HIV Infection and the Risk of Acute Myocardial Infarction

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**Importance:** Whether people infected with human immunodeficiency virus (HIV) are at an increased risk of acute myocardial infarction (AMI) compared with uninfected people is not clear. Without demographically and behaviorally similar uninfected comparators and without uniformly measured clinical data on risk factors and fatal and nonfatal AMI events, any potential association between HIV status and AMI may be confounded.

**Objective:** To investigate whether HIV is associated with an increased risk of AMI after adjustment for all standard Framingham risk factors among a large cohort of HIV-positive and demographically and behaviorally similar (ie, similar prevalence of smoking, alcohol, and cocaine use) uninfected veterans in care.

**Design and Setting:** Participants in the Veterans Aging Cohort Study Virtual Cohort from April 1, 2003, through December 31, 2009.

**Participants:** After eliminating those with baseline cardiovascular disease, we analyzed data on HIV status, age, sex, race/ethnicity, hypertension, diabetes mellitus, dyslipidemia, smoking, hepatitis C infection, body mass index, renal disease, anemia, substance use, CD4 cell count, HIV-1 RNA, antiretroviral therapy, and incidence of AMI.

**Main Outcome Measure:** Acute myocardial infarction.

**Results:** We analyzed data on 82,459 participants. During a median follow-up of 5.9 years, there were 871 AMI events. Across 3 decades of age, the mean (95% CI) AMI events per 1000 person-years was consistently and significantly higher for HIV-positive compared with uninfected veterans: for those aged 40 to 49 years, 2.0 (1.6-2.4) vs 1.5 (1.3-1.7); for those aged 50 to 59 years, 3.9 (3.3-4.5) vs 2.2 (1.9-2.5); and for those aged 60 to 69 years, 5.0 (3.8-6.7) vs 3.3 (2.6-4.2) (P < .05 for all). After adjusting for Framingham risk factors, comorbidities, and substance use, HIV-positive veterans had an increased risk of incident AMI compared with uninfected veterans (hazard ratio, 1.48; 95% CI, 1.27-1.72). An excess risk remained among those achieving an HIV-1 RNA level less than 500 copies/mL compared with uninfected veterans in time-updated analyses (hazard ratio, 1.39; 95% CI, 1.17-1.66).

**Conclusions and Relevance:** Infection with HIV is associated with a 50% increased risk of AMI beyond that explained by recognized risk factors.


**See Invited Commentary at end of article**

With the success of antiretroviral therapy (ART), people infected with human immunodeficiency virus (HIV) are now living longer and are at risk for heart disease. Determining whether HIV-positive people have an increased risk of acute myocardial infarction (AMI) compared with uninfected people is a central question with important clinical implications. Although prior studies have reported an association between HIV and AMI, the results may have been confounded by the choice of reference group, the lack of adjudicated AMI outcomes, a lack of fatal events, and/or missing risk factor data. We investigated whether HIV is associated with an increased risk of AMI after adjustment for all standard Framingham risk factors among a large cohort of HIV-positive and demographically and behaviorally similar (ie,
The Veterans Aging Cohort Study (VACS) Virtual Cohort (VC) is a prospective longitudinal cohort of HIV-positive and -negative veterans included in the VA electronic medical record system. Data for this cohort are extracted from the immunology case registry, the National Pharmacy Benefits Management database, the Decision Support System, the National Patient Care Database, and the VA electronic medical record health factor data set. Deaths are identified using the VA vital status file, the Social Security Administration death master file, the Beneficiary Identification and Records Locator Subsystem, and the Veterans Health Administration medical Statistical Analysis Systems inpatient data sets. Cause of death was obtained from the National Death Index. The University of Pittsburgh, Yale University, and West Haven VA Medical Center institutional review boards approved this study.

