HIV and Cardiovascular Disease: Practical Management Strategies

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I have no relevant financial disclosures or conflicts of interest and will not be discussing non-FDA approved drug uses.
Learning Objectives

By the end of this presentation, participants will be able to:

- Explain contribution of traditional risk factors and ART to incidence of CVD in HIV
- Describe two pathogenic mechanisms that lead to increased CVD in HIV
- Apply JNC 8 guidelines to the management of hypertension
- List four specific patient groups with an indication for statin therapy based on current ACC/AHA cholesterol guidelines
Outline

- Summary Overviews
  - CVD Epidemiology in HIV
  - CVD Pathogenesis in HIV
  - CVD Risk Prediction in HIV

- Atherosclerotic CVD Primary and Secondary Prevention in HIV: Clinical Management Strategies
Topics Not Covered

- Other Manifestations of Cardiac Disease
  - Pericardial Disease
  - Heart failure and Cardiomyopathy
  - Arrhythmias and Sudden Cardiac Death
  - Pulmonary HTN

- Acute Management of ACS
CVD EPIDEMIOLOGY IN HIV
HIV-related CVD – Significant Mortality

- 1,876 deaths among 39,727 patients
- Non-AIDS related deaths accounted for 50.5%
- ~16% were due to CVD

**13 HIV Cohorts 1996-2006**

- Non-AIDS Malignancy 23.5%
- Non-AIDS infection 16.3%
- CVD 15.7%
- Liver-related 14.1%
- Violence, Substance abuse 15.4%
- Other 9.0%
- Respiratory 3.1%
- Renal 3%

Slide courtesy JS Currier
CVD Incidence Rates in HIV

- Increased CVD incidence in HIV-infected patients compared to uninfected controls\(^1-3\)
  - RR for MI and clinical CVD events: 1.5 - 2.0
  - Significant even after controlling for traditional risk factors
  - RR more pronounced in younger age groups
  - Absolute risk remains low in most cohorts due to youth

- Data limited by small event numbers and incomplete capture of other cardiac risk factors

# CVD Incidence Rates in HIV

## Summary of MI Rates and RR Across Studies\(^1\)-\(^3\)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>HIV + Pts/CVD Events</th>
<th>HIV + Event Rate (per 1000 pt yrs)</th>
<th>HIV – Event Rate (per 1000 pt yrs)</th>
<th>HR or RR of CVD event: HIV+/HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaiser</td>
<td>5000 / 162</td>
<td>3.7</td>
<td>2.2</td>
<td>1.68</td>
</tr>
<tr>
<td>MGH</td>
<td>3851 / 189</td>
<td>11.13</td>
<td>6.98</td>
<td>1.75</td>
</tr>
<tr>
<td>MediCal</td>
<td>28512 / 294</td>
<td>4.12</td>
<td>3.32</td>
<td>1.24</td>
</tr>
<tr>
<td>FHDH</td>
<td>74958 / 360</td>
<td>1.24</td>
<td>NR</td>
<td>1.5</td>
</tr>
<tr>
<td>DAD II</td>
<td>23437 / 345</td>
<td>3.6</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>VA</td>
<td>36766 / 1207</td>
<td>8.1</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>VACS</td>
<td>82549 / 871</td>
<td>5.0(^*)</td>
<td>3.3(^*)</td>
<td>1.48(^#)</td>
</tr>
</tbody>
</table>

MGH, Massachusetts General Hospital; MediCal, California Medicaid Database; FHDH, French Hospital Database on HIV; DAD, Data Collection on Adverse Events of Anti-HIV Drugs Study Group; VA, Veterans Affairs; VACS, VA Aging Cohort Study; N/A, not available; NR, not reported; * Event rate for ages 60-69, # RR for entire cohort

Paradigms of HIV-CVD Interplay

HYPOTHESIS #1: MARKER OF RISK FACTORS
HIV AND ART → TRADITIONAL RISK FACTORS → CVD

HYPOTHESIS #2: WORSENS RISK FACTORS
HIV AND ART → TRADITIONAL RISK FACTORS → CVD

HYPOTHESIS #3: INDEPENDENT EFFECT BEYOND RISK FACTORS
HIV AND ART ↔ TRADITIONAL RISK FACTORS → CVD
CVD Risk Factors

<table>
<thead>
<tr>
<th>TRADITIONAL CVD RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Genetics (Race/Family History)</td>
</tr>
<tr>
<td>HTN</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Diabetes/Insulin Resistance</td>
</tr>
<tr>
<td>Obesity/Sedentary Lifestyle</td>
</tr>
</tbody>
</table>

Modifiable risk factors in **bold**.

