UCLA
UCLA Previously Published Works

Title

HIV Infection and the Risk of Acute Myocardial Infarction

Authors

Freiberg, Matthew S
Chang, Chung-Chou H
Kuller, Lewis H
et al.

HIV Infection and the Risk of Acute Myocardial Infarction

Matthew S. Freiberg, MD, MSc; Chung-Chou H. Chang, PhD; Lewis H. Kuller, MD, DrPH; Melissa Skanderson, MSW;
Elliott Lowy, PhD; Kevin L. Kraemer, MD, MSc; Adeel A. Butt, MD, MS; Matthew Bidwell Goetz, MD;
David Leaf, MD, MPH; Kris Ann Oursler, MD, ScM; David Rimland, MD; Maria Rodriguez Barradas, MD;
Sheldon Brown, MD; Cynthia Gibert, MD; Kathy McGinnis, MS; Kristina Crothers, MD; Jason Sico, MD;
Heidi Crane, MD, MPH; Alberta Warner, MD; Stephen Gottlieb, MD; John Gottdiener, MD; Russell P. Tracy, PhD;
Matthew Budoff, MD; Courtney Watson, MPH; Kaku A. Armah, BA; Donna Doebler, DrPH, MS;
Kendall Bryant, PhD; Amy C. Justice, MD, PhD

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.

JAMA Intern Med. 2013;173(8):614-622.
Published online March 4, 2013.
doi:10.1001/jamainternmed.2013.3728

Author Affiliations are listed at the end of this 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[1] with important clinical implications. Although prior studies[2-6] 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

See Invited Commentary at end of article

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.

<hr>

METHODS

The Veterans Aging Cohort Study (VACS) Virtual Cohort (VC)[7] is a prospective longitudinal cohort of HIV-positive and age-, race/ethnicity–, and clinical site–matched uninfected veterans enrolled in the same calendar year. Participants have been continually enrolled each year since 1998 using a validated existing algorithm from the US Department of Veterans Affairs (VA) national electronic medical record system.[7] 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.[8,9] 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 final 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 and/or 2 or more outpatient *ICD-9* codes for HIV and was included in the VA Immunology Case Registry.[7]

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.[9,10] 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.[11] Based on Cardiovascular Health Study criteria,[11] 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).

COVARIATES

We determined age, sex, and race/ethnicity using administrative data. Hypertension, diabetes mellitus,[12] dyslipidemia, renal disease, and anemia were measured using outpatient and clinical laboratory data collected closest to the baseline date. The HMG-CoA [(3-hydroxy-3-methylglutaryl)–coenzyme A] reductase-inhibitor use and ART were based on pharmacy data, and smoking and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) were measured from health factor data that are collected in a standardized form within the VA. Hypertension was categorized as no hypertension (blood pressure <140/90 mm Hg and no antihypertensive medication), controlled hypertension (<140/90 mm Hg with antihypertensive medication), and uncontrolled hypertension (≥140/90 mm Hg).[13] Our blood pressure measurement was the average of the 3 routine outpatient clinical measurements closest to the baseline date. Diabetes was diagnosed using a previously validated metric that considers glucose measurements, antidiabetic agent use, and/or at least 1 inpatient and/or 2 or more outpatient *ICD-9* codes for this diagnosis.[12] The HMG-CoA reductase-inhibitor use was within 180 days of the baseline date. Current, past, and never smoking and BMI were assessed using documentation from the VA electronic medical record health factor data set, which contains information collected from clinical reminders that clinicians are required to complete for patients. Prior work[14] demonstrates the high agreement between health factor documentation and VACS-8 self-reported smoking survey data. Hepatitis C virus infection was defined as a positive hepatitis C virus antibody test result or at least 1 inpatient and/or 2 or more outpatient *ICD-9* codes for this diagnosis.[15] History of cocaine and alcohol abuse or dependence was defined using *ICD-9* codes.[16] We collected data on CD4 cell counts and HIV-1 RNA values from baseline through the last follow-up date. Baseline and recent ART was categorized by drug class and types of regimen within 180 days of the baseline enrollment date and the date closest to AMI, death, or last follow-up date, respectively. Regimen was defined as protease inhibitors plus nucleoside reverse-transcriptase inhibitors (NRTI), nonnucleoside reverse-transcriptase inhibitors (NNRTI) plus NRTI, other, and no ART use (ie, reference). Prior work[7] demonstrated in a nested sample that 96% of HIV-positive veterans obtain all their ART medications from the VA.