For this analysis, we considered all VACS-VC participants alive and enrolled in VACS-VC on or after 2003. The baseline was a participant’s first clinical encounter on or after April 1, 2003. All participants were followed up from their baseline date to either an AMI event, death, or the last follow-up date. Participants were followed up through December 31, 2009. These data were merged with data from Medicare, Medicaid, and the Ischemic Heart Disease–Quality Enhancement Research Initiative, an initiative designed to improve the quality of care and health outcomes of veterans with ischemic heart disease. In the Ischemic Heart Disease–Quality Enhancement Research Initiative, data from all participants with AMIs from 2003 through 2009 were reviewed to assess variations in acute coronary syndrome outcomes within the VA health care system. We excluded participants with prevalent cardiovascular disease on the basis of International Classification of Diseases, Ninth Revision (ICD-9) codes for AMI, unstable angina, cardiovascular revascularization, stroke or transient ischemic attack, peripheral vascular disease, or heart failure on or before their baseline date (n=17,229). After this exclusion, our sample included 82,459 veterans (33.2% HIV positive).

INDEPENDENT VARIABLE

We considered HIV to be present if a participant had at least 1 inpatient or 2 or more outpatient ICD-9 codes for HIV and was included in the VA Immunology Case Registry.

DEPENDENT VARIABLES

Our primary outcome was AMI. All primary outcomes were defined using VA, Medicare, and death certificate data. For events within the VA, including transfers from non-VA hospitals, AMI was determined using data collected by trained abstractors from the VA External Peer Review program. Adjudication required documentation of AMI in the discharge summary followed by a review of the physician notes and medical records. Medical information abstracted included evidence of elevated serum markers of myocardial damage including elevated troponin I, troponin T, or creatine kinase–muscle brain and electrocardiography findings. Thresholds for positive serum markers were defined by the assay used. The ST-segment elevation was defined as 1 mV or higher elevation in 2 or more contiguous leads and/or left bundle branch block. For AMI events occurring at non-VA hospitals that were not transferred to a VA facility, we used Medicare inpatient ICD-9 code 410 data. This code was selected on the basis of its high agreement with adjudicated AMI outcomes in the Cardiovascular Health Study. Based on Cardiovascular Health Study criteria, definite fatal AMI was a death within 4 weeks of an AMI event. Possible fatal AMI was a death with a death certificate documenting AMI as the underlying cause (ICD-10 code I21.0–9).
factors using established cut points. Our final model adjusted for demographic characteristics, Framingham risk factors, comorbid diseases, and substance abuse or dependence. Our primary analyses included nonfatal and fatal AMI (definite and possible). In separate secondary analyses, we examined the association between HIV and AMI in subgroups (eg, never smokers) and expanded our analyses to include VA, Medicare, and Medicaid AMI event data (ie, inpatient ICD-9 code 410). Analyses involving Medicaid were truncated to 2007 to correspond with the end of our available Medicaid data. We determined whether the risk of AMI persisted among HIV-positive veterans with HIV-1 RNA levels less than 500 copies/mL over time compared with uninfected veterans using the counting process technique for a time-updated Cox proportional hazards model. Analogous analyses examined CD4 cell count over time and AMI risk. Older age, a higher burden of comorbid disease and substance use, and very complete capture of mortality events in the VACS translates into high mortality rates. Because of the high mortality among HIV-positive (4928 [18.0%]; mortality rate [95% CI], 36.9 [35.9-38.0] deaths per 1000 person-years) compared with uninfected veterans (4042 [7.3%]; 14.4 [13.9-14.8] deaths per 1000 person-years), we conducted 1 secondary analysis adjusting for competing risk of death. Analyses of VACS participant data and methods from D’Agostino et al. Among HIV-positive veterans, we examined the association between Framingham risk factors, comorbidities, substance use, HIV biomarkers, ART, and AMI. Missing covariate data were included in the analyses using multiple imputation techniques that generated 5 data sets with complete covariate values to increase the robustness and efficiency of the estimated HR.

