HIV & Cardiovascular Disease

*How worried should we be?*

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*Associate Professor*
*Site Leader, University of North Carolina AIDS Clinical Trials Unit at Chapel Hill*

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Pre-Test

- The **main** driver of cardiovascular disease in patients living with HIV is:
  - Smoking and other ‘traditional’ risks
  - Antiretroviral therapy
  - Chronic kidney disease
  - Microbial translocation from the gut
  - Immune activation and inflammation
Outline

• There are data suggesting increased risk of co-morbidities, including CVD
• Fact: CVD *is* clearly more common in people with HIV
• What is unclear is *why*
  — Possibilities
    • More risk factors (smoking, sedentariness, stress, depression)
    • HIV (via immune and inflammatory mechanisms, microbial translocation, CMV)
    • ART
• Assessing Risk
• Approaches to Prevention
The Link between HIV and CVD

- Rates of AMI compared in HIV+ and HIV- patients at 2 Boston hospitals
  - N of ~3,800 for HIV+ patients; > 1 million for HIV- patients
  - 8-year period 1996 to 2004
- The HIV cohort had significantly > proportions of hypertension (21.2% vs. 15.9%), diabetes (11.5% vs. 6.6%), and dyslipidemia (23.3% vs. 17.6%) (P < 0.0001 for each).
- *Adjustment was made for these plus age, gender, race, hypertension.


 bruk
CVD: HIV-positive patients are at higher risk for AMI events over time

- A number of studies over the past decade showed increased risk of CVD in HIV-positive patients vs uninfected individuals, ranging from about 1.5 times to more than 2 times risk.

AMI, acute myocardial infarction; VACS, Veterans Aging Cohort Study.


AMI Rates in HIV-Positive Patients vs Uninfected Individuals (VACS Virtual Cohort, 2003-2009)

![Graph showing AMI rates in HIV-positive patients vs uninfected individuals.](image)

- AMI: acute myocardial infarction; VACS: Veterans Aging Cohort Study.


With HIV, growing older.

Larry Gibson first spotted Dennis Golay outside West Market Place. By the time he was halfway across Salt Lake in 1982, it was already.

It was Nov. 14, 1982 — Golay’s 34th birthday.

Seven years later, both men tested positive for the AIDS virus, an arrest in the days before antiretroviral drugs. Having achieved...
Outline

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- *Adjustment was made for these plus age, gender, race, hypertension.


How big is the contribution of HIV and HIV-related factors to CVD and other conditions associated with aging?
Increased Acute Myocardial Infarction Rates and Cardiovascular Risk Factors among Patients with Human Immunodeficiency Virus Disease

Virginia A. Triant, Hang Lee, Colleen Hadigan, and Steven K. Grinspoon

Massachusetts General Hospital Program in Nutritional Metabolism (V.A.T., C.H., S.K.G.), Brigham and Women’s Hospital and Massachusetts General Hospital Divisions of Infectious Diseases (V.A.T.), and the Massachusetts General Hospital Biostatistics Center (H.L.), Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114

Context: Metabolic changes and smoking are common among HIV patients and may confound increased cardiovascular risk.

Objective: The aim of the study was to determine acute myocardial infarction (AMI) rates and cardiovascular risk factors in HIV compared with non-HIV patients in two tertiary care hospitals.

Design, Setting, and Participants: We conducted a health care system-based cohort study using a large data registry with 3,061 HIV and 1,044,889 non-HIV patients. AMI rates were determined among patients receiving longitudinal care between October 1, 1996, and June 30, 2004.

Main Outcome Measures: The primary outcome was myocardial infarction, identified by International Classification of Disease coding criteria.

