td>0.76 (0.54, 1.07)</td>
<td>1521</td>
<td>0.72 (0.54, 1.07)</td>
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<tr>
<td>&gt;10</td>
<td>288</td>
<td>0.70 (0.51, 0.95)</td>
<td>275</td>
<td>0.70 (0.51, 0.95)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
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</tr>
<tr>
<td>40-49</td>
<td>1842</td>
<td>0.62 (0.48, 0.81)</td>
<td>1848</td>
<td>0.62 (0.48, 0.81)</td>
</tr>
<tr>
<td>50-59</td>
<td>1712</td>
<td>0.76 (0.54, 1.07)</td>
<td>1849</td>
<td>0.76 (0.54, 1.07)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>334</td>
<td>0.30 (0.22, 0.50)</td>
<td>344</td>
<td>0.30 (0.22, 0.50)</td>
</tr>
<tr>
<td><strong>Natal Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1211</td>
<td>0.64 (0.38, 1.08)</td>
<td>1208</td>
<td>0.64 (0.38, 1.08)</td>
</tr>
<tr>
<td>Male</td>
<td>2677</td>
<td>0.66 (0.48, 0.90)</td>
<td>2673</td>
<td>0.66 (0.48, 0.90)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>571</td>
<td>0.28 (0.10, 0.74)</td>
<td>567</td>
<td>0.28 (0.10, 0.74)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>1569</td>
<td>0.71 (0.48, 1.05)</td>
<td>1639</td>
<td>0.71 (0.48, 1.05)</td>
</tr>
<tr>
<td>White</td>
<td>1364</td>
<td>0.76 (0.49, 1.18)</td>
<td>1340</td>
<td>0.76 (0.49, 1.18)</td>
</tr>
<tr>
<td>Other</td>
<td>384</td>
<td>0.61 (0.23, 1.60)</td>
<td>335</td>
<td>0.61 (0.23, 1.60)</td>
</tr>
<tr>
<td><strong>Smoking Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/Former Smoker</td>
<td>920</td>
<td>0.75 (0.49, 1.14)</td>
<td>1014</td>
<td>0.75 (0.49, 1.14)</td>
</tr>
<tr>
<td>Never</td>
<td>2965</td>
<td>0.62 (0.44, 0.88)</td>
<td>2862</td>
<td>0.62 (0.44, 0.88)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2496</td>
<td>0.47 (0.31, 0.69)</td>
<td>2499</td>
<td>0.47 (0.31, 0.69)</td>
</tr>
<tr>
<td>Yes</td>
<td>1392</td>
<td>0.91 (0.63, 1.31)</td>
<td>1582</td>
<td>0.91 (0.63, 1.31)</td>
</tr>
<tr>
<td><strong>LDL-C (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;110</td>
<td>2973</td>
<td>0.64 (0.48, 0.87)</td>
<td>3044</td>
<td>0.64 (0.48, 0.87)</td>
</tr>
<tr>
<td>&gt;110</td>
<td>915</td>
<td>0.69 (0.39, 1.21)</td>
<td>837</td>
<td>0.69 (0.39, 1.21)</td>
</tr>
<tr>
<td><strong>CD4 count (cells/mm³)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤500</td>
<td>1257</td>
<td>0.67 (0.43, 1.09)</td>
<td>1253</td>
<td>0.67 (0.43, 1.09)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>2631</td>
<td>0.65 (0.47, 0.90)</td>
<td>2628</td>
<td>0.65 (0.47, 0.90)</td>
</tr>
<tr>
<td><strong>HIV-1 RNA (copies/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;400</td>
<td>2641</td>
<td>0.74 (0.53, 1.02)</td>
<td>2609</td>
<td>0.74 (0.53, 1.02)</td>
</tr>
<tr>
<td>≥400</td>
<td>368</td>
<td>0.68 (0.36, 1.28)</td>
<td>379</td>
<td>0.68 (0.36, 1.28)</td>
</tr>
<tr>
<td><strong>NadirCD4 count (cells/mm³)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤200</td>
<td>1890</td>
<td>0.65 (0.45, 0.94)</td>
<td>1911</td>
<td>0.65 (0.45, 0.94)</td>
</tr>
<tr>
<td>&gt;200</td>
<td>1019</td>
<td>0.88 (0.51, 1.49)</td>
<td>1032</td>
<td>0.88 (0.51, 1.49)</td>
</tr>
<tr>
<td><strong>ART Duration (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>847</td>
<td>0.42 (0.21, 0.83)</td>
<td>857</td>
<td>0.42 (0.21, 0.83)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>1190</td>
<td>0.66 (0.34, 1.27)</td>
<td>1118</td>
<td>0.66 (0.34, 1.27)</td>
</tr>
<tr>
<td><strong>GBD Super Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Income</td>
<td>2044</td>
<td>0.67 (0.49, 0.91)</td>
<td>2051</td>
<td>0.67 (0.49, 0.91)</td>
</tr>
<tr>
<td>Latin Am. &amp; Caribbean</td>
<td>709</td>
<td>1.12 (0.49, 2.54)</td>
<td>714</td>
<td>1.12 (0.49, 2.54)</td>
</tr>
<tr>
<td>S. East/ East Asia</td>
<td>304</td>
<td>0.47 (0.12, 1.59)</td>
<td>286</td>
<td>0.47 (0.12, 1.59)</td>
</tr>
<tr>
<td>South Asia</td>
<td>246</td>
<td>0.12 (0.04, 0.35)</td>
<td>258</td>
<td>0.12 (0.04, 0.35)</td>
</tr>
<tr>
<td>Sub-Saharan African</td>
<td>485</td>
<td>0.60 (0.24, 1.50)</td>
<td>572</td>
<td>0.60 (0.24, 1.50)</td>
</tr>
</tbody>
</table>