RESULTS

Although VACS-VC HIV-positive and uninfected veterans were age- and race-matched at the time of enrollment, after participants with baseline cardiovascular disease were excluded (n=17 229), some differences by HIV status existed (final sample size=82 459) (Table 1). The prevalence of Framingham risk factors differed by HIV status (P < .001 for all). Only current smoking, low high-density lipoprotein (HDL) cholesterol, and elevated triglycerides were more common among HIV-positive veterans. The median baseline coronary heart disease (CHD) risk was intermediate for both groups (Framingham risk score = 6) (Table 1).
During a median follow-up of 5.9 years, there were 871 AMI events (41.7% HIV positive). Of these 871 events, 534 (61.3%) were within or transferred to VA facilities (Medicare events), and 176 (20.2%) were deaths. The AMI rates per 1000 person-years were significantly higher among HIV-positive compared with uninfected veterans (Table 3), whereas the median age at event (56.4 vs 56.2 years, \( P = .42 \)) and time to event (3.3 vs 3.4 years, \( P = .28 \)) were similar.

After adjusting for Framingham risk factors, comorbidities, and substance use, HIV-positive veterans had an increased risk of incident AMI compared with uninfected veterans (HR, 1.48; 95% CI, 1.27-1.72) (Table 3). Framingham risk factors, hepatitis C virus infection, renal disease, and anemia were independently associated with AMI (Table 3). This association persisted when we restricted the sample to never smokers (HR, 1.75; 95% CI, 1.27-2.42) or to those without hepatitis C virus infection, renal disease, and obesity (1.50; 1.20-1.88) or when we expanded our outcomes to include VA, Medicare, and Medicaid events (1.58; 1.25-1.99). Although AMI risk was highest among those with HIV-1 RNA levels of at least 500 copies/mL and CD4 cell count less than 200 cells/mL in time-updated analyses (Table 4), this higher risk remained even among those who achieved HIV-1 RNA levels less than 500 copies/mL over time compared with uninfected veterans (Table 4). This was also true after adjusting for competing risk of death (HR, 1.45; 95% CI, 1.25-1.69). The C statistic for a model to predict AMI was 0.71 (95% CI, 0.70-0.73). When we added HIV infection to the model, the C statistic increased by 0.01 (\( P < .001 \)).

Among HIV-positive veterans, baseline HIV-1 RNA, CD4 cell count, and ART (both by class and regimen), as well as recent NNRTI, NRTI, and ART regimens were not associated with AMI. However, recent HIV-1 RNA of at least 500 copies/mL (HR, 1.60; 95% CI, 1.14-2.22) and recent CD4 cell count less than 200 cells/mL (1.57; 1.10-2.24) were associated with AMI, and recent protease inhibitor use (1.34; 0.98-1.81; \( P = .06 \)) had bor-
derline significance with AMI after being included in a model that adjusted for Framingham risk factors, co-morbidities, and substance use (data otherwise not shown).

**COMMENT**

Veterans with HIV infection have a significantly higher risk of AMI compared with demographically and behaviorally similar uninfected veterans even after adjustment for Framingham risk factors, co-morbidities, and substance use. This risk persisted among those achieving HIV-1 RNA levels less than 500 copies/mL over time. When added to a model including Framingham risk factors, HIV status modestly improved AMI risk discrimination.

Although consistent with prior studies, our analyses are more definitive. This study included adjudicated AMI events within the VA, transfers to the VA and events not treated at the VA (Medicare and Medicaid), and fatal and nonfatal AMI events. Moreover, most of the prior studies were missing confounders such as smoking, and none had fatal events or compared rates with uninfected demographically and behaviorally similar participants.

Our results are consistent with prior studies linking ART with AMI risk among HIV-positive people. Although the association between recent protease inhibitor use and AMI achieved only borderline significance, in combination with our analysis reporting an excess risk of AMI among HIV-positive veterans who have HIV-1 RNA levels less than 500 copies/mL over time compared with uninfected veterans, this suggests that ART contributes to AMI risk.