- Higher prevalence of many traditional CVD risk factors in HIV-infected pts compared to non-infected pts\(^1\)-\(^2\)
- Relative contribution to CVD risk appears to be similar to general population\(^3\)
- Increased CVD risk appears to persist despite adjustment for these risk factors

## Comparison of Risk Factor Prevalence: HIV vs. non-HIV

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>APROCO VS. WHO MONICA&lt;sup&gt;1&lt;/sup&gt; (Data for men 34-44 yo)</th>
<th>WIHS/MACS COHORTS&lt;sup&gt;2&lt;/sup&gt; (Data for men only shown)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>HIV-POS 56.6% HIV-NEG 32.7%</td>
<td>HIV-POS 35% HIV-NEG 28%</td>
</tr>
<tr>
<td>HTN</td>
<td>HIV-POS 5.2% HIV-NEG 12.8%</td>
<td>HIV-POS 33% HIV-NEG 34%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>HIV-POS 2% HIV-NEG 3%</td>
<td>HIV-POS 16% HIV-NEG 11%</td>
</tr>
<tr>
<td>Elevated TC</td>
<td>HIV-POS 59.6% HIV-NEG 60.8%</td>
<td>HIV-POS NR HIV-NEG NR</td>
</tr>
<tr>
<td>Elevated TG</td>
<td>HIV-POS 32.3% HIV-NEG 13.5%</td>
<td>HIV-POS 10% HIV-NEG 2%</td>
</tr>
<tr>
<td>Low HDL</td>
<td>HIV-POS 44.9% HIV-NEG 23.1%</td>
<td>HIV-POS 43% HIV-NEG 21%</td>
</tr>
</tbody>
</table>

Statistically significant differences in **bold**

## CVD Risk Factors

<table>
<thead>
<tr>
<th>TRADITIONAL CVD RISK FACTORS</th>
<th>NON-TRADITIONAL CVD RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Direct effects of HIV infection</td>
</tr>
<tr>
<td>Gender</td>
<td>- Chronic inflammation</td>
</tr>
<tr>
<td>Genetics (Race/Family History)</td>
<td>- Endothelial dysfxn / Hypercoaguability</td>
</tr>
<tr>
<td>HTN</td>
<td>- Immune deficiency/senescence</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>ART (in general or specific agents)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Lipodystrophy syndrome</td>
</tr>
<tr>
<td>Diabetes/Insulin Resistance</td>
<td>HCV co-infection</td>
</tr>
<tr>
<td>Obesity/Sedentary Lifestyle</td>
<td>Renal disease, albuminuria</td>
</tr>
</tbody>
</table>

- Residual excess risk has led to investigation of novel/nontraditional risk factors.
HAART and the Heart

- Association between ART exposure and increased CV events in most studies (except early large VA study) \(^1-^3\)
- Exposure to older protease inhibitors (e.g. lopinavir-ritonavir) most consistent association of risk, likely mediated by lipids; limited data but less concern with newer PIs\(^1-^2\)
- Some but not all studies show association with recent use of abacavir; failure to account for confounding from CKD possible explanation\(^4-^5\)
- ART interruption associated with higher rates of CV events in SMART study compared to continuous arm (1.3/100 py vs. 0.8/100 py) \(^6\)

Darunavir: The Heartbreak Kid?

Recent presented analysis from D:A:D cohort suggests increased CVD risk with darunavir/ritonavir

- 2009-2016, 7 yr median f/u; 35,711 pts, 1157 CVD events
- Cumulative darunavir exposure, after adjustment for traditional risk factors and lipids, associated with higher rates of all CVD events (IRR 1.59 per 5 years), MI alone (IRR 1.51 per 5 years), and stroke alone (IRR 1.49 per 5 years)
- Similar to rates with older PIs (indinavir, lopinavir/ritonavir) but not seen with atazanavir/ritonavir
- Did not report on darunavir/cobicistat impact

CVD Epidemiology Summary

- Increased relative risk of CVD events in HIV-infected patients compared to uninfected patients

- Higher prevalence of traditional CVD risk factors (such as smoking) partially explains increased risk

- Select ART (primarily PIs and abacavir) may be associated with increased CVD risk

- Benefits of HAART and CVD risk associated with treatment interruption outweigh CVD risks of treatment
CVD PATHOGENESIS IN HIV
We will briefly discuss:

- Chronic inflammation and immune activation
- Abnormal lipid metabolism
Role of Chronic Inflammation

Deeks, SG et al. NEJM 2012; 367:1246-54.

Figure 2. Role of Chronic Inflammation in the Pathogenesis of HIV-Associated Coronary Artery Disease during Antiretroviral Therapy.
Several mechanisms contribute to a high risk of coronary artery disease in HIV-infected adults who have received treatment with antiretroviral agents, including a high prevalence of traditional risk factors, toxic effects associated with antiretroviral drugs, and chronic inflammation. HIV-mediated loss of CD4+ T cells contributes directly or indirectly to irreversible destruction of lymphoid tissues, breakdown of mucosal integrity, loss of thymic function, and loss of hematopoietic stem cells. As a consequence, immune reconstitution during treatment is often suboptimal, resulting in persistent immunodeficiency, excess pathogen burden, and loss of immunoregulatory responses. This chronic inflammatory state persists during therapy and has several potentially harmful effects on vascular function and the coagulation system. CMV denotes cytomegalovirus.
Chronic Inflammation Persists in the Setting of Treated HIV Infection