STATISTICAL ANALYSIS

Descriptive statistics for all variables by HIV status were assessed using *t* tests or the nonparametric counterparts for continuous variables and the χ^2 test or Fisher exact test for categorical variables. We calculated incident AMI rates per 1000 person-years stratified by age group and HIV status. We used Cox proportional hazards models to estimate the hazard ratio (HR) and 95% CIs to assess whether HIV infection was associated with incident AMI after adjusting first for age, sex, and race/ethnicity and then additionally for the Framingham risk

Table 1. Baseline Characteristics of HIV-Infected and Matched HIV-Uninfected Veterans[a]

Baseline Characteristic	Uninfected (n = 55 109)	HIV Infected (n = 27 350)
Age, y		
Mean (SD)	48.8 (9.2)	48.2 (9.5)
Median	49.0	48.0
Male sex, %	97.2	97.3
Race/ethnicity, %		
African American	47.8	48.2
White	37.8	37.8
Hispanic	7.8	7.1
Other	6.6	6.9
Framingham Risk Factors, %		
Hypertension[b]		
None	58.4	67.2
Controlled	9.7	7.4
Uncontrolled	31.9	25.4
Diabetes mellitus[b]	20.7	14.0
Lipids, mg/dL[b]		
LDL cholesterol <100	31.7	46.4
LDL cholesterol 100-129	33.3	29.6
LDL cholesterol 130-159	22.8	15.8
LDL cholesterol ≥160	12.2	8.2
HDL cholesterol ≥60	14.8	11.0
HDL cholesterol 40-59	47.3	37.8
HDL cholesterol <40	38.0	51.2
Triglycerides >150	38.2	47.4
Smoking, %[b]		
Current	54.0	60.2
Past	16.0	13.2
Never	30.0	26.6
Framingham risk score		
Mean (SD)	6.1 (3.0)	5.8 (3.1)
Median	6	6
Other risk factors, %		
Current HMG-CoA reductase-inhibitor use	9.8	6.5
HCV infection	15.6	35.0

(continued)

factors using established cut points.[17,18] 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.[19] 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.[20,21] We assessed the change in the C statistic on the addition of HIV to a model that included risk factors as defined by the Framingham risk score

using VACS participant data and methods from D'Agostino et al.[22] 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 ($P \leq .001$ 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).

Table 1. Baseline Characteristics of HIV-Infected and Matched HIV-Uninfected Veterans[a] (continued)

Baseline Characteristic	Uninfected (n = 55 109)	HIV Infected (n = 27 350)
Renal disease, mL/min/1.73 m²[b]		
EGFR ≥60	95.2	93.3
EGFR 30-59	4.2	5.2
EGFR <30	0.6	1.5
BMI ≥30, %[b]	38.8	14.3
Anemia, g/dL[b]		
Hemoglobin ≥14	72.5	55.1
Hemoglobin 12-13.9	23.4	32.0
Hemoglobin 10-11.9	3.3	9.5
Hemoglobin <10	0.8	3.5
History of substance use, %		
Alcohol abuse or dependence	13.2	14.1
Cocaine abuse or dependence	7.2	11.3
HIV-specific biomarkers[c]		
CD4 cell count, mm³[b]		
Mean (SD)	. . .	390.7 (287.1)
Median	. . .	361.5
HIV-1 RNA, copies/mL[b]		
Mean (SD)	. . .	50 317.4 (126 797.8)
Median	. . .	680
ART regimen, %[c]		
NRTI plus PI	. . .	20.6
NRTI plus NNRTI	. . .	21.9
Other	. . .	6.8
No ART	. . .	50.8

Abbreviations: ART, antiretroviral therapy; 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; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

SI conversion factors: To convert LDL and HDL to millimoles per liter, multiply by 0.0259; hemoglobin to grams per liter, multiply by 10; and triglycerides to millimoles per liter, multiply by 0.0113.