Results: AMI was identified in 189 HIV and 26,142 non-HIV patients. AMI rates per 1000 person-years were increased in HIV vs. non-HIV patients (1.13 vs. 0.08 per 1000 person-years; 95% CI 1.08–1.18; P < 0.0001). The HIV cohort had significantly higher proportions of hypertension (21.2% vs. 15.9%), diabetes (13.3% vs. 6.6%), and dyslipidemia (22.3% vs. 17.6%) than the non-HIV cohort (P < 0.0001 for each comparison). The difference in AMI rates between HIV and non-HIV patients was significant, with a relative risk (RR) of 1.15 (95% CI 1.05–2.02; P = 0.0011), adjusting for age, gender, race, hypertension, diabetes, and dyslipidemia. In gender-stratified models, the unadjusted AMI rates per 1000 person-years were higher for HIV patients among women (2.31 vs. 0.49 for HIV compared with non-HIV women), but not among men (15.48 vs. 11.44 for HIV compared with non-HIV men). The RR for HIV vs. non-HIV was 2.10 (95% CI 1.33–3.37; P = 0.0003) for women and 1.40 (95% CI 1.36–1.47; P = 0.0001) for men, adjusting for age, gender, race, hypertension, diabetes, and dyslipidemia. A limitation of this database is that it contains incomplete data on smoking status; smoking could not be included in the overall regression model, and some of the increased risk may be accounted for by differences in smoking rates.

Conclusion: AMI rates and cardiovascular risk factors were increased in HIV compared with non-HIV patients, particularly among women. Cardiac risk modification strategies are important for the long-term care of HIV patients.

Table 3. Associations Between HIV Serostatus and Coronary Artery Plaque

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minimally Adjusted Model</th>
<th>Adjusted for CAD Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR (95% CI) P Value</td>
<td>PR (95% CI) P Value</td>
</tr>
<tr>
<td>Prevalence of plaque</td>
<td>Noncontrast CT scans (n = 1001)</td>
<td></td>
</tr>
<tr>
<td>CAC present</td>
<td>1.21 (1.08 to 1.35) 0.001</td>
<td>1.12 (0.99 to 1.26) 0.076</td>
</tr>
<tr>
<td>Contrast-enhanced CT scans (n = 579)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any plaque present</td>
<td>1.14 (1.09 to 1.24) 0.001</td>
<td>1.13 (1.04 to 1.23) 0.006</td>
</tr>
<tr>
<td>Noncalcified plaque present</td>
<td>1.28 (1.13 to 1.45) -0.001</td>
<td>1.25 (1.10 to 1.42) 0.001</td>
</tr>
<tr>
<td>Mixed plaque present</td>
<td>1.35 (1.15 to 1.60) 0.004</td>
<td>1.21 (1.05 to 1.39) 0.010</td>
</tr>
<tr>
<td>Calcified plaque present</td>
<td>1.05 (0.88 to 1.27) 0.58</td>
<td>1.02 (0.84 to 1.21) 0.88</td>
</tr>
<tr>
<td>Coronary artery stenosis &gt;50%</td>
<td>1.48 (1.06 to 2.07) 0.020</td>
<td>1.26 (0.86 to 1.81) 0.26</td>
</tr>
<tr>
<td>Coronary artery stenosis &gt;10%</td>
<td>1.20 (1.07 to 1.38) 0.51</td>
<td>1.16 (0.94 to 1.40) 0.30</td>
</tr>
</tbody>
</table>

Mean Difference (95% CI) P Value

Mean Difference (95% CI) P Value

Extent of plaque
Noncontrast CT scans | CAC Agatston score (n = 527)
| 0.07 (0.23 to 0.38) 0.65 | 0.03 (0.34 to 0.29) 0.88 |
| Segment involvement score | 0.14 (0.02 to 0.26) 0.021 | 0.11 (0.01 to 0.22) 0.075 |
| Total coronary plaque score (n = 579) | 0.19 (0.05 to 0.33) 0.009 | 0.13 (0.01 to 0.27) 0.062 |
| Noncalcified plaque score (n = 449) | 0.16 (0.03 to 0.29) 0.013 | 0.19 (0.02 to 0.26) 0.003 |
| Mixed plaque score (n = 254) | 0.15 (0.05 to 0.25) 0.13 | 0.16 (0.04 to 0.36) 0.109 |
| Calcified plaque score (n = 208) | 0.02 (0.21 to 0.41) 0.83 | 0.02 (0.27 to 0.12) 0.47 |

CAC = coronary artery calcium; CAD = coronary artery disease; CT = computed tomography; PR = prevalence ratio.

