HIV Infection and Cardiovascular Disease

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Disclosures

• None
HIV and CVD - Outline

• Context of non-communicable diseases in HIV
• Epidemiology of HIV and CVD
• Pathophysiology of CVD in HIV
• Prevention and management of CVD in HIV
HIV and CVD - Outline

- Context of non-communicable diseases in HIV
- Epidemiology of HIV and CVD
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HIV Patients are Aging

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

HIV Patients will Face Increased Rates of NCDs as they Age

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

HIV Patients will Face Increased Rates of NCDs compared with HIV-negative

- Projected distribution of NCDs by age group in HIV versus non-HIV in 2030

*Smit Lancet ID 2015.*
HIV and CVD - Outline

• Context of non-communicable diseases in HIV
• Epidemiology of HIV and CVD
• Pathophysiology of CVD in HIV
• Prevention and management of CVD in HIV
Mike Godfrey was 19 when he found out he had H.I.V. He was 29 when he began antiretroviral therapy. He was 43 when he had a heart attack.

"I felt fluttery," he said. "Weird and flu-like, and I ignored it. A week later, it was gone, and this time I felt something in my heart too. I was too stupid to call an ambulance, so I got a cab and went to the hospital."

Mr. Godfrey's experience exemplifies a growing trend: Many AIDS specialists have long suspected that heart disease and other cardiovascular problems may be more common among people with H.I.V. than previously thought. A new study published in the Journal of the American College of Cardiology suggests that people with HIV have heart attacks and have them earlier in life than patients whose infection is well suppressed, and that the risk is highest among patients whose drugs are at higher risk.

HIV and Your Heart

Co-developed with the American Academy of HIV Medicine

HIV and Your Risk for Cardiovascular Disease

By learning about the risk factors for cardiovascular disease associated with HIV, you can take steps to reduce your risk.

HIV Medications

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

Your Healthcare Team

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

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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<td>Kaiser</td>
<td>4159</td>
<td>↑ MI and CHD in HIV vs. control</td>
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<td>Currier</td>
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<td>Lang</td>
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<td>↑ MI in HIV vs. 3 population registries</td>
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<td>↑ MI and CHD in HIV vs. 10:1 matched control</td>
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CVD Incidence by Gender and Age

- Increased relative risk in patients traditionally considered low risk
- May reflect the different distribution of CVD risk factors in HIV

Triant CROI 2014, abstract 738.
CVD Mortality in HIV

- AIDS
- Non-AIDS-defining nonhepatitis-related malignancy
- Liver disease
- Cardiovascular
- Non-AIDS-defining infection
- Suicide
- Unexplained sudden death
- Various causes
- Unknown

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<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>AIDS</td>
<td>456 (47)</td>
<td>375 (36)</td>
<td>182 (25)</td>
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<tr>
<td>NaNH malignancy</td>
<td>104 (11)</td>
<td>173 (17)</td>
<td>161 (22)</td>
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<tr>
<td>Liver disease</td>
<td>122 (13)</td>
<td>154 (15)</td>
<td>77 (11)</td>
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<tr>
<td>Cardiovascular</td>
<td>87 (7)</td>
<td>88 (8)</td>
<td>73 (10)</td>
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<tr>
<td>Other</td>
<td>215 (22)</td>
<td>252 (24)</td>
<td>235 (32)</td>
</tr>
</tbody>
</table>

*P*-value adjusted for age and sex < 0.0001 (multinomial logistic model)

NaNH malignancy: non-AIDS defining and non-viral hepatitis related malignancy
Hospitalization Rates by Diagnosis

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

Berry IAC 2010. Abstract TUPE0221; Crum-Cianflone JAIDS 2010;54:2478-257
# HIV and CVD in South Africa: Impact on Mortality