[a] All characteristics were statistically different ($P < .001$) except sex ($P = .51$) and race/ethnicity ($P = .004$) using analysis of variance, χ^2 test, or Wilcoxon rank sum test. We did not compare CD4 cell count, HIV-1 RNA, or ART use because these were collected only among HIV-positive veterans.

[b] All variables had complete data except the following: hypertension data were available on 27 062 (HIV positive) and 53 968 (uninfected); HDL cholesterol data were available on 20 832 (HIV positive) and 40 532 (uninfected); LDL cholesterol data were available on 19 910 (HIV positive) and 38 563 (uninfected); triglyceride data were available on 22 817 (HIV positive) and 42 488 (uninfected); smoking data were available on 25 510 (HIV positive) and 50 876 (uninfected); EGFR data were available on 25 593 (HIV positive) and 48 155 (uninfected); BMI data were available on 26 872 (HIV positive) and 53 539 (uninfected); anemia data were available on 25 008 (HIV positive) and 46 631 (uninfected); CD4 cell count data were available on 21 810 HIV positive; and HIV-1 RNA data were available on 22 631 (HIV positive).

[c] Because HIV-uninfected veterans do not have HIV-specific biomarkers or ART regimens, these cells contain only ellipses.

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 the VA (Quality Enhancement Research Initiative), 161 (18.5%) were outside the VA and never 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 2**), 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-

Table 2. Rates of AMI by HIV Status and Age Group[a]

Status	Age Group, y							
	<30	30-39	40-49	50-59	60-69	70-79	80-89	>89
Uninfected								
No. of participants	1175	6783	21 866	19 805	4209	1120	148	3
No. of AMI events	0	10	164	218	66	36	14	0
AMI rates per 1000 person-years (95% CI)	...	0.3 (0.2-0.6)	1.5 (1.3-1.7)	2.2 (1.9-2.5)	3.3 (2.6-4.2)	6.7 (4.8-9.2)	21.5 (12.7-36.4)	...
HIV Infected								
No. of participants	725	3848	10 575	9342	2065	557	56	0
No. of AMI events	0	13	105	171	46	25	3	0
AMI rates per 1000 person-years (95% CI)	...	0.7 (0.4-1.2)	2.0 (1.6-2.4)	3.9 (3.3-4.5)	5.0 (3.8-6.7)	10.0 (6.7-14.7)	13.5 (4.3-42.0)	...
Incidence rate ratio (95% CI)	...	2.19 (0.89-5.58)	1.34 (1.04-1.72)	1.80 (1.47-1.21)	1.53 (1.03-2.26)	1.50 (0.86-2.57)	0.63 (0.12-2.25)	...

Abbreviations: AMI, acute myocardial infarction; HIV, human immunodeficiency virus.
[a] An ellipsis indicates that a rate was not calculated because there were 0 events.

derline significance with AMI after being included in a model that adjusted for Framingham risk factors, comorbidities, and substance use (data otherwise not shown).

<div style="text-align:center">**COMMENT**</div>

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, comorbidities, 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,[2-6] 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,[3-6] and none had fatal events or compared rates with uninfected demographically and behaviorally similar participants.

Our results are consistent with prior studies[23,24] 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,[25] ART,[23,24,26] and the burden of comorbid disease including Framingham risk factors.[23] 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,[27] CD4 cell count depletion,[28] altered coagulation,[29] dyslipidemia,[30] impaired arterial elasticity,[31] and endothelial dysfunction.[32] Among HIV-infected people, ART is associated with metabolic changes[33] and abnormal fat distribution,[34,35] which in turn are linked with insulin resistance,[33] diabetes,[33] and dyslipidemia.[33,36] Although HIV and ART are associated with AMI risk, results from the Strategies for Management of Antiretroviral Therapy study[25] showing 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[37,38] suggest 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.[22] 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.[22] 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 3. The Association Between HIV and AMI