1 Adjusted for age, sex, CT imaging center, and cohort (before vs. after 2001).
2 Adjusted for age, race, CT scanning center, and cohort (before vs. after 2001).
3 Ratio of HIV-infected to HIV-uninfected men.
4 Analyses (in natural log scale) include men with plaque present (plaque score >0).
5 HIV-uninfected men vs. HIV-infected men.
Polling Question

- Over time, rates of CVD among HIV+ persons has:
  - Gone up
  - Gone down
  - Stayed the same

The reduced MI incidence rates for HIV+ in recent years is likely a result of:

- CVD risk factor reduction,
- use of more lipid-friendly ART,
- and reduced immunodeficiency

Klein D, et al Abst 737, 741CROI 2014
2001-2012
- The NY Nation
- 145,000 people
  - 29,000 deaths
- Over time, as HIV+ persons were less likely to die of HIV-related causes, the proportion succumbing to CVD increased

Risk factors for CVD events in HIV+ patients

Estimated Risk Ratio of CVD Events Among 22,625 HIV-Positive Patients
(D:A:D Study)

* Risk ratios for PI and boosted PI were estimated per additional year, TC and HDL cholesterol per mmol/L higher, and systolic BP per 10mmHg higher.

BP, blood pressure; D:A:D, Data collection on Adverse events of Anti-HIV Drugs; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

NA-ACCORD: Risk factors for MI

<table>
<thead>
<tr>
<th>Demographic &amp; traditional risk factors</th>
<th>aIRR [95% CI]</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Elevated total cholesterol</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td>40-64</td>
<td>2.03 (1.51, 2.72)</td>
<td>1.00 (0.87, 1.15)</td>
</tr>
<tr>
<td>65-84</td>
<td>2.76 (2.01, 3.99)</td>
<td>1.08 (0.97, 1.22)</td>
</tr>
<tr>
<td>Sex</td>
<td>Low HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>0.94 (0.72, 1.22)</td>
<td>1.14 (0.99, 1.30)</td>
</tr>
<tr>
<td>Race and ethnicity</td>
<td>asting impairment</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Black</td>
<td>1.51 (1.31, 1.75)</td>
<td>0.96 (0.84, 1.10)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>No</td>
<td>Statistic use</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>0.88 (0.80, 1.00)</td>
<td>1.00</td>
</tr>
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<td>HIV-related risk factors</td>
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<tr>
<td>NSM</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>CD4</td>
<td>2.29 (1.70, 3.06)</td>
<td>0.99 (0.90, 1.10)</td>
</tr>
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<td>0.95 (0.72, 1.27)</td>
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<tr>
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<td>2.00 (1.69, 2.37)</td>
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<td>Current encephalopathy</td>
<td>0.80 (0.67, 0.98)</td>
<td>0.99 (0.84, 1.18)</td>
</tr>
<tr>
<td>CD4+</td>
<td>3.00</td>
<td>1.00</td>
</tr>
<tr>
<td>CD4-</td>
<td>1.50</td>
<td>1.00</td>
</tr>
<tr>
<td>CD4+ and CD4-</td>
<td>0.89 (0.78, 1.00)</td>
<td>0.99 (0.84, 1.18)</td>
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271 primary MIs (55%), 219 secondary MIs (45%), and 24,604 cohort members without an MI.

Crude incidence rates were 2.68 per 1000 person-years (95% confidence interval [CI] 2.38 to 3.02) for primary MIs and 2.17 per 1000 person-years (95% CI 1.90 to 2.48) for secondary MIs

Lower current CD4 count, detectable viral load, a history of clinical AIDS, and traditional cardiovascular risk factors all predicted primary atherosclerotic MI

Chronic inflammation is associated with increased risk for comorbidities in HIV+ patients

- Untreated HIV infection
- Loss of immunoregulatory cells
- HIV replication
- Loss of gut mucosal integrity and microbial translocation
- Decreased but persistent chronic inflammation, immune activation, elevated coagulation markers, microbial translocation, and increased risk of coinfection
- Traditional comorbidity risk factors, such as dyslipidemia, smoking, lipodystrophy, HTN, obesity, substance use
- Increased incidence of comorbidities and clinical disease

BIOMARKERS OF INFLAMMATION ARE ELEVATED IN HIV-POSITIVE PATIENTS EVEN ON ART

*Adjusted for age, race, smoking, hepatitis C (HCV) infection, obesity, diabetes and MACS site; Error bars represent 99.7% confidence intervals, calculated with Bonferroni adjustment to maintain a family-wise error rate of 0.05. Filled markers represent statistical significance (P < 0.002).