- T-cell activation higher in treated HIV vs controls\(^1\)
- Lipopolysaccharide higher in treated HIV vs controls\(^2\)
- Tissue factor elevated in treated HIV vs controls\(^3\)

Low CD4+ Count Associated With CVD

- Nadir CD4+ cell count ≤ 200 cells/mm³ independently associated with carotid IMT\(^1,2\)
- Proximal CD4+ cell count during therapy associated with incident CVD and AMI\(^3\)
- Kaiser study: higher risk of CHD seen only in treated HIV+ pts with either recent or lowest CD4+ cell count ≤ 200 cells/mm³\(^4\)
- Nadir CD4+ cell count < 350 cells/mm³ independently associated with worsened arterial stiffness and endothelial function\(^5,6\)
- **Will there be a CV benefit in earlier initiation of antiretroviral therapy?**

# Lipid Parameters in HIV Patients Compared to Uninfected Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>TG</th>
<th>TC</th>
<th>LDL</th>
<th>HDL</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV +, ART naïve</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Small, dense LDL particles</td>
</tr>
<tr>
<td>HIV +, PI-based ART</td>
<td>↑↑</td>
<td>↔ / ↑</td>
<td>↔ / ↑</td>
<td>↓</td>
<td>More apoB lipoproteins (VLDL/LDL)</td>
</tr>
</tbody>
</table>

- HIV-infected patients have “pro-atherogenic” lipid profile at baseline
- ART, esp. older PIs, increase TG and “normalize” LDL and TC while HDL remains low

HIV-induced LCAT and CETP activity shunts cholesterol into apoB lipoproteins (and thus extrahepatic tissue)

CVD RISK PREDICTION IN HIV
CVD Risk Prediction

- Goal is to match the intensity of CV risk factor modification to the predicted risk of CVD?
Framingham Risk Score

- Was used for general population to determine lipid targets
- Appeared to underestimate risk in HIV pts (based on D:A:D cohort and others)
- Doesn’t include HIV-specific risk factors (CD4, ART exposure)

http://hp2010.nhlbihin.net/atpiii/calculator.asp
D:A:D CVD Risk Calculator

- Classic CVD risk factors important in HIV+ pts
- Framingham appears to underestimate risk compared with D:A:D models
- Risk related to current use of ABC lower than previous estimates
  - HR: 1.47 vs no current ABC use

CVD PREVENTION IN THE HIV CLINIC
CVD Primary Prevention

- To prevent CVD, first provider has to CONSIDER THE PATIENT AT RISK!

- HIV guidelines generally follow those for general public with special consideration of drug-drug interactions and metabolic effects of ART

- Suggested Approaches:
  - Have Systematic Approach to assessing CV risk factors
  - Design workflow to make it “easy” to follow guidelines
  - Understand and maximize non-physician resources
  - Consider dedicated “Metabolic” visit (in stable pts)
  - Evaluate your practice as part of QI process
V. What are the metabolic comorbidities associated with HIV and antiretroviral therapy?

Recommendations

67. Fasting blood glucose and/or hemoglobin A1c should be obtained prior to and within 1–3 months after starting ART. Patients with diabetes mellitus should have a hemoglobin A1c level monitored every 6 months with a goal of <7%, in accordance with the American Diabetes Association Guidelines (strong recommendation, moderate quality evidence).

68. Fasting lipid levels should be obtained prior to and within 1–3 months after starting ART. Patients with abnormal lipid levels should be managed according to the National Cholesterol Education Program Guidelines (strong recommendation, moderate quality evidence).

69. Baseline bone densitometry (DXA) screening for osteoporosis in HIV-infected patients should be performed in postmenopausal women and men aged ≥50 years (strong recommendation, moderate quality evidence).
Clinical Inertia in CVD Prevention

- Retrospective study of 90 pts in UAB HIV clinic not at LDL goal showed 44% of patients failed to have appropriate intervention over 12-month span\(^1\)
  - Women and pts in highest CVD risk category most likely affected by inertia, higher absolute LDL less likely

- Same clinic reported study of 397 patients qualifying for ASA for primary prevention based on USPSTF guidelines, found that only 66 (17%) patients received therapy\(^2\)
  - OR of receipt of ASA doubled for each additional CVD risk factor

**Conclusions:** Clinical inertia major issue in CVD prevention in HIV clinic and clinicians tend to rely on clinical impression rather than practice guidelines

ABCs of CVD Prevention

A: Aspirin
B: Blood pressure
C: Cholesterol
D: Diet
E: Exercise
F: Fumes (smoking)
G: Glucose (DM/insulin resistance)
H: HAART