Characteristic	HR (95% CI)[a]		
	First Model[b]	Second Model[c]	Third Model[d]
HIV infection	1.57 (1.37-1.80)	1.72 (1.49-1.97)	1.48 (1.27-1.72)
Age[e]	1.87 (1.75-2.00)	1.85 (1.72-1.99)	1.78 (1.65-1.92)
Female sex	0.51 (0.26-0.99)	0.58 (0.30-1.13)	0.53 (0.27-1.02)
Race/ethnicity			
White	1 [Reference]	1 [Reference]	1 [Reference]
African American	0.86 (0.74-0.99)	0.79 (0.69-0.92)	0.71 (0.61-0.82)
Hispanic	1.01 (0.79-1.29)	1.04 (0.82-1.32)	1.00 (0.79-1.28)
Other	0.66 (0.47-0.92)	0.70 (0.50-0.99)	0.69 (0.49-0.97)
Hypertension			
None	. . .	1 [Reference]	1 [Reference]
Controlled	. . .	1.48 (1.18-1.85)	1.36 (1.08-1.70)
Uncontrolled	. . .	1.70 (1.47-1.97)	1.64 (1.41-1.91)
Diabetes mellitus	. . .	1.74 (1.50-2.02)	1.74 (1.49-2.02)
Lipids, mg/dL			
LDL cholesterol <100	. . .	1 [Reference]	1 [Reference]
LDL cholesterol 100-129	. . .	1.01 (0.93-1.31)	1.20 (1.01-1.42)
LDL cholesterol 130-159	. . .	1.38 (1.11-1.70)	1.53 (1.24-1.90)
LDL cholesterol ≥160	. . .	1.66 (1.33-2.07)	1.88 (1.50-2.35)
HDL cholesterol ≥60	. . .	1 [Reference]	1 [Reference]
HDL cholesterol 40-59	. . .	1.05 (0.81-1.35)	1.05 (0.81-1.35)
HDL cholesterol <40	. . .	1.07 (0.84-1.36)	1.05 (0.83-1.35)
Triglycerides >150	. . .	1.12 (0.98-1.30)	1.16 (1.00-1.34)
Never smoker	. . .	1 [Reference]	1 [Reference]
Current smoking	. . .	1.84 (1.53-2.23)	1.78 (1.47-2.16)
Past smoking	. . .	1.06 (0.81-1.40)	1.06 (0.80-1.40)
Current HMG-CoA reductase inhibitor use	. . .		0.84 (0.68-1.03)
HCV infection	. . .	. . .	1.19 (1.01-1.40)
Renal disease, mL/min/1.73 m²			
EGFR ≥60	. . .	. . .	1 [Reference]
EGFR 30-59	. . .	. . .	1.57 (1.23-1.99)
EGFR <30	. . .	. . .	3.64 (2.54-5.20)
Anemia, mg/dL			
Hemoglobin ≥14.0	. . .	. . .	1 [Reference]
Framingham risk score			
Mean (SD)	6.1 (3.0)	5.8 (3.1)	
Median	6	6	
Other risk factors, %			
Current HMG-CoA reductase-inhibitor use	9.8	6.5	
HCV infection	15.6	35.0	
Hemoglobin 12-13.9	. . .	. . .	1.20 (1.01-1.42)
Hemoglobin 10-11.9	. . .	. . .	1.93 (1.49-2.50)
Hemoglobin <10	. . .	. . .	2.28 (1.49-3.51)
BMI ≥30	. . .	. . .	0.92 (0.78-1.08)
History			
Cocaine abuse or dependence	. . .	. . .	1.03 (0.78-1.37)
Alcohol abuse or dependence	. . .	. . .	1.11 (0.88-1.39)

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.

SI conversions: See Table 1.