Grinspoon S, et al. IAS 2023; Brisbane, Australia; July 23-26, 2023. Abst. SY06.
Effects on Muscle Aches and Myalgias

Diabetes Rates in REPRIEVE vs. General Population Aged 45-64 per US Centers for Disease Control

RENSLOW SHERER, MD
Key Points: REPRIEVE Trial

- Pitavastatin calcium 4mg reduces MACE risk 35% vs placebo over 5.1yrs in low/moderate CVD risk pLWH of age > 40 yrs
- Treatment effect is similar across sex, race and baseline ASCVD baseline risk
  - Lipid lowering observed but does not explain degree of reduced risk alone due to lower LDL
- NNT 106 overall, 35 in this with ASCVD risk >10% at baseline
- Low risk of safety issues, small increase in DM2 incidence
- Suggests statins would be widely offered to PLWH age 40-55 years with low/moderate CVD risk
  - Pitavastatin, atorvastatin, rosuvastatin, pravastatin are reasonable options
Effect Larger than Anticipated Based on Lowering of LDL

- LDL lowering matters but the statin effect is beyond what is expected for LDL lowering alone

Relative reduction in JUPITER was -44%, predicted ~23%

Slide credit: Peter Hunt, UCSF, 11.6.23
# How Does REPRIEVE Result Compare to Existing Treatment Thresholds?

(https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/)

<table>
<thead>
<tr>
<th>ACC/AHA</th>
<th>ASCVD Risk</th>
<th>NNT-5y</th>
<th>USPSTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat</td>
<td>10-20%</td>
<td>40-60</td>
<td>Treat</td>
</tr>
<tr>
<td>Consider</td>
<td>7.5-10%</td>
<td>60-80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-7.5%</td>
<td>80-120</td>
<td>Don’t Consider</td>
</tr>
<tr>
<td>Don’t Consider</td>
<td>&lt;5%</td>
<td>&gt;120</td>
<td></td>
</tr>
</tbody>
</table>