Maximize non-MD resources

Utilize pharmacist and specialist expertise in complex cases
Management: Aspirin

- USPSTF recommend ASA for primary prevention:
  - Men 45-79 with net benefit for preventing MI
  - Women 55-79 with net benefit for preventing stroke
  - Younger pts: Not recommended; Age > 80: insufficient evidence
  - Net benefit considers risk of GIB (NSAIDs 3-4x; prior ulcer or GIB 2-3x)
  - Use dose 81 mg daily

<table>
<thead>
<tr>
<th>Age</th>
<th>10-year MI risk (men)</th>
<th>Age</th>
<th>10-year stroke risk (women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–59</td>
<td>≥ 4 %</td>
<td>55–59</td>
<td>≥ 3 %</td>
</tr>
<tr>
<td>60–69</td>
<td>≥ 9 %</td>
<td>60–69</td>
<td>≥ 8 %</td>
</tr>
<tr>
<td>70–79</td>
<td>≥ 12 %</td>
<td>70–79</td>
<td>≥ 11 %</td>
</tr>
</tbody>
</table>

Recent CV Guideline Changes

- Updated Guidelines in late 2013:
  - JNC 8: Hypertension
  - ACC/AHA Management of Blood Cholesterol
  - ACC/AHA Lifestyle Management
  - ACC/AHA Cardiovascular Risk Assessment
  - ACC/AHA Management of Obesity

- Intended to apply RCT evidence to specific clinical research questions, NOT comprehensive guidelines

- Controversial from outset of publication (HTN and Chol)
Management: Blood Pressure

- Definition of HTN and prehypertension not addressed

- **Key Changes from JNC-7:**
  - Goal BP: < 140/90 (age 18-60), < 150/90 (age ≥ 60)
  - Goal BP in diabetes/CKD: < 140/90 regardless of age
  - **Recommended drug classes:** thiazide diuretics, ACE-I, ARB or CCB (except in AA and pts with CKD)
  - 3 drug treatment titration strategies suggested

JNC 8 Guidelines for Mgmt of HTN. JAMA. Published online 12/18/13.
Figure. 2014 Hypertension Guideline Management Algorithm

Adult aged ≥18 years with hypertension

Implement lifestyle interventions (continue throughout management).

Set blood pressure goal and initiate blood pressure lowering medication based on age, diabetes, and chronic kidney disease (CKD).

General population (no diabetes or CKD) + Diabetes or CKD present

- Age ≥60 years
  - Blood pressure goal: SBP <150 mm Hg, DBP <90 mm Hg
  - Nonblack: Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination.³
  - Black: Initiate thiazide-type diuretic or CCB, alone or in combination.

- Age <60 years
  - Blood pressure goal: SBP <140 mm Hg, DBP <90 mm Hg
  - Nonblack: Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination.

- All ages Diabetes present
  - No CKD: Blood pressure goal: SBP <140 mm Hg, DBP <90 mm Hg
  - Nonblack or Black: Initiate thiazide-type diuretic or CCB, alone or in combination.

- All ages CKD present with or without diabetes
  - Blood pressure goal: SBP <140 mm Hg, DBP <90 mm Hg
  - All races: Initiate ACEI or ARB, alone or in combination with other drug class.³

Select a drug treatment titration strategy
- A. Maximize first medication before adding second or
- B. Add second medication before reaching maximum dose of first medication or
- C. Start with 2 medication classes separately or as fixed-dose combination.

JNC 8 Guidelines for Mgmt of HTN. JAMA. Published online 12/18/13.
Select a drug treatment titration strategy
A. Maximize first medication before adding second or
B. Add second medication before reaching maximum dose of first medication or
C. Start with 2 medication classes separately or as fixed-dose combination.

At goal blood pressure?

Yes

Reinforce medication and lifestyle adherence.

For strategies A and B, add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB).

For strategy C, titrate doses of initial medications to maximum.

At goal blood pressure?

Yes

Reinforce medication and lifestyle adherence.

Add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB).

At goal blood pressure?

Yes

Reinforce medication and lifestyle adherence.

Add additional medication class (eg, β-blocker, aldosterone antagonist, or others) and/or refer to physician with expertise in hypertension management.

Yes

At goal blood pressure?

Yes

Continue current treatment and monitoring.
## HTN Examples

<table>
<thead>
<tr>
<th>Example Patient</th>
<th>BP Target</th>
<th>BP Drugs to Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 yo WM, BP 142/85</td>
<td>&lt; 150/90</td>
<td>Lifestyle mgmt, no meds at this time</td>
</tr>
<tr>
<td>50 yo AAF, BP 148/95</td>
<td>&lt; 140/90</td>
<td>Thiazide or CCB</td>
</tr>
<tr>
<td>63 yo AAM, BP 149/84, Cr 0.9, + microalbuminurina</td>
<td>&lt; 140/90</td>
<td>ACE-I or ARB</td>
</tr>
<tr>
<td>72 yo WF, BP 138/85, on ACE-I/HCTZ combo</td>
<td>&lt; 150/90</td>
<td>No change; continue if tolerating without AEs</td>
</tr>
</tbody>
</table>

* CKD defined as eGFR < 60 mL/min if age < 70 or microalbuminuria
Changes to Come?