Markers of inflammation and outcomes

• SMART and ESPRIT
• 19,000 person-years of follow-up among 4304 pvs (median age 42y, median CD4 526, 77% men)
  – 157 all-cause deaths,
  – 117 non-AIDS deaths
  – 101 progressions to AIDS
  – 121 CVD
  – 99 NADM
• IL-6 (baseline) was found to be a stronger predictor of all cause mortality and many fatal non-AIDS events than the other two markers.
• Adjustment attenuated the associations but IL-6 remained significant including for CVD.

Borges A, et al. #761 CROI 2015
From: Arterial Inflammation in Patients With HIV

**Figure Legend:**

18F-FDG-PET indicates 18-fluorine-2-deoxy-D-glucose positron emission tomography; CT, computed tomography; FRS, Framingham risk score; HIV, human immunodeficiency virus; SVC, superior vena cava; TBR, target-to-background ratio. There is increased aortic PET-FDG uptake (red coloration) in a participant infected with HIV compared with a non-HIV FRS-matched control participant. Neither participant had known heart disease. For each participant, the FRS was low with a score of 2 and calcium was not present on the cardiac CT scan. Neither participant was receiving a statin. A indicates anterior-posterior orientation and F, foot-head orientation.

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**Role of monocytes in atheromatous plaque development**

Crowe S. IAS 2014

HIV activates monocytes & endothelial cells (in conjunction with proatherogenic lipids),
- Increase monocyte transmigra;on
- Increase uptake of oLDL
- Promote differentiation into foam cells
- And contribute to atherosclerotic plaque formation

Campbell J et al AIDS 2014 in press
Factors That Contribute to Chronic Immune Activation: Microbial Translocation

Pathogenesis of Microbial Translocation in HIV-Positive Patients

A Marker of Microbial translocation declines during suppressive art but does not normalize

* Progressors were chronically HIV-positive individuals and individuals with AIDS (<200 CD4+ cells/mm³)

Each group contains combined patient data from two unique cohorts, grouped according to HIV status and study design.

Polling Question

- Based on the data presented to date, I believe abacavir causes cardiovascular events in HIV+ people:
  - Yes
  - No
  - I remain unsure

NA-ACCORD: Abacavir Use and Risk of MI

- Retrospective analysis to explore ABC use and MI
- Data on MI collected from 1995-2010
- Three analyses:
  - FULL population (n=16,733): All ART users EXCEPT those on ABC at study entry
  - RESTRICTED population (n=6,485): Only ART naive on entry who initiated ART thereafter
  - D:A:D Replication: Simulates D:A:D analysis
- Endpoint of incident MIs: Presence of clinical diagnosis or elevation of cardiac enzymes
- 301 MIs in Full, 93 in Restricted
- ABC initiators more likely to be black, IDU, heterosexual risk, HCV, HTN, renal impairment, high total cholesterol, a CD4 <200, and history of AIDS

- Recent ABC use associated with MI in adjusted analyses of D:A:D Replication and Restricted population but not the Full population.
- Significant independent risk factors for MI
  - Both: Age 60+, HTN, eGFR < 30, AIDS
  - Full: Smoking, DM

D:A:D Renal disease and CVD

Take Homes:

- This is complex
- Clear signals for role of discrimination in risk of CVD
- There are underlying psychosocial, genetic, and sex differences in one’s susceptibility to exposure to discrimination
- Depression is major co-occurrence
- Discrimination is a factor that needs to be included in CVD research
Toxic effects of Stress

• Helplessness and health
  • More helplessness > risk of CVD, DM and depression
• Effects occur early and linger
  • Early hardships continue to be associated with illness later in life despite SE ascendancy
• Poverty by definition produces Stress for which there are fewer resources to address problems
• Stress leads to leads to biological changes (hypercortisolism, increases in markers of inflammation)
  • ? CNS changes such as reduced hippocampus volume?
Chronic depressive symptoms and Framingham coronary risk in HIV-infected and HIV-uninfected women


