

# Increased Acute Myocardial Infarction Rates and Cardiovascular Risk Factors among Patients with Human Immunodeficiency Virus Disease

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**Context:** Metabolic changes and smoking are common among HIV patients and may confer 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 3,851 HIV and 1,044,589 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 Diseases 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 [11.13 (95% confidence interval [CI] 9.58–12.68) vs. 6.98 (95% CI 6.89–7.06)]. The HIV cohort had significantly higher proportions of hypertension (21.2 vs. 15.9%), diabetes (11.5 vs. 6.6%),

and dyslipidemia (23.3 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 1.75 (95% CI 1.51–2.02;  $P < 0.0001$ ), 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 (12.71 vs. 4.88 for HIV compared with non-HIV women), but not among men (10.48 vs. 11.44 for HIV compared with non-HIV men). The RRs (for HIV vs. non-HIV) were 2.98 (95% CI 2.33–3.75;  $P < 0.0001$ ) for women and 1.40 (95% CI 1.16–1.67;  $P = 0.0003$ ) for men, adjusting for age, gender, race, hypertension, diabetes, and dyslipidemia. A limitation of this database is that it contains incomplete data on smoking. 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.

**Conclusions:** 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. (*J Clin Endocrinol Metab* 92: 2506–2512, 2007)

**M**ETABOLIC ABNORMALITIES ARE known to occur frequently in HIV-infected individuals and include dyslipidemia (1), insulin resistance and diabetes (2, 3), endothelial dysfunction (4, 5), and altered fat distribution (1, 6–9). Myocardial infarction rates have been increased in association with protease inhibitor (PI) use (10) and duration of antiretroviral (ARV) therapy in studies limited to HIV patients (11). However, it remains unclear as to whether HIV-infected patients demonstrate increased rates of acute myocardial infarction (AMI) compared with non-HIV-infected patients.

In the current study, we compared myocardial infarction

rates among HIV-infected patients receiving longitudinal care in two large U.S. hospitals with background longitudinal rates among the entire population not diagnosed with HIV infection at these hospitals. We determined the relative risk (RR) for AMI associated with HIV, adjusting for age, race, gender, and common cardiac risk factors, including hypertension, diabetes, and dyslipidemia.

## Patients and Methods

### Study design

We conducted a cohort study of 3,851 patients diagnosed with HIV disease and 1,044,589 patients not diagnosed with HIV disease. All patients in the analysis, HIV and non-HIV infected, presented on at least two occasions to one of two Boston health care facilities, Brigham and Women's Hospital (BWH) or Massachusetts General Hospital (MGH), comprising the Partners HealthCare System. The non-HIV cohort represents all patients not diagnosed with HIV disease who presented to BWH or MGH on at least two occasions. Cohorts were identified by querying a data registry of all billed hospital encounters, the Research Patient Data Registry (RPDR).

The primary outcome was AMI, defined according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Institutional Review Board approval was obtained from the Partners Human Research Committee.

### First Published Online April 24, 2007

Abbreviations: AMI, Acute myocardial infarction; ARV, antiretroviral; BWH, Brigham and Women's Hospital; CHD, coronary heart disease; CI, confidence interval; DAD, Data Collection on Adverse Events of Anti-HIV Drugs; ICD, International Classification of Diseases; ICD-9-CM, ICD, Ninth Revision, Clinical Modification; MGH, Massachusetts General Hospital; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PY, person-years; RPDR, Research Patient Data Registry; RR, relative risk.

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

### Eligibility criteria

Patients with at least two encounters of any kind between October 1, 1996, and June 30, 2004, were included. The start date of 1996 marks the full integration of BWH and MGH inpatient and outpatient data into the RPDR. Patients under the age of 18 and over the age of 84 were excluded based on inadequate representation in the cohort of HIV-infected patients. Patients with only one encounter and patients for whom an AMI event was the first encounter were excluded from the analysis because duration of follow-up in the cohort could not be calculated. In cases of recurrent AMIs, patients were only counted once in the analysis.