- SPRINT trial
  - RCT of 9300 non-diabetics with increased CVD risk pts
  - Goal SBP < 120 or < 140
  - Strongly favors goal SBP < 120

- Revision of BP guidelines may come in the future

Management: Cholesterol

- **Key Changes from New Lipid Guidelines:**
  - Highlights 4 groups most likely to benefit from statins
  - Focus on statin intensity, NOT treatment to specific LDL or non-HDL targets
  - New Pooled Risk Equation to predict 10-year ASCVD risk
  - No “routine role” for non-statin therapy
  - Emphasis on “patient-centered” approach with discussion of individual risk/benefits of therapy

4 Patient Groups which benefit from statins:
- Clinical ASCVD (includes CAD, CVA/TIA, PVD)
- LDL ≥ 190 mg/dL
- Diabetes age 40-75 with LDL 70-189 mg/dL
- 10-year ASCVD est. risk ≥ 7.5% with LDL 70-189 mg/dL

For NYHA II-IV heart failure and hemodialysis pts, no recommendation made due to lack of evidence proving efficacy in these populations

# New ASCVD Risk Equation

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
<th>Value</th>
<th>Acceptable range of values</th>
<th>Optimal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M (for males) or F (for females)</td>
<td>M or F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>20-79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>AA (for African Americans) or WH (for whites or others)</td>
<td>AA or WH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>mg/dl</td>
<td>130-200</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>mg/dl</td>
<td>20-60</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>mm Hg</td>
<td>90-200</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Treatment for High Blood Pressure</td>
<td>Y (for yes) or N (for no)</td>
<td>Y or N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y (for yes) or N (for no)</td>
<td>Y or N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>Y (for yes) or N (for no)</td>
<td>Y or N</td>
<td>N</td>
<td></td>
</tr>
</tbody>
</table>

**Your 10-Year ASCVD Risk (%)**

Enter M or F for Gender Enter WH or AA for race
Enter 130-200 for TC value Enter 20-100 for HDL value Enter 90-200 for SBP value Enter Y or N for treatment for hypertension Enter Y or N for Diabetes Enter Y or N for Smoker

**10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)**

Enter M or F for Gender This calculator only provides 10-year risk estimates for individuals 40 to 79 years of age Enter WH or AA for race

**Your Lifetime ASCVD Risk (%)**

This calculator only provides lifetime risk estimates for individuals 20 to 59 years of age Enter M or F for Gender Enter 130-200 for TC value Enter 90-200 for SBP value Enter Y or N for treatment for hypertension Enter Y or N for Diabetes Enter Y or N for Smoker

**Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (shown above in column E)**

Enter M or F for gender

*This is the lifetime ASCVD risk for a person of your age and gender with your risk factor levels. In rare cases, 10-year risks may exceed lifetime risks given that the estimates come from different approaches. While 10-year risk estimates are derived from methods and data using continuous variables, the reported estimate of lifetime risk is based on assigning each person into one of 5 mutually exclusive sex-specific groups, as per Lloyd-Jones et al., Circulation 2009; 119(1):291-8. Within each of the 5
# CVD/CHD Prevention Guidelines: Key Differences

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Prediction</strong></td>
<td>Framingham Risk Score (FRH*) CHD 10-year risk</td>
</tr>
<tr>
<td>- Limitations:</td>
<td>- Includes:</td>
</tr>
<tr>
<td>- White race</td>
<td>- AA race</td>
</tr>
<tr>
<td>- No Diabetes mellitus (DM)</td>
<td>- DM</td>
</tr>
<tr>
<td><strong>Lipid-Lowering Therapy / Statins for:</strong></td>
<td>LDL target, determined by:</td>
</tr>
<tr>
<td>- # of risk factors</td>
<td>- 10-year FRH risk score</td>
</tr>
<tr>
<td>- CHD or CHD equivalent</td>
<td>- DM (LDL &gt; 70)</td>
</tr>
</tbody>
</table>

* 2004 Framingham Score for CHD, not “general” Framingham Score for CVD (2008)
Defining Statin Intensity

- Defined by average % reduction in LDL seen in RCTs
- Must take into account HIV drug interactions

<table>
<thead>
<tr>
<th>High-Intensity Statins</th>
<th>Moderate-Intensity Statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower LDL by ≥ 50%</td>
<td>Lower LDL by 30-50%</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg/d</td>
<td>Pravastatin 40-80 mg/d</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg/d</td>
<td>Simvastatin 20-40 mg/d</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin 10-20 mg/d</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin 5-10 mg/d</td>
</tr>
</tbody>
</table>

In HIV, start low and slowly titrate!