[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.

ing the Framingham risk score as originally described by D'Agostino et al[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

Table 4. Time-Updated Analyses Assessing the Association of HIV-1 RNA and CD4 Cell Count Values and the Risk of AMI in Separate Models[a]

Category	HR (95% CI)	P Value[b]
HIV-1 RNA		
Uninfected	1 [Reference]	
≥500	1.75 (1.40-2.18)	.05
<500	1.39 (1.17-1.66)	
CD4 cell count		
Uninfected	1 [Reference]	
<200	1.88 (1.46-2.40)	.04
≥200	1.43 (1.21-169)	

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

[a] HIV-1 RNA and CD4 cell count models are time updated and adjust for age, sex, race/ethnicity, hypertension, lipids, smoking, HMG-CoA reductase-inhibitor use, hepatitis C virus infection, renal disease, body mass index, and cocaine and alcohol abuse and dependence.

[b] For comparison of HIV-1 RNA and CD4 cell count categories.

as C-reactive protein or D-dimer, into our analysis. Similarly, as HIV-1 RNA assays that detect lower HIV-1 RNA levels (<40 copies) were not available in the VA in 2003, we could not use this definition to assess viral suppression. Third, the Framingham risk score predicts CHD (ie, AMI and CHD death). Because this study focused on AMI, we could not validate the Framingham risk score in the VACS-VC to determine whether the Framingham risk score underestimates CHD risk in our cohort. Fourth, the use of *ICD-9* codes to identify substance use may have resulted in some misclassification. Fifth, some of our AMI events were defined using only *ICD-9* codes and death certificate data without confirmatory data (eg, enzymes and electrocardiography findings). However, it is reassuring that the association between HIV and AMI remained the same across several sensitivity analyses exploring the influence of these data. Sixth, there is the possibility that some non-VA events were not captured. However, after surveying 6000 VACS[39] participants (half HIV positive) as to whether or not they had (1) had any cardiovascular event and (2) been hospitalized for it outside the VA, 25% reported an event occurring outside the VA. In this analysis, 23% of the AMI events occurred at non-VA hospitals. Moreover, the association between HIV and AMI remained unchanged when we excluded Medicare and Medicaid events (HR, 1.47; 95% CI, 1.25-1.73), suggesting that non-VA health care use for AMI did not substantially differ by HIV status. Our rates for white uninfected men (2.6 per 1000 person-years) were also similar to the age-adjusted rates in the 2006 Atherosclerosis Risk in Communities study from the community surveillance (2.9 per 1000 persons). More important, these rates are not adjusted for the higher mortality rate among veterans compared with Atherosclerosis Risk in Communities participants and competing risks of death. Finally, we considered differences in the proportion of missing data on all Framingham risk factors by HIV status. Although there were statistically different proportions, these differences were small (eTable; http://www.jamainternalmed.com).

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.

Author Affiliations: University of Pittsburgh School of Medicine (Drs Freiberg, Chang, Kraemer, and Butt) and Graduate School of Public Health (Drs Freiberg, Chang, Kuller, and Doebler and Mr Armah), Pittsburgh, Pennsylvania; Veterans Affairs (VA) Connecticut Health Care System, West Haven Veterans Administration Medical Center, West Haven (Mss Skanderson and McGinnis and Drs Sico and Justice), and Yale University School of Medicine, New Haven (Drs Sico and Justice), Connecticut; VA Puget Sound Health Care System (Dr Lowy) and the University of Washington School of Public Health (Dr Lowy) and School of Medicine (Drs Crothers and Crane), Seattle; David Geffen School of Medicine, UCLA (University of California, Los Angeles) (Drs Bidwell Goetz and Leaf), the VA Greater Los Angeles Health Care System (Drs Bidwell Goetz, Leaf, and Warner), and the Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute (Dr Budoff), Los Angeles; University of Maryland School of Medicine (Drs Oursler, Gottlieb, and Gottdiener) and the Baltimore VA Health Care System (Dr Oursler), Baltimore, and the National Institute on Alcohol Abuse and Alcoholism, Bethesda (Dr Bryant), Maryland; Emory University School of Medicine and Atlanta VA Medical Center, Atlanta, Georgia (Dr Rimland); Baylor College of Medicine and Michael E. DeBakey VA Medical Center, Houston, Texas (Dr Rodriguez Barradas); James J. Peters VA Medical Center, Bronx, and Mount Sinai School of Medicine, New York (Dr Brown), New York; George Washington University School of Medicine and the Washington, DC, VA Medical Center (Dr Gibert), Washington, DC; University of Vermont College of Medicine, Burlington (Dr Tracy); and University of South Carolina Arnold School of Public Health, Columbia (Ms Watson).