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<thead>
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<tr>
<td><strong>Men aged 50-64 years</strong></td>
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<td></td>
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<tr>
<td>1. Vascular disease*</td>
<td>13 (19%)</td>
<td></td>
<td>20 (22%)</td>
<td></td>
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<tr>
<td>2. Neoplasms†</td>
<td>6 (9%)</td>
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<td>8 (9%)</td>
<td></td>
</tr>
<tr>
<td>3. Other NCDs†</td>
<td>6 (9%)</td>
<td></td>
<td>8 (9%)</td>
<td></td>
</tr>
<tr>
<td>4. HIV/tuberculosis</td>
<td>4 (6%)</td>
<td></td>
<td>7 (8%)</td>
<td></td>
</tr>
<tr>
<td>5. Chronic liver disease¶</td>
<td>3 (4%)</td>
<td></td>
<td>6 (7%)</td>
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<tr>
<td><strong>Total</strong></td>
<td>70</td>
<td>93</td>
<td>124</td>
<td>275</td>
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<tr>
<td><strong>Men aged 65 years</strong></td>
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<tr>
<td>1. Other cardiac disorders§</td>
<td>16 (18%)</td>
<td>19 (11%)</td>
<td>30 (13%)</td>
<td>32 (11%)</td>
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<td>2. Tuberculosis</td>
<td>10 (12%)</td>
<td>15 (9%)</td>
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<tr>
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<td>7 (8%)</td>
<td>13 (8%)</td>
<td>24 (10%)</td>
<td>25 (9%)</td>
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<tr>
<td>4. Neoplasms†</td>
<td>4 (5%)</td>
<td>9 (5%)</td>
<td>18 (8%)</td>
<td>20 (7%)</td>
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<td>5. Vehicle accidents</td>
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<td>8 (5%)</td>
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<td>87</td>
<td>168</td>
<td>232</td>
<td>287</td>
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<td><strong>Women aged 50-64 years</strong></td>
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<tr>
<td>1. Vascular disease*</td>
<td>7 (20%)</td>
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<td>5 (8%)</td>
<td>15 (16%)</td>
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<tr>
<td>2. Chronic liver disease¶</td>
<td>5 (14%)</td>
<td>4 (7%)</td>
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<tr>
<td>3. Other cardiac disorders§</td>
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<td>4 (7%)</td>
<td>11 (6%)</td>
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<tr>
<td>4. Female genital neoplasm</td>
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<td>4 (4%)</td>
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<tr>
<td>5. Accidental injuries</td>
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<td>4 (4%)</td>
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<tr>
<td><strong>Total</strong></td>
<td>35</td>
<td>61</td>
<td>93</td>
<td>178</td>
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<tr>
<td><strong>Women aged 65 years</strong></td>
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<tr>
<td>1. Other cardiac disorders§</td>
<td>14 (13%)</td>
<td>24 (13%)</td>
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<td>45 (16%)</td>
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<td>11 (10%)</td>
<td>20 (11%)</td>
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<td>33 (11%)</td>
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<tr>
<td>3. Female genital neoplasm</td>
<td>7 (7%)</td>
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<td>19 (8%)</td>
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<td>4. Tuberculosis</td>
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<td></td>
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<td>5. Neoplasms†</td>
<td>4 (4%)</td>
<td>9 (5%)</td>
<td>12 (5%)</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>106</td>
<td>187</td>
<td>247</td>
<td>291</td>
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</tbody>
</table>

Adapted from data in reference 2. NCDs—non-communicable diseases. *Cerebrovascular disease, Ischaemic heart disease, and hypertensive disease. †All malignant neoplasms, excluding those of female genital organs. ‡Includes disorders not included in other categories, such as anaemia, dementia, chronic obstructive airways disease, asthma, peptic ulcer disease, etc. §All circulatory system diseases excluding hypertensive disease, Ischaemic heart disease, and cerebrovascular disease. ¶Excludes all infectious causes.

Table: Five most common causes of death in men and women aged 50-64 years and 65 years and older in Agincourt subdistrict, 1992-2005.