Drug Interactions: Lipid-lowering Agents and PI-based ART

- **Fibrates**: Fluvastatin, Pravastatin*, Ezetimibe, Fish oil
- **Statin + fibrate**: Atorvastatin, Rosuvastatin, Niacin
- **Lovastatin**, **Simvastatin**

*Low interaction potential*

*Use cautiously*

*Contraindicated*

*AUC ↑↑↑ with DRV.*


Management Algorithm

ASCVD Statin Benefit Groups
Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL–C 70-189 mg/dL.

- Adults age >21 y and a candidate for statin therapy → Yes
- Clinical ASCVD
  - Yes → Age ≤75 y
    - High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
  - No
    - LDL–C ≥190 mg/dL
      - Yes → Age >75 y OR if not candidate for high-intensity statin
        - Moderate-intensity statin
      - No → High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
Management Algorithm

Diabetes
Type 1 or 2
Age 40-75 y

Yes

Moderate-intensity statin

Yes

Estimated 10-y ASCVD risk ≥7.5%
High-intensity statin

No

Estimate 10-y ASCVD Risk
with Pooled Cohort Equations

≥7.5% estimated 10-y ASCVD risk
and age 40-75 y

Yes

Moderate-to-high intensity statin

No

ASCVD prevention benefit of statin
therapy may be less clear in other groups
In selected individuals, consider additional factors
influencing ASCVD risk and potential ASCVD risk
benefits and adverse effects, drug-drug interactions,
and patient preferences for statin treatment

Recommended Follow-Up

- Repeat lipid panel 4-12 weeks after starting or changing statin
- Repeat lipids to monitor adherence and therapeutic response, NOT to target specific LDL
Do these guidelines apply to HIV patients?

“Clinician judgment is especially important for several patient groups for whom the RCT evidence is insufficient for guiding clinical recommendations. These patient groups include ... those with serious comorbidities and increased ASCVD risk (e.g., individuals with HIV, etc.)”

Which Risk Prediction Score is Best?
Time to event analysis

Slide courtesy Dr. Henning Drechsler
Statin Therapy in HIV: Other Benefits?

- ALLRT cohort (3601 subjects) evaluated statin use and non-accidental death or non-AIDS defining complications
  - Adjusted HR for death 0.81 [0.53-1.24], for non-AIDS malignancy 0.43 [0.19-.94]

- Hopkins cohort of 1538 virologically-suppressed pts
  - HR for death of 0.33 [0.14-0.76] associated with statin use in multivariate analysis controlling for demographic and clinical factors

- VA HIV cohort from 1995-2009 including > 25k patients and 6435 deaths
  - Significant reduction in all-cause mortality per year of cumulative statin exposure
  - Any statin: HR 0.95 [0.93-0.98]; Potent statin: HR 0.86 [0.81-0.93]

## PI Switch vs. Lipid-Lowering Rx

- **When switching antiretroviral therapy**
  - Maintenance of virologic suppression is paramount
  - Any switch carries some risk of loss of virologic suppression
- **Lipid-lowering agents**
  - May avoid risks associated with switch but at the price of polypharmacy
  - More commonly used in US; European guidelines suggest lipid-lowering therapy only after dietary modification and switch strategies

### Metabolic Parameter

<table>
<thead>
<tr>
<th>Metabolic Parameter</th>
<th>PI Switch</th>
<th>Statin</th>
<th>Fibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>-10% to -30%</td>
<td>-11% to -45%</td>
<td>0% to -5%</td>
</tr>
<tr>
<td>HDL</td>
<td>0% to +3%</td>
<td>0% to +6%</td>
<td>0% to +17%</td>
</tr>
<tr>
<td>TG</td>
<td>-10% to -25%</td>
<td>0% to -25%</td>
<td>-20% to -45%</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Variable</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

Cholesterol Conclusions (Tentative)

- Follow guidelines for pts with clinical ASCVD, LDL > 190 mg/dL, and diabetics
- Consider “individualized” risk/benefit ratio of statin Rx in others (with predicted 10-year ASCVD risk as only one component)
- Start lower dose statin and slowly titrate to achieve % LDL reduction goals (rather than a specific LDL)
- Reserve non-statin therapy for statin intolerance or ↑↑ triglycerides
- Consider more “lipid-friendly” ART if viral suppression possible
- Need validation of risk calculators in HIV patients and RCT data on statins in HIV patients w/o clinical ASCVD (REPRIEVE trial)
The New Frontier: PCSK9 and HIV

- Despite lower LDL levels, PCSK9 and IL-6 levels were higher in HIV/HCV co-infected and monoinfected pts