### Data source

Patient data were obtained from the RPDR, a centralized clinical data registry containing comprehensive demographic and clinical information for more than 2.1 million patients seen at BWH since 1996 or MGH since 1992. Data are derived from several sources, including hospital billing systems and a clinical data repository. The data warehouse has an online query tool that can be used to return a set of patients that match complex search criteria. Patient identifiers are encrypted throughout the database. Information on demographics, encounters, diagnoses, and laboratories is accessible.

### Ascertainment of outcomes

The primary endpoint was AMI. Cases were determined by International Classification of Diseases (ICD) coding, and included all patients with ICD-9-CM code 410 (AMI) and all subtypes as entered in the RPDR. The diagnosis of HIV was based on ICD-9-CM coding of either 042 (HIV disease) or 043 (HIV infection causing other specified conditions).

Information was also collected on traditional cardiac risk factors, including hypertension, diabetes, and dyslipidemia, using ICD-9-CM codes 401 (essential hypertension), 250 (diabetes mellitus), and 272 (disorders of lipid metabolism) and all subtypes, respectively. Information on the use of PIs, nucleoside reverse transcriptase inhibitors (NRTIs), and non-NRTIs was determined through medication records when available. Available smoking data were recorded.

### Statistical analysis

AMI incidence rates per 1000 person-years (PY) contributed during the observation period were determined for the HIV and non-HIV cohorts. Duration of individual patient follow-up was determined from date of first encounter to date of last encounter or date of event. Data on exact duration of follow-up were available for 1,048,440 patients and was approximated to the relevant boundary of the follow-up period (October 1, 1996, or June 30, 2004) for the remaining patients if the initiation date was before the beginning of the study time period or the end date was after the end of the study time period. Age-specific rates were determined, and 95% confidence intervals (CIs) were obtained using the method of large sample approximation. Age categories were constructed with the following breakdown: 18–34, 35–44, 45–54, 55–64, 65–74, and 75–84 yr. Multivariate Poisson regression models were used to assess the incidence rate ratio, the measure of RR, for AMI by HIV status in a combined model of all patients, adjusting for age, gender, race, hypertension, diabetes, and dyslipidemia. The multivariate model was constructed *a priori* using relevant demographic and clinical covariates for which information was available. Covariate effects were simultaneously determined. A sensitivity analysis was also performed, investigating the effects of individual covariates in Poisson regression modeling. Stratified analyses were then performed to examine these effects among the HIV and non-HIV cohorts, and among women and men.

To assess validity of the models, we first assessed the Poisson model and did not find evidence of overdispersion. We also performed a Cox proportional hazards regression analysis. The hazard ratios were almost identical to the incidence rate ratios from Poisson regression analysis, and the data satisfied the Cox proportional hazard assumptions. In addition, we used the Generalized Estimating Equations estimation to obtain a robust SE of the RR, allowing for the potential of misspecification of the model. Poisson regression analysis incidence rate ratios and person-time incidence rate estimates are reported in this manuscript.

AMI diagnoses were validated in a subset of patient medical records (100 HIV and 100 non-HIV patients randomly selected from the entire study population). Validation criteria included one or more of the following in the medical record: elevation of cardiac enzymes above the normal laboratory limit, coronary artery bypass graft or cardiac catheterization with angioplasty, or clear documentation of clinical myocardial infarction event. Using these criteria, AMI rates could be validated in up to approximately 50% for both the HIV and non-HIV groups. We conducted a sensitivity analysis to reflect the possibility of misclassification bias. In this analysis, we randomly discarded 50% of the observed AMI cases from both the HIV and non-HIV groups (to reflect the estimated maximal boundary of error), and fit a proportional hazards model to each data set. The analysis was repeated 20 times.

To evaluate the effect of smoking, we compared the proportion of AMI between HIV and non-HIV patients with a stratified Mantel-Haenszel analysis in which smoking strata were never *vs.* ever (current or past) smoking. SAS statistical software (SAS Institute Inc., Cary, NC) was used for all analyses.