Findings from this and prior studies suggest that the increased risk of AMI among HIV-positive people is likely a function of HIV, ART, and the burden of co-morbid disease including Framingham risk factors. Unlike in prior studies, we did not observe a significant association between HDL cholesterol and AMI in our multivariable models. However, in univariate analyses, HDL less than 40 mg/dL (to convert to millimoles per liter, multiply by 0.0259) was associated with AMI (HR, 1.27; 95% CI, 1.01-1.59). When we added each Framingham risk factor and HIV separately to our univariate HDL model, diabetes (HR, 1.16; 95% CI, 0.92-1.46) and to a lesser extent HIV (1.21; 0.96-1.52) attenuated the association between HDL and AMI.

The mechanism by which HIV infection increases the risk of AMI is not known. Possible mechanisms may involve inflammation, altered CD4 cell count depletion, altered coagulation, dyslipidemia, impaired arterial elasticity, and endothelial dysfunction. Among HIV-infected people, ART is associated with metabolic changes and abnormal fat distribution, which in turn are linked with insulin resistance, diabetes, and dyslipidemia. Although HIV and ART are associated with AMI risk, results from the Strategies for Management of Antiretroviral Therapy study suggesting that HIV viral suppression results in lower cardiovascular disease risk than drug conservation therapy suggest that the virus plays the larger role.

In this study, HIV-positive veterans had a higher risk of AMI while having the same baseline Framingham risk score as uninfected veterans. Human immunodeficiency virus infection was associated with an increase in AMI risk when added to a model of Framingham risk factors. These findings combined with prior work by the D:A:D study suggesting that the Framingham risk score may underestimate AMI risk among HIV-positive people and that the addition of HIV and ART to a model of established AMI risk factors may be clinically useful. When the Framingham risk score was validated in other uninfected multiethnic cohorts, recalibration was required in some instances to account for the different prevalences of risk factors and underlying rates of developing CHD.

A comparison of the VACS-VC with participants in the Framingham Heart Study demonstrates substantial differences in the prevalence of diabetes, smoking, and low HDL cholesterol as well as race/ethnicity. Of note, the Framingham risk score does not incorporate risk factors significantly associated with AMI in this study (ie, hepatitis C virus, anemia, renal disease, HIV-1 RNA, or CD4 cell count). Future studies should focus on validat-

### Table 2. Rates of AMI by HIV Status and Age Group

<table>
<thead>
<tr>
<th>Status</th>
<th>Age Group, y</th>
<th>Uninfected</th>
<th>HIV Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;30</td>
<td>30-39</td>
<td>40-49</td>
</tr>
<tr>
<td>No. of participants</td>
<td>1175</td>
<td>6783</td>
<td>21886</td>
</tr>
<tr>
<td>No. of AMI events</td>
<td>0</td>
<td>10</td>
<td>164</td>
</tr>
<tr>
<td>AMI rates per 1000 person-years (95% CI)</td>
<td>...</td>
<td>0.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>
| Incidence rate ratio (95% CI) | ...       | (0.2-0.6)   | (1.3-1.7)   | (1.9-2.5)   | (2.6-4.2)   | (4.8-9.2)   | (12.7-36.4)  | ...

Abbreviations: AMI, acute myocardial infarction; HIV, human immunodeficiency virus.

An ellipsis indicates that a rate was not calculated because there were 0 events.
ing the Framingham risk score as originally described by D’Agostino et al.\textsuperscript{22} and then assess whether the inclusion of HIV status, race/ethnicity, comorbidities (eg, hepatitis C virus, renal disease, and anemia), HIV-specific biomarkers and ART, and/or inflammatory biomarkers improves CHD risk prediction for HIV-positive people.

There are limitations that warrant discussion. First, because this sample is overwhelmingly male, our findings may not generalize to women. Second, as with any observational study, there is always the possibility of residual confounding. For example, we do not have biomarker data beyond what is available in the clinical setting; therefore, we could not incorporate biomarkers, such as Framingham risk score and other risk factors.