[Mayosi Lancet 2009.]
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- Context of non-communicable diseases in HIV
- Epidemiology of HIV and CVD
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Pathophysiology of HIV-Associated CVD

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

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

AMI Incidence Increased with ART/Pis

- D:A:D - prospective observational cohort of 33,347 patients
- Relative risk of AMI 1.16 per year ART exposure
- PIs but not NNRTIs conferred increased risk

AMI Incidence Increased with Abacavir

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

SMART, Inflammation and CVD

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

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

Decreased CD4 Count Linked to CVD

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

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

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

Chow JAIDS 2014; Lang CID 2012.
Pathophysiology of HIV-Associated CVD

Increase risk
Decrease risk
HIV and CVD - Outline

• Context of non-communicable diseases in HIV
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Challenges in Management of HIV-Associated CVD

- Understanding of mechanism has not yet translated into clinical interventions
- Unclear applicability of general population guidelines
- Limitations of HIV-specific guidelines

<table>
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<tr>
<th>Intervention</th>
<th>Traditional Risk Factors</th>
<th>Novel Risk Factors</th>
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<td>Statins</td>
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<tr>
<td>ASA</td>
<td></td>
<td></td>
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<tr>
<td>ART</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>
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<td></td>
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<tr>
<td>Diabetes management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN management</td>
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</tbody>
</table>
CVD Risk Prediction in HIV

• Partners HIV longitudinal cohort, 2239 patients
• ACC/AHA risk score and FRS underestimate CVD risk in HIV
  – 5-year observed versus predicted event rates

Regan CROI 2015, abstract 751.
Implications for CVD Risk Prediction in HIV?

- Unknown accuracy of FRS and new ACC/AHA calculator in HIV
- New ACC/AHA risk score overestimates risk in general population but may underestimate risk in HIV
- In HIV, risk scores discordant in approximately 19%
  - FRS assigns low risk and ACC/AHA high risk in 99% of discordant cases

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

Preliminary data, Partners HIV cohort.
Role of ART in CVD Risk

- **Paradigm shift** in role of ART in relation to CVD risk in HIV
- CVD-related benefit from virologic suppression and immune reconstitution achieved by treating HIV thought to outweigh possible proatherogenic effects of individual medications
- **START trial** was first RCT to assess rates of comorbidities including CVD by early versus deferred ART initiation

Clinical strategy
- Treat HIV to reduce inflammation, immune activation, and associated cardiovascular risk
- Consider underlying CVD risk when selecting specific drugs, as individual ART medications may have varying risk

Thompson JAMA 2010; clinicaltrials.gov NCT00867048.
START

- Strategic Timing of AntiRetroviral Treatment (START) study
- First RCT to assess rates of events including non-AIDS/CVD by early (>500) versus deferred (<350) ART initiation
- Interim DSMB review → study stopped early with results released May 2015
- Early treatment reduced serious illness/death by 53%
  - 41 vs 86 AIDS events, non-AIDS events, or death in early vs deferred treatment
  - <3% overall event rate
  - Greater risk reduction for AIDS events (70%) vs non-AIDS events (33%)

Insight Start Study Group NEJM 2015
Paradigm Shift in Cholesterol Treatment for General Population

- New cholesterol/statin guidelines released November 2013 (replaced NCEP ATP-III)
- Statin initiation: 4 major benefit groups
  - Clinical ASCVD
  - LDL ≥ 190 mg/dL
  - DM age 40-75
  - Estimated 10-year ASCVD risk ≥ 7.5%
- No LDL treatment targets
Dyslipidemia in HIV

- Dyslipidemia in HIV common
- Statins are mainstay of treatment. In HIV, they:
  - Effectively lower LDL
  - Decrease immune activation (T cell and monocyte)
  - Contribute to immune reconstitution independent of ART
  - Decreased mortality in HIV observational cohort
- Unclear role of statins in preventing CVD in HIV
  - HIV patients excluded from RCTs
  - Different mechanism of CVD
  - Different typical cholesterol profile
  - Unclear role of new ACC/AHA risk calculator
  - Statin intensity definition not directly applicable