Table 2. Correlations of Framingham Risk Score (FRS) in HIV-infected and uninfected women in the Women’s Integrapy HIV Study (WHIS).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted estimated FRS (Mean ± SE)</th>
<th>p-Value</th>
<th>Adjusted estimated FRS</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic depressive symptoms</td>
<td>3.6 ± 0.6</td>
<td>&lt;0.01</td>
<td>1.3 ± 0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>0.1 ± 0.1</td>
<td></td>
<td>0.3 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.8 ± 0.3</td>
<td>0.07</td>
<td>0.3 ± 0.4</td>
<td>0.52</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.4 ± 0.4</td>
<td></td>
<td>0.2 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>1.2 ± 0.6</td>
<td>&lt;0.01</td>
<td>0.9 ± 0.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Age</td>
<td>83 ± 0.5</td>
<td></td>
<td>83 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>83 ± 0.5</td>
<td></td>
<td>83 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td>83 ± 0.5</td>
<td></td>
<td>83 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td>83 ± 0.5</td>
<td></td>
<td>83 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>83 ± 0.5</td>
<td></td>
<td>83 ± 0.5</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Bold values denote p < 0.01.
Outline

• There are data suggesting increased risk of co-morbidities, including CVD
• CVD is clearly more common in people with HIV
• What is unclear is why
  – Possibilities
    • More risk factors (smoking, sedentariness, stress, depression)
    • HIV (via immune and inflammatory mechanisms, microbial translocation, CMV)
    • ART
• Assessing Risk
• Approaches to Prevention

Polling Question

• To assess CVD risk in patients with HIV, which of the following do you use:
  – Framingham Risk Score
  – American Heart Assoc/American College of Cardiology formula
  – I don’t use risk calculators to assess risk of CVD
Polling Question

- In the setting of HIV do CVD risk calculators:
  - Overestimate CVD risk
  - Underestimate CVD risk
  - Are spot on

CVD risk prediction equations developed for the general population consistently underestimate CVD risk in HIV-Positive patients

*An outpatient study cohort (n=2392) had similar findings of underestimated CVD risk (15%-25%)²

1 ACC/AHA, American College of Cardiology/American Heart Association.
Outline

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• Fact: CVD is clearly more common in people with HIV
• What is unclear is why
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    • HIV (via immune and inflammatory mechanisms, microbial translocation, CMV)
    • ART
• Assessing Risk
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Polling Question

• Statins:
  – Should be given to HIV+ patients even when not indicated so to reduce inflammation
  – Have been demonstrated to prevent CVD in HIV+ patients
  – Should be avoided in people with HIV
Address: Reducing traditional CVD risk factors can decrease risk of CVD in older HIV-positive Patients

- Effective treatment of modifiable risk factors, such as smoking, cholesterol, and BP, can significantly reduce an individual’s CVD risk

Model for Change in Relative Risk of CVD from Smoking Cessation, Reducing Cholesterol*, or Reducing Systolic BP* in a Cohort of 24,323 HIV-Positive Patients Without Prior CVD (D:A:D Study)

*Reduced by 1 mmol/L; *Reduced by 10 mm Hg

Rosuvastatin affects on Carotid Intimal Thickness and Coronary Calcium Score

Rosuvastatin affects on Carotid Intimal Thickness and Coronary Calcium Score

- As expected, LDL-C drop was greater ROS arm.
- 3 (2 on statin) with premature study drug DC

![Graphs showing Mean Change in CIMT and Mean Change in CCA in those with BL calcification](image)


Randomized Trial of Statin Therapy and Coronary Plaque Progression

- Randomized 12-mo trial in HIV+ pts on stable ART with LDL-c < 130 and ≥ 1 coronary plaque by CTA
  - Atorvastatin 20 mg (↑ to 40 mg at 3 mos) (n = 19) vs
  - Placebo (n = 21)
- Statin therapy reduced progression of coronary plaques over a year
  - Reduced overall plaque volume, including lipid-laden plaques
    - Plaque volume decreased 4.7% with atorva; increased 18.0% in the placebo arm
  - Reduced high-risk morphology plaques by 19% in atorva arm (20% increase in placebo arm)

![Images showing plaque progression and regression](image)

Contributing factors to CVD in HIV+ patients

- Traditional risk factors
- cART toxicity
- Co-infection with eg CMV

- Monocyte & mφ activation
- Other pro-inflammatory & pro-coagulant pathways
- Chronic inflammation

Cardiovascular disease

Crowe S. IAS 2014
Contributing factors to CVD in HIV+ patients

- Traditional risk factors
- cART toxicity
- Co-infection with eg CMV

- Monocyte & mφ activation
- Other pro-inflammatory & pro-coagulant pathways
- Chronic inflammation
- Cardiovascular disease