### Table 3. The Association Between HIV and AMI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>First Model\textsuperscript{b}</th>
<th>Second Model\textsuperscript{c}</th>
<th>Third Model\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>1.57 (1.37-1.80)</td>
<td>1.72 (1.49-1.97)</td>
<td>1.48 (1.27-1.72)</td>
</tr>
<tr>
<td>Age\textsuperscript{e}</td>
<td>1.87 (1.75-2.00)</td>
<td>1.85 (1.72-1.99)</td>
<td>1.78 (1.65-1.92)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.51 (0.26-0.99)</td>
<td>0.58 (0.30-1.13)</td>
<td>0.53 (0.27-1.02)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>African American</td>
<td>0.86 (0.74-0.99)</td>
<td>0.79 (0.69-0.92)</td>
<td>0.71 (0.61-0.82)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.01 (0.79-1.29)</td>
<td>1.04 (0.82-1.32)</td>
<td>1.00 (0.79-1.28)</td>
</tr>
<tr>
<td>Other</td>
<td>0.66 (0.47-0.92)</td>
<td>0.70 (0.50-0.99)</td>
<td>0.69 (0.49-0.97)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>1.48 (1.18-1.85)</td>
<td>1.36 (1.08-1.70)</td>
</tr>
<tr>
<td>Controlled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrolled</td>
<td></td>
<td>1.70 (1.47-1.97)</td>
<td>1.64 (1.41-1.91)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>1.74 (1.50-2.02)</td>
<td>1.74 (1.49-2.02)</td>
</tr>
<tr>
<td>Lipids, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol &lt;100</td>
<td></td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>LDL cholesterol 100-129</td>
<td></td>
<td>1.01 (0.93-1.31)</td>
<td>1.20 (1.01-1.42)</td>
</tr>
<tr>
<td>LDL cholesterol 130-159</td>
<td></td>
<td>1.38 (1.11-1.70)</td>
<td>1.53 (1.24-1.90)</td>
</tr>
<tr>
<td>LDL cholesterol ≥160</td>
<td></td>
<td>1.66 (1.33-2.07)</td>
<td>1.88 (1.50-2.35)</td>
</tr>
<tr>
<td>HDL cholesterol ≥60</td>
<td></td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>HDL cholesterol 40-59</td>
<td></td>
<td>1.05 (0.81-1.35)</td>
<td>1.05 (0.81-1.35)</td>
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<tr>
<td>HDL cholesterol &lt;40</td>
<td></td>
<td>1.07 (0.84-1.36)</td>
<td>1.05 (0.83-1.35)</td>
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<tr>
<td>Triglycerides &gt;150</td>
<td></td>
<td>1.12 (0.98-1.30)</td>
<td>1.16 (1.00-1.34)</td>
</tr>
<tr>
<td>Never smoker</td>
<td></td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
<td>1.84 (1.33-2.33)</td>
<td>1.78 (1.47-2.16)</td>
</tr>
<tr>
<td>Past smoking</td>
<td></td>
<td>1.06 (0.81-1.40)</td>
<td>1.06 (0.80-1.40)</td>
</tr>
<tr>
<td>Current HMG-CoA reductase inhibitor use</td>
<td></td>
<td>0.84 (0.68-1.03)</td>
<td>1.19 (1.01-1.40)</td>
</tr>
<tr>
<td>HCV infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal disease, mL/min/1.73 m\textsuperscript{2}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR ≥60</td>
<td></td>
<td></td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>EGFR 30-59</td>
<td></td>
<td></td>
<td>1.57 (1.23-1.99)</td>
</tr>
<tr>
<td>EGFR &lt;30</td>
<td></td>
<td></td>
<td>3.64 (2.54-5.20)</td>
</tr>
<tr>
<td>Anemia, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin ≥14.0</td>
<td></td>
<td></td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Framingham risk score</td>
<td></td>
<td>6.1 (3.0)</td>
<td>5.8 (3.1)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other risk factors, %</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Current HMG-CoA reductase-inhibitor use</td>
<td>9.8</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>HCV infection</td>
<td>15.6</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin 12-13.9</td>
<td></td>
<td></td>
<td>1.20 (1.01-1.42)</td>
</tr>
<tr>
<td>Hemoglobin 10-11.9</td>
<td></td>
<td></td>
<td>1.93 (1.49-2.50)</td>
</tr>
<tr>
<td>Hemoglobin &lt;10</td>
<td></td>
<td></td>
<td>2.28 (1.49-3.51)</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td></td>
<td>0.92 (0.76-1.10)</td>
<td></td>
</tr>
<tr>
<td>History</td>
<td></td>
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<tr>
<td>Cocaine abuse or dependence</td>
<td></td>
<td>1.03 (0.78-1.37)</td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse or dependence</td>
<td></td>
<td>1.11 (0.88-1.39)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HMG-CoA, (3-hydroxy-3-methylglutaryl)-coenzyme A; HR, hazard ratio; LDL, low-density lipoprotein.