Correspondence: Matthew S. Freiberg, MD, MSc, University of Pittsburgh School of Medicine, 230 McKee Pl, Ste 600, Pittsburgh, PA 15213 (Freibergms@upmc.edu).

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, Crothers, Sico, Warner, Gottdiener, Tracy, Budoff, Watson, Armah, Doebler, and Justice. *Drafting of the manuscript:* Freiberg, 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, Crothers, Sico, Crane, Gottlieb, Gottdiener, Tracy, Budoff, Watson, Armah, Bryant, and Justice. *Statistical analysis:* Freiberg, Chang, Butt, McGinnis, Sico, and Doebler. *Obtained funding:* Freiberg, Kraemer, Bryant, and Justice. *Administrative, technical, and material support:* Skanderson, Lowy, Bidwell Goetz, Leaf, Oursler, Rimland, Rodriguez Barradas, Brown, Gottdiener, Tracy, Budoff, and Justice. *Study supervision:* Kuller, Skanderson, Kraemer, Leaf, Oursler, Rimland, Budoff, and Justice.

REFERENCES

1. Luther VP, Wilkin AM. HIV infection in older adults. *Clin Geriatr Med*. 2007;23(3): 567-583, vii.
2. Klein D, Hurley LB, Quesenberry CP Jr, Sidney S. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? *J Acquir Immune Defic Syndr*. 2002;30(5):471-477.
3. Currier JS, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr*. 2003;33(4):506-512.
4. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007;92(7):2506-2512.
5. Obel N, Thomsen HF, Kronborg G, et al. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. *Clin Infect Dis*. 2007;44(12):1625-1631.
6. Durand M, Sheehy O, Baril JG, Lelorier J, Tremblay CL. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Québec's public health insurance database. *J Acquir Immune Defic Syndr*. 2011;57(3):245-253.
7. Fultz SL, Skanderson M, Mole LA, et al. Development and verification of a "virtual" cohort using the National VA Health Information System. *Med Care*. 2006; 44(8)(suppl 2):S25-S30.
8. United States Department of Veteran Affairs. Ischemic Heart Disease (IHD)–Quality Enhancement Research Initiative. http://www.queri.research.va.gov/ihd /default.cfm. Published 2011; updated March 12, 2012. Accessed January 22, 2013.
9. Every NR, Fihn SD, Sales AE, Keane A, Ritchie JR; QUERI IHD Executive Committee. Quality Enhancement Research Initiative in ischemic heart disease: a quality initiative from the Department of Veterans Affairs. *Med Care*. 2000;38(6) (suppl 1):I49-I59.
10. Maynard C, Lowy E, Rumsfeld J, et al. The prevalence and outcomes of in-hospital acute myocardial infarction in the Department of Veterans Affairs Health System. *Arch Intern Med*. 2006;166(13):1410-1416.
11. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events: the Cardiovascular Health Study. *Ann Epidemiol*. 1995;5(4): 278-285.
12. Butt AA, Fultz SL, Kwoh CK, Kelley D, Skanderson M, Justice AC. Risk of diabetes in HIV-infected veterans pre- and post-HAART and the role of HCV coinfection. *Hepatology*. 2004;40(1):115-119.
13. Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-1252.
14. McGinnis KA, Brandt CA, Skanderson M, et al. Validating smoking data from the Veterans Affairs Health Factors dataset, an electronic data source. *Nicotine Tob Res*. 2011;13(12):1233-1239.
15. Goulet JL, Fultz SL, McGinnis KA, Justice AC. Relative prevalence of comorbidities and treatment contraindications in HIV-monoinfected and HIV/HCV–coinfected veterans. *AIDS*. 2005;19(suppl 3):S99-S105.
16. Kraemer KL, McGinnis KA, Skanderson M, et al. Alcohol problems and health care services use in human immunodeficiency virus (HIV)–infected and HIV-uninfected veterans. *Med Care*. 2006;44(8)(suppl 2):S44-S51.
17. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287(3):356-359.
18. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998; 97(18):1837-1847.
19. Powell TM, Bagnell ME. Your "survival" guide to using time-dependent covariates. SAS Global Forum 2012. http://support.sas.com/resources/papers /proceedings12/168-2012.pdf. Published 2012. Accessed January 22, 2013.
20. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.
21. Freiberg MS, Chang CC, Skanderson M, et al; Veterans Aging Cohort Study. The risk of incident coronary heart disease among veterans with and without HIV and hepatitis C. *Circ Cardiovasc Qual Outcomes*. 2011;4(4):425-432.
22. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286(2):180-187.
23. Friis-Møller N, Sabin CA, Weber R, et al; Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med*. 2003;349(21):1993-2003.
24. Friis-Møller N, Reiss P, Sabin CA, et al; DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356(17):1723-1735.
25. El-Sadr WM, Lundgren JD, Neaton JD, et al; Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count–guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296.
26. Sabin CA, Worm SW, Weber R, et al; D:A:D Study Group. Use of nucleoside reverse-transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multicohort collaboration. *Lancet*. 2008; 371(9622):1417-1426.
27. Triant VA, Meigs JB, Grinspoon SK. Association of C-reactive protein and HIV infection with acute myocardial infarction. *J Acquir Immune Defic Syndr*. 2009; 51(3):268-273.
28. Lichtenstein KA, Armon C, Buchacz K, et al; HIV Outpatient Study (HOPS) Investigators. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clin Infect Dis*. 2010;51(4):435-447.
29. Kuller LH, Tracy R, Belloso W, et al; INSIGHT SMART Study Group. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med*. 2008;5(10):e203. doi: 10.1371/journal.pmed.0050203.
30. Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. *JAMA*. 2003;289(22):2978-2982.