REPRIEVE with ASCVD score >5% (<1/2 participants)

Overall REPRIEVE result

REPRIEVE with ASCVD score <5% (>1/2 participants)

AHA/ACC Guidelines, Circulation, 2018; USPSTF, JAMA, 2022

Slide credit: Peter Hunt, UCSF, 11.6.23
In PWH with Low ASCVD Risk (2.5-5%), More Women than Men Should be Considered for Statins

(https://tools.acc.org/ascvd-risk-estimator-plus/#/calculate/estimate/)

<table>
<thead>
<tr>
<th>ACC/AHA</th>
<th>ASCVD Risk</th>
<th>NNT-5y</th>
<th>USPSTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat</td>
<td>10-20%</td>
<td>40-60</td>
<td>Treat</td>
</tr>
<tr>
<td>Consider</td>
<td>7.5-10%</td>
<td>60-80</td>
<td>Consider</td>
</tr>
<tr>
<td>Don’t Consider</td>
<td>5-7.5%</td>
<td>80-120</td>
<td>Don’t Consider</td>
</tr>
<tr>
<td></td>
<td>&lt;5%</td>
<td>&gt;120</td>
<td></td>
</tr>
</tbody>
</table>

AHA/ACC Guidelines, Circulation, 2018; USPSTF, JAMA, 2022

REPRIEV with ASCVD score >5% (<1/2 participants)
REPRIEV women with ASCVD score 2.5-5%
REPRIEV men with ASCVD score <5%
Remaining Questions

• Mechanisms of disease and effect by CoA reductase inhibitors
• Further analysis of race, gender effects, alternate statins
• Mechanisms of reduced CV/vascular disease
  – LDL lowering vs other anti-inflammatory actions of statins
• Non-CV effects of statins
• Impact on cancer incidence
• Effects on age < 40 years with higher degrees of CV risk
• How should guidelines change?
  – HIV+, age > 40 with low-moderate CV risk
  – HIV+, age < 40 with high CV risk? With mow-moderate CV risk? Any HIV+?
Cost Effectiveness of Pitavastatin

Even with 30% additional ASCVD preventative efficacy, the price of pitavastatin needed to drop below 50% of the base-case price to become cost-effective compared with no statin.
Lipids: Four Statin Benefit Groups; ART DDIs

**Benefit Group**

- **Clinical ASCVD**
  - ≤75 yo
  - High-intensity statin
  - Moderate-intensity statin

- **Diabetes mellitus (age 40-75)**
  - ≥7.5%
  - High-intensity statin
  - <7.5%
  - Moderate-intensity statin

- **LDL-C ≥ 190**
  - High-intensity statin

- **≥7.5% 10-y risk (age 40-75)**
  - Moderate-to-high intensity statin

**Statin Dose**

- **Statin**
  - **Level with PI/c, PI/r**
  - **Use**
  - Pitavastatin
    - --
    - Safe (Prava caution with DRV/r)
  - Pravastatin
    - --
    - Use with caution/low dose
  - Atorvastatin
    - ↑
    - Use with caution/low dose
  - Rosuvastatin
    - ↑
    - Use with caution/low dose
  - Simvastatin
    - ↑↑↑
    - Contraindicated
  - Lovastatin
    - ↑↑↑
    - Contraindicated

**Screen w/ fasting lipids: At HIV diagnosis**
- Start of ART
- Change of ART
- Every 6-12 months

Aberg J. ACTHIV 2019.

Sosman J. MATEC Annual Update 2019
DHHS Guidelines: Excess CV Risk with Certain ART Agents

- **Abacavir**
  - “Increase in CV events is associated with abacavir use in some cohort studies.”

- **Darunavir**
  - “Increased CV risk reported in one observational cohort study.”