a HIV status and all covariates listed in the 3 models were adjusted for simultaneously in the Cox proportional hazards model.
b Model is adjusted for demographic characteristics only.
c Model is adjusted for demographic characteristics and Framingham risk factors.
d Model is adjusted for all covariates.
e Age is given in 10-year increments.
In conclusion, HIV infection is independently associated with AMI after adjustment for Framingham risk, comorbidities, and substance use. Unsuppressed HIV viremia, low CD4 cell count, Framingham risk factors, hepatitis C virus, renal disease, and anemia are also associated with AMI. Moreover, this risk also extends to HIV-positive veterans with an HIV-1 RNA level less than 500 copies/mL over time compared with uninfected veterans. When added to a model of Framingham risk factors, HIV infection is associated with improved AMI risk discrimination. Future studies should focus on validating the Framingham risk score in cohorts with HIV-positive people using hard CHD end points and assessing whether the inclusion of HIV status; race/ethnicity; comorbidities such as hepatitis C virus, renal disease, and anemia; HIV-specific biomarkers and ART; and/or inflammatory biomarkers improves CHD risk prediction for HIV-positive people.

Accepted for Publication: November 30, 2012.
Published Online: March 4, 2013. doi:10.1001/jamainternmed.2013.3728

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Author Contributions: Drs Freiberg and Kuller had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Freiberg, Kuller, Skanderson, Kraemer, Butt, Bidwell Goetz, Rimland,
Brown, Gibert, Crane, Bryant, and Justice. Acquisition of data: Chang, Skanderson, Lowy, Kraemer, Leaf, Oursler, Rimland, Brown, Gottlieb, Gottdiener, Tracy, Budoff, Bryant, and Justice. Analysis and interpretation of data: Chang, Kuller, Skanderson, Butt, Bidwell Goetz, Rimland, Rodriguez Barradas, McGinnis, Broehrs, Sico, Warner, Gottdiener, Tracy, Budoff, Watson, Armain, Doebler, and Justice. Drafting of the manuscript: Freiberger, Chang, Kraemer, Sico, Warner, Doebler, and Bryant. Critical revision of the manuscript for important intellectual content: Chang, Kuller, Skanderson, Lowy, Kraemer, Butt, Bidwell Goetz, Leaf, Oursler, Rimland, Rodriguez Barradas, McGinnis, Brown, Gibert, Broehrs, Sico, Crane, Gottlieb, Gottdiener, Tracy, Budoff, Watson, Armain, and Justice. Statistical analysis: Freiberger, Chang, Butt, McGinnis, Sico, and Doebler. Obtained funding: Freiberger, Kraemer, Bryant, and Justice. Administrative, technical, and material support: Skanderson, Lowy, Bidwell Goetz, Leaf, Oursler, Rimland, Rodriguez Barradas, Brown, Gottlieber, Tracy, Budoff, and Justice. Study supervision: Kuller, Skanderson, Kraemer, Leaf, Oursler, Rimland, Budoff, and Justice.

Conflict of Interest Disclosures: Dr Butt reports that he received Investigator-Initiated Studies Program grant P08569 MIISP 39996 from Merck and gave a scientific talk for Gilead in 2011.