# Diet

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendations</th>
<th>Evidence Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ LDL</td>
<td>Consume “heart-healthy” dietary pattern (DASH diet, AHA diet, USDA Food Pattern)</td>
<td>I. A</td>
</tr>
<tr>
<td></td>
<td>Consume 5-6% of daily calories from saturated fat</td>
<td>I. A</td>
</tr>
<tr>
<td></td>
<td>Limit calories from saturated and trans fat</td>
<td>I. A</td>
</tr>
<tr>
<td>↑ BP</td>
<td>Consume “heart-healthy” dietary pattern (DASH diet, AHA diet, USDA Food Pattern)</td>
<td>I. A</td>
</tr>
<tr>
<td></td>
<td>Limit Na⁺ intake to &lt; 2.4 gm/d (preferably &lt; 1.5 gm/d)</td>
<td>Ila. B</td>
</tr>
<tr>
<td></td>
<td>Combine DASH diet with lower Na⁺ intake</td>
<td>I. A</td>
</tr>
</tbody>
</table>

## Exercise

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendations</th>
<th>Evidence Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ LDL</td>
<td>Engage in aerobic exercise 3-4 sessions/wk, average duration 40 minutes/session, moderate to vigorous intensity</td>
<td>IIa. A</td>
</tr>
<tr>
<td>↑ BP</td>
<td>Engage in aerobic exercise 3-4 sessions/wk, average duration 40 minutes/session, moderate to vigorous intensity</td>
<td>IIa. A</td>
</tr>
</tbody>
</table>

SMOKING CESSATION

- Smoking cessation has GREATEST impact (≈ 50%) on CVD risk reduction of any single intervention

- DHHS guidelines recommend pharmacotherapy for all patients except those with medical contraindications
  - Approved agents: Nicotine patch, gum, inhaler, nasal spray, bupropion and varenicline
  - No drug interactions with varenicline; caution with bupropion and boosted PIs

- More intensive counseling interventions with better results in HIV+ patients, particularly when initiated by MD

Insulin Resistance / Diabetes

- Definitions of Diabetes: 2013 ADA Guidelines
  - HbA1c ≥ 6.5%* or
  - Fasting plasma glucose (FPG) ≥ 126 mg/dL* or
  - Plasma glucose ≥ 200 mg/dL after 2 hrs during OGTT* or
  - Random plasma glucose ≥ 200 mg/dL with symptoms
* Should be confirmed on repeat testing

- Screening Frequency:
  - Prior to and 1-3 months after starting HAART
  - FPG or HbA1c in all patients every 6-12 months

HbA1c Underestimates Glycemia in HIV-Infected Persons

- Prospective cross-sectional study of 100 HIV-infected adults with type 2 diabetes (77%) or fasting hyperglycemia (23%)

HbA1c Goal for the Prevention of Diabetes Complications

< 7%

**Individualization is key:**

Tighter control (HbA1c 6.0% to 6.5%): younger, healthier

Looser control (HbA1c 7.5% to 8.0%+): older, hypoglycemia prone, comorbidities

Should HbA1c goal be lower in HIV-positive patient if it underestimates glycemia?

HAART: CVD CONSIDERATIONS

- Guidelines for Starting HAART:
  - DHHS: all patients regardless of CD4 count

- Primary focus is choosing a regimen which will achieve virologic suppression

- In patients with CV risk factors, consideration given to:

<table>
<thead>
<tr>
<th>High cardiac risk</th>
<th>Consider avoiding ABC- and LPV/r -based regimens.</th>
<th>Increased cardiovascular risk in some studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia</td>
<td>• The Following ARV Drugs have been Associated with Dyslipidemia: PI/r or PI/c • EFV • EVG/c</td>
<td>DTG and RAL have fewer lipid effects. TDF has been associated with more favorable lipid effects than ABC or TAF</td>
</tr>
</tbody>
</table>
START Trial: Does early ART reduce CV risk?

Table 2. Primary and Secondary End Points.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Immediate-Initiation Group (N = 2326)</th>
<th>Deferred-Initiation Group (N = 2359)</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite primary end point</td>
<td>42 (no.) 0.60</td>
<td>96 (no.) 1.38</td>
<td>0.43 (0.30–0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Components of the primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious AIDS-related event</td>
<td>14 (no.) 0.20</td>
<td>50 (no.) 0.72</td>
<td>0.28 (0.15–0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serious non–AIDS-related event</td>
<td>29 (no.) 0.42</td>
<td>47 (no.) 0.67</td>
<td>0.61 (0.38–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>12 (no.) 0.17</td>
<td>21 (no.) 0.30</td>
<td>0.58 (0.28–1.17)</td>
<td>0.13</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>6 (no.) 0.09</td>
<td>20 (no.) 0.28</td>
<td>0.29 (0.12–0.73)</td>
<td>0.008</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1 (no.) 0.01</td>
<td>11 (no.) 0.16</td>
<td>0.09 (0.01–0.71)</td>
<td>0.02</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>3 (no.) 0.04</td>
<td>10 (no.) 0.14</td>
<td>0.30 (0.08–1.10)</td>
<td>0.07</td>
</tr>
<tr>
<td>Cancer not related to AIDS</td>
<td>9 (no.) 0.13</td>
<td>18 (no.) 0.26</td>
<td>0.50 (0.22–1.11)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>12 (no.) 0.17</td>
<td>14 (no.) 0.20</td>
<td>0.84 (0.39–1.81)</td>
<td>0.65</td>
</tr>
</tbody>
</table>
Impact on Lipids: TAF vs. TDF