<table>
<thead>
<tr>
<th>High Cardiac Risk</th>
<th>Avoid abacavir and LPV/r</th>
<th>Increased risk of CV events w/ PI/rss (LPV, DRV, IDV, FPV) in observational studies, not seen with ATV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If a PI/r is needed, ATV/r may have advantages</td>
<td>TDF has been associated with lower lipid levels than TAF or ABC</td>
</tr>
<tr>
<td></td>
<td>See lipid guidelines below for more favorable lipid profiles, tho evidence that this leads to improved CVD outcomes is lacking</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hyperlipidemia</th>
<th>The following ARVs associated with dyslipidemia: PI/r, PI/c, EVG/c, EFV</th>
<th>TDF lowers lipids; therefore, switch from TDF-&gt;TAF is associated w/ lipid elevations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More favorable lipid profiles w/ BIC, DOR, RAL, DTG, RPV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF lowers lipids; therefore, switch from TDF-&gt;TAF is associated w/ lipid elevations</td>
<td></td>
</tr>
</tbody>
</table>

SWISS Cohort: No Increase Risk of MI With INSTI in Naive Subjects

116 CVC events within 4.9 years (IQR 2.4 – 7.4)
Smoking in PWHIV vs US population, 2009

Table 3. Adjusted Prevalence and Adjusted Prevalence Difference of Current Cigarette Smoking Among Adults With HIV Who Received Medical Care (MMP) and the General Adult Population (NHIS) in the United States in 2009

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted Current Smoking</th>
<th>Adjusted Prevalence Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than high school</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At or above the poverty line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below the poverty line</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interventions:
- Talk about it at every visit!
- Bupropion (Wellbutrin)
- Varenicline
- Nicotine patch, gum
- Cognitive behavioral therapy
- Provider recommendation
- Team support and reinforcement
- Other non-pharmacologic Rx
Impact of Smoking & Cessation on AMI in PWHIV

- 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

Aspirin Effective for Secondary Prevention of MI, CVA
Not Recommended for Primary CVD Prevention (except in DM)

Figure 1 - Summary of Three Aspirin Trials for Primary Prevention of Cardiovascular Disease
Case 1

- CJ is a 23 yo MSM with new HIV w/ CD4 660, VL 18,000
  - Was on PrEP for 1 year, but moved and lost insurance
- Non-smoker, no significant PMHx other than STIs x 2
  - No HTN, DM, non-smoker
  - Works as a waiter, grad student
- Unremarkable labs

Does CJ have an increased risk of CV disease?

What ART choices and other steps are appropriate for his care?
Case 1

• CJ is a 23 yo MSM with new HIV w/ CD4 660, VL 18,000
  – Was on PrEP for 1 year, but moved and lost insurance
• Non-smoker, no significant PMHx other than STIs x 2
  – No HTN, DM, non-smoker
  – Works as a waiter, grad student in economics
• Unremarkable labs

• Does CJ have an increased risk of CV disease?
  – YES vs HIV-, but still very low risk overall, << 7.5%
• What ART choices and other steps are appropriate for his care?
  – Any recommended option (w/o ABC, PI/r). Healthy food, exercise, lifestyle from start.
  – Discussion of weight gain w/ INSTIs, monitoring
Case 2

- GT is a 53-year-old man with stable HIV
- Diagnosed in 2011 on routine screening; MSM risk factor; baseline CD4 440, HIV RNA 12,000; no viral hepatitis or co-infections
  - No history of HIV-related complications
- Started ART and rapidly achieved viral suppression
- Currently asymptomatic, receiving BIC/FTC/TAF with no side effects
  - Taking no other medications
  - Lipids: Total cholesterol 197; HDL 43; LDL 141
- ASCVD 2013 Risk Calculator from AHA/ACC: 4.6% risk of cardiovascular event (coronary or stroke death or non-fatal MI or stroke) in next 10 years

Acknowledgement: Paul Sax
Case 2

• You cite for him a study showing that statin therapy reduces risk of major CV in PWH.