STRATEGIES ARE NEEDED TO PREVENT HEART-RELATED DISEASE AMONG PEOPLE LIVING WITH HIV

REPRIEVE WAS DESIGNED TO ADDRESS THIS UNMET NEED

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

• REPRIEVE stands for: www.reprievetrial.org
The REPRIEVE trial will test whether treatment with a statin medication (pitavastatin) lowers the risk of heart-related disease among HIV-infected individuals who may not be recommended for statins by current US Cholesterol guidelines.

6500 people living with HIV will be assigned to take pitavastatin or placebo once daily and will be followed for 3-5 years.

Statins are a widely prescribed class of medications which lower cholesterol levels and also decrease inflammation.
Management of Dyslipidemia in HIV

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

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

Novel Interventions Targeting Inflammation and Immune Activation

- ART treatment intensification
- Methotrexate
- CCR5 antagonists
- Rifaximin
- Sevelamer
- Mesalamine
- Pentoxifylline
- Hydroxychloroquine

HIV Wellness

- www.heart.org
- 9 health components
  - T cell, viral load, cholesterol, smoke-free, fasting glucose, body mass index, blood pressure, physical activity, nutrition
- Patients can assess where they stand
- Measurable and actionable steps to reach goals
- Can take HIV wellness quiz

Prevention of HIV-Associated CVD

- ART
  - PREVENT CVD
    - COUNSEL
    - STATINS
    - ANTI-INFLAMMATORIES AND IMMUNE MODULATORS
    - TRADITIONAL RISK FACTOR MODIFICATION
      - STATINS
      - SMOKING CESSATION
      - LIFESTYLE
Management of CVD in HIV: Key Questions

• Are the new ACC/AHA risk calculator and cholesterol guidelines applicable and accurate in HIV?
• What is the role for statins in HIV?
• Will tailored immunomodulatory agents further decrease CVD risk in HIV?
• Are CVD prevention strategies similar in critical subgroups, including HIV-infected women and patients in resource-limited settings?
• Should HIV be considered a cardiovascular risk equivalent?
• How can CVD risk reduction best be integrated into HIV care models?
HIV DIAGNOSIS
- CVD education
- Public awareness
- CVD risk factor screening

LINK TO CARE
- Individualized education
- Check BP, lipids, glucose
- Assess smoking status
- Calculate FRS

TREATMENT INITIATION
- Review CVD risk factor guidelines
- Benefits/risks
- Counsel sodium/diet/exercise
- Counsel smoking cessation
- Start ASA/HTN/lipid/DM rx

FOLLOW UP
- Clinical assessment
- Monitor side effects rx
- Lab monitoring

CONTINUED ENGAGEMENT IN CARE
- Establish patient relationship
- Continued counseling
- Repeat risk assessment

CVD
- Clinical assessment
- Monitor side effects rx
- Lab monitoring

HIV
- Individualized education
- Counseling risk reduction
- Check CD4/VL
- Assess for TB/OIs

HIV education
- Public awareness
- HIV test accessibility

HIV rx guidelines
- Weigh benefits/risks
- Counsel adherence
- Start ART

Establish patient relationship
- Continued counseling
Management of CVD in HIV: Key Principles

• Significant impact of CVD in HIV populations anticipated
• Pathophysiology driven in large part by HIV-related immunologic and inflammatory changes
• Current treatment paradigms do not reflect this pathophysiology
• Recommended strategies
  – Build CVD risk assessment into practice
  – Manage traditional CVD risk factors aggressively (e.g. smoking)
  – Start appropriate statin if candidate by general population guidelines
  – Low threshold for diagnostic workup in traditionally low-risk groups
  – Treat HIV to reduce CVD risk
• Intensity and consistency of HIV care provide opportunity to prevent and manage chronic disease complications