Funding/Support: This work was supported by grant HL095136-04 from the National Heart, Lung, and Blood Institute and grants AA013566-10, AA20790, and AA20794 from the National Institute on Alcohol Abuse and Alcoholism at the National Institutes of Health.

Role of the Sponsors: The National Institutes of Health did not participate in the design and conduct of the study or the collection, management, analysis, or interpretation of the data; nor did the National Institutes of Health prepare, review, or approve of the article.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policies of the Department of Veterans Affairs.

Previous Presentations: This work was presented as a poster (March 1, 2011) and as part of a themed discussion (March 2, 2011) at the 18th Conference on Retroviruses and Opportunistic Infections; Boston, Massachusetts.

Online-Only Material: The eTable is available at http://www.jamainternalmed.com.

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Getting to the Heart of HIV and Myocardial Infarction

For people infected with the human immunodeficiency virus (HIV) with access to antiretroviral therapy (ART), the benefits, particularly for those with low CD4 + T-cell counts, have been clearly established. Management strategies have shifted firmly toward earlier HIV diagnosis to reduce HIV-related morbidity alongside increased ART access to maximize its benefits with a view to mitigating the potential detrimental effects of HIV infection on overall lifelong survival.

As the current era in HIV management evolves, it is increasingly apparent that, despite effective ART, people living with HIV experience excess comorbidities that may increase mortality and limit overall survival. Not surprisingly, as in the general population, cardiovascular diseases, such as myocardial infarction (MI), rank among the most common causes of death in treated HIV-positive populations.

In determining the causes of excess comorbidities such as MI, 3 main issues arise:

1. Is there a truly increased incidence of MI as a result of HIV infection or do observed, elevated rates simply reflect background disease rates that would be expected in a group of people with the demographic characteristics and risk factor profiles present within a HIV-positive population?
2. If HIV infection is implicated, what are the mechanisms whereby HIV infection and/or immune dysfunction drive increased MI?
3. How do potential ART-related toxicities influence the incidence of MI?

Until recently, much of the estimation of MI risk in HIV relied on cross-study comparisons of MI rates in HIV-positive populations with either published population rates or those derived from separate cohort studies of uninfected populations. These comparisons were based on a presumption that the HIV-positive populations were broadly similar to the comparator populations, with most studies unable to consider the likely effect of differences in socioeconomic factors within HIV-positive populations on resulting MI rates. Indeed, the potential effects of socioeconomic factors on treatment outcomes in HIV were recently discussed in this journal, where a study of mortality rates within an HIV-positive population showed significantly different mortality depending on sex, educational status, and race/ethnicity. To date, relatively few studies have attempted to correct for this potential bias.

In this issue of JAMA Internal Medicine, Freiberg and colleagues attempt to do exactly this by drawing their control population from broadly similar demographic and geographic backgrounds, therefore attempting to limit potential bias. They followed up a large (82,459 participants and 33.2% HIV positive) prospective cohort, examining incident MI rates in participants with and without HIV drawn from the Veterans Aging Cohort Study Virtual Cohort. The cohort has several advantages: its large size, the ability to draw detailed data on both HIV and MI from a number of linked databases, the diverse population, and the ability to match HIV-positive participants and HIV-negative controls for a variety of potential confounders, providing the capacity to better estimate the effect of HIV infection itself on MI rates.

Although the cohort studied was almost exclusively male (>97%), the results demonstrate a clear and consistent excess risk of MI (approximately 50% increase) in HIV-positive people across a range of age groups, with the association between HIV status and MI remaining significant when controlled for a number of covariates including traditional cardiovascular risk factors, such as lipids, blood pressure, and smoking status. In addition, study findings suggest that use of the Framingham risk assessment likely underestimates the risk of MI in HIV-positive populations.

For HIV-positive men, this study goes a long way toward clearly addressing the first of the 3 fundamental issues previously mentioned: that HIV-positive populations carry an approximately 50% relative increased risk of incident MI.