Fig. 5 Fasting lipids at 96 weeks in treatment-naïve patients receiving elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide (E/C/F/TAF) or elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate (E/C/F/TDF). The percentage of subjects who initiated treatment with lipid-modifying agents was 3.8% for the E/C/F/TAF group and 4.4% for the E/C/F/TDF group (P = 0.63). HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol [47,60].
**METABOLIC PROFILE OF ART**

<table>
<thead>
<tr>
<th>Metabolic impact of drugs</th>
<th>Less</th>
<th>More</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less</td>
<td>NNRTI</td>
<td>NRTI</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>3TC / FTC ABC TDF</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>ZDV</td>
</tr>
<tr>
<td></td>
<td>ddi</td>
<td>LPV/r fAPV/r DRV/r</td>
</tr>
<tr>
<td></td>
<td>d4T</td>
<td>IDV/r TPV/r RTV (full dose)</td>
</tr>
<tr>
<td>More</td>
<td>PI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV/r SQV/r</td>
<td></td>
</tr>
</tbody>
</table>

1Limited data from use of fusion inhibitors (enfuvirtide), integrase inhibitors (raltegravir), and CCR5 inhibitors (maraviroc) suggest these drugs to have little metabolic impact, but length of experience for some of these is limited.

**Fig. 2** Metabolic impact of individual antiretroviral drugs and drug classes. 3TC, lamivudine; ABC, abacavir; ATZ, atazanavir; d4T.
Conclusions

- CVD is prevalent among HIV patients with significant morbidity and mortality
- Pathogenesis of CVD in HIV is multifactorial including chronic inflammation/immune activation and abnormal lipid metabolism
- Consistent delivery of CVD prevention strategies require a systematic, multi-disciplinary approach
- Applicability of CVD guideline changes to HIV patients is unclear
- Improved CV risk prediction and validated guidelines specific for HIV patients are urgently needed
The End
Mortality Trends in HIV

- Introduction of HAART in 1996 led to dramatic reductions in AIDS-related morbidity and mortality\(^1\)

- Non-AIDS related causes of morbidity and mortality of increasing importance, with 3 dominant players\(^2\)
  - Cardiovascular Disease (CVD)
  - Chronic liver disease, primarily from viral hepatitis
  - Non-AIDS defining malignancies

## Initial Screening for Metabolic Complications

<table>
<thead>
<tr>
<th>HISTORY</th>
<th>PE</th>
<th>LABS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hx of CHD, CVA, PVD, DM2, HTN, HLD</td>
<td>• Blood Pressure</td>
<td>• Fasting glucose</td>
</tr>
<tr>
<td>• FHx of premature CVD (male &lt; 55, female &lt;65)</td>
<td>• BMI, Height, Weight</td>
<td>• Fasting lipid profile</td>
</tr>
<tr>
<td>• Menopausal status in women</td>
<td>• Waist Circumference</td>
<td>• Serum Cr (eGFR)</td>
</tr>
<tr>
<td>• Smoking status</td>
<td>• Signs of lipodystrophy</td>
<td>• Consider reflex TSH, HCV Ab, micro-</td>
</tr>
<tr>
<td>• Diet and exercise hx</td>
<td>• Signs of cardiac dz or PAD</td>
<td>albuminuria (if CKD)</td>
</tr>
<tr>
<td>• Substance abuse (EtOH, IVDU)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Medications with metabolic AEs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COMMUNICATING CVD RISK TO PATIENTS

• FRS 10-year predicted risk may be difficult for patients to conceptualize

• “Heart age” calculates the age of a reference patient with ideal risk profile that shares same risk as the patient

• Endorsed by British Heart Federation as tool to communicate risk to patients

• Bristol HIV cohort study found HIV+ patients had significantly higher heart age than actual age, with deviation greatest in smokers and older patients

• May be a useful tool for communicating risk to HIV+ patients

http://www.heartagecalculator.com

CV Risk Persists in Treated HIV Infection; Inflammation Predictive of This Risk

- ART-treated/virologically suppressed HIV-infected patients have greater carotid IMT vs controls[1,2]
  - hsCRP strongly associated with IMT in bifurcation region[2]

- HIV-infected patients with well-controlled disease have greater arterial inflammation (using FDG-PET)
  - Associated with sCD163 but not CRP or D-dimer[3]

Meta-Analysis of MI Risk in HIV vs. non-HIV Patients

HIV – no ART
RR 1.61 (1.43-1.81)
p<0.001

HIV – on ART
RR 2.0 (1.7-2.37)
P<0.001

Causes of Death in French HIV National Survey, 2005

Underlying cause of death in HIV-infected adults: Overall distribution in 2000 (n = 964) and 2005 (n = 1042), and most recent CD4 cell count by cause; Mortalité 2000 and 2005 surveys, France.