31. Baker JV, Duprez D, Rapkin J, et al. Untreated HIV infection and large and small artery elasticity. *J Acquir Immune Defic Syndr*. 2009;52(1):25-31.

32. Torriani FJ, Komarow L, Parker RA, et al; ACTG 5152s Study Team. Endothelial function in human immunodeficiency virus–infected antiretroviral-naive subjects before and after starting potent antiretroviral therapy: the ACTG (AIDS Clinical Trials Group) Study 5152s. *J Am Coll Cardiol*. 2008;52(7):569-576.

33. Hadigan C, Meigs JB, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis*. 2001;32(1):130-139.

34. Jacobson DL, Knox T, Spiegelman D, Skinner S, Gorbach S, Wanke C. Prevalence of, evolution of, and risk factors for fat atrophy and fat deposition in a cohort of HIV-infected men and women. *Clin Infect Dis*. 2005;40(12):1837-1845.

35. Grunfeld C, Saag M, Cofrancesco J Jr, et al; Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Regional adipose tissue measured by MRI over 5 years in HIV-infected and control participants indicates persistence of HIV-associated lipoatrophy. *AIDS*. 2010;24(11):1717-1726.

36. Wohl D, Scherzer R, Heymsfield S, et al; FRAM Study Investigators. The associations of regional adipose tissue with lipid and lipoprotein levels in HIV-infected men. *J Acquir Immune Defic Syndr*. 2008;48(1):44-52.

37. Friis-Møller N, Thiébaut R, Reiss P, et al; DAD study group. Predicting the risk of cardiovascular disease in HIV-infected patients: the Data Collection on Adverse Effects of Anti-HIV Drugs Study. *Eur J Cardiovasc Prev Rehabil*. 2010;17(5):491-501.

38. Law MG, Friis-Møller N, El-Sadr WM, et al; D:A:D Study Group. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. *HIV Med*. 2006;7(4):218-230.

39. Justice AC, Dombrowski E, Conigliaro J, et al. Veterans Aging Cohort Study (VACS): overview and description. *Med Care*. 2006;44(8)(suppl 2):S13-S24.

INVITED COMMENTARY

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.[1] 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 and lifestyle 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.[2] To date, relatively few studies have attempted to correct for this potential bias.

In this issue of *JAMA Internal Medicine*, Freiberg and colleagues[3] 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.