• He is strongly opposed to taking more medications – “I’m a therapeutic nihilist.”

• How would you counsel him? Does his ART regimen contribute to excess CV risk?
Case 2

• You explain to him that the ASCVD risk score might be underestimating his CV risk since he has HIV
• Atorvastatin 20 mg recommended
  – Would start of 10 mg reduce chance of side effects?
• He says he’ll consider it, but declines for now – but will work to improve his diet and increase exercise in the meantime
Key Points

• Numerous studies have shown an increased risk of cardiovascular disease in PWH compared to population without HIV
• Some argue that HIV be listed a major CV risk factor
• Immune activation and inflammation, and traditional CV risk factors, contribute to excess risk
  – risk only partially reversed by ART
• Current data do not support excess CV risk from the INSTI class – contrasts with PIs (atazanavir excepted)
• Pitavastatin lowers risk in PWH at low-moderate risk of cardiovascular disease
HIV and CVD: Summary I

• 2x increased risk of CVD in PWHIV; 50% of PWHIV are age > 50
• Early, life long CVD prevention based on modifiable risk factors
• Stop smoking; BP, lipid, & glucose control; exercise, healthy food
• Many ART options w/ favorable CVD profile
  – Avoid PIs (or use ATV/r), avoid abacavir
  – Statins effective for lipid control, consider DDIs
  – Any diabetic w/ LDL >70 should be on a statin and aspirin (often overlooked population in HIV clinical practice)
How can we help our aging PWHIV to lead the healthiest, longest and most meaningful life possible?
HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity

Steven G Deeks, Andrew N Phillips

Box 2 Non-AIDS related complications that may be more common in patients with HIV

- Hypertension
- Diabetes mellitus and insulin resistance
- Cardiovascular disease
- Pulmonary hypertension
- Cancer
- Osteopenia and osteoporosis
- Liver failure
- Kidney failure
- Peripheral neuropathy
- Frailty
- Cognitive decline and dementia

EXERCISE Is Effective Prevention & Treatment
A 12-Week Multicomponent Exercise Program Reverses Frailty in Older Adults With HIV

Frailty (Frailty Phenotype), physical function (Senior Fitness Test (SFT), hand grip strength, SPPB), mood (HADS, GDS-SF), and quality of life (WHOQOL-HIV-BREF)

HIV and CVDx: Summary II

• Weight gain on INSTIs increase metabolic syndrome
  – CV effects unclear, no strong association with CVD to date

• 50% of PWHIV age > 50 years
  – Rising co-morbidities and polypharmacy in older PWHIV
  – Aging and frailty are increasingly common; plan for fall prevention

• Critical role for HIV primary caregiver
  – Set early goals of mobility and independence, monitor progress
  – Coordination with geriatrician useful for age > 65 years
Useful References


Illinois Tobacco Quitline: quityes.org

American Heart Association guidelines: professional.heart.org
MATEC Resources

- National Clinician Consultation Center
  http://nccc.ucsf.edu/
  • HIV Management
  • Perinatal HIV
  • HIV PrEP
  • HIV PEP line
  • HCV Management
  • Substance Use Management

- AETC National HIV Curriculum
  https://aidsetc.org/nhc

- AETC National HIV-HCV Curriculum
  https://aidsetc.org/hivhcv

- Hepatitis C Online
  https://www.hepatitisc.uw.edu

- AETC National Coordinating Resource Center
  https://aidsetc.org/

- Additional Trainings https://matec.info
Atlanta, May 2-4, 2024
www.acthiv.org
Acknowledgements

• David Pitrak
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• Peter Hunt
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• Collette Dejong
• Melanie Thompson
• Cathy Creticos

• Jose Arribas
• Jim Sosman
• Paul Sax
• Ian Frank
• Graeme Moyle
• Juergen Rockstroh
• Judy Currier
• Judy Aberg
Thank you

Please complete the post evaluation survey.
The link is in the chatbox.