## Results

### Demographic and clinical characteristics

The HIV cohort included 3851 patients. Of these, 1172 (30.4%) were women, and 2679 (69.6%) were men. In the HIV cohort, there were 16,983 PY contributed during the study period, of which 5,430 PY were contributed by women. The mean time of observation for HIV patients was 4.5 yr. Percentages using major classes of ARV drugs are shown in Table 1.

The non-HIV cohort included 1,044,589 patients, of whom 617,396 (59.1%) were women, and 427,189 (40.9%) were men. Total patients in the non-HIV cohort contributed 3,747,329 PY during the observation period. Of these, women contributed 2,217,127 PY. The mean time of observation for non-HIV patients was 3.7 yr.

The mean and median ages were similar between the groups. Median age was 38 (interquartile range 12) for HIV *vs.* 39 (interquartile range 26) for non-HIV patients (Table 1). However, within the HIV group, men in younger age categories contributed a greater percentage to the person-time denominator relative to the non-HIV group than did younger women.

The HIV cohort had a higher proportion of African-American and Hispanic patients than the non-HIV cohort, with patients categorized as African-American comprising 23.5 *vs.* 6.7%, and patients categorized as Hispanic comprising 12.7 *vs.* 7.1% of the HIV *vs.* non-HIV cohort, respectively. Distribution of race according to gender is shown in Table 1.

As shown in Table 2, the HIV cohort had significantly higher proportions of hypertension (21.2 *vs.* 15.9%), diabetes (11.5 *vs.* 6.6%), and dyslipidemia (23.3 *vs.* 17.6%) than the non-HIV cohort ( $P < 0.0001$  for each comparison). Increased percentages of these risk factors were also seen in the gender-stratified comparisons of men and women.

### Myocardial infarction rates

AMI was identified in 189 patients in the HIV cohort and in 26,142 patients in the non-HIV cohort. Across all age groups, the rate of AMI was consistently higher for patients in the HIV cohort compared with the non-HIV cohort (Table 3 and Fig. 1B).

The rates of AMI were 11.13 per 1000 PY for HIV (95% CI 9.58–12.68) and 6.98 per 1000 PY for non-HIV (95% CI 6.89–

**TABLE 1.** Demographic characteristics of HIV and non-HIV cohorts

Characteristic	HIV (n = 3,851)	Non-HIV (n = 1,044,589)
No. of females (%)	1,172 (30.4)	617,396 (59.1)
No. of Asian	8 (0.7)	4,225 (0.7)
No. of African-American	406 (34.6)	43,205 (7.0)
No. of Caucasian	472 (40.3)	400,967 (65.0)
No. of Hispanic	177 (15.1)	42,718 (6.9)
No. of other <sup>a</sup>	73 (6.2)	101,597 (16.5)
No. not recorded	36 (3.1)	24,684 (4.0)
No. of males (%)	2,679 (69.6)	427,193 (40.9)
No. of Asian	13 (0.5)	2,268 (0.5)
No. of African-American	499 (18.6)	26,662 (6.2)
No. of Caucasian	1,611 (60.1)	289,822 (67.8)
No. of Hispanic	312 (11.6)	31,655 (7.4)
No. of other <sup>a</sup>	176 (6.6)	59,801 (14.0)
No. not recorded	68 (2.5)	16,981 (4.0)
Median age of all (25th, 75th percentile)	38 (32, 44)	39 (28, 54)
Median age of females (25th, 75th percentile)	36 (29, 42)	38 (28, 52)
Median age of males (25th, 75th percentile)	38 (33, 44)	41 (29, 56)
Race		
No. of Asians (%)	21 (0.6)	6,493 (0.6)
No. of African-Americans (%)	905 (23.5)	69,869 (6.7)
No. of Caucasians (%)	2,083 (54.1)	690,790 (66.1)
No. of Hispanics (%)	489 (12.7)	74,373 (7.1)
No. of others (%) <sup>a</sup>	249 (6.5)	161,399 (15.5)
No. not recorded (%)	104 (2.7)	41,665 (4.0)
ARV medication use <sup>b</sup>		
No. of protease inhibitors (%)	996 (63.1)	N/A
No. of NRTIs (%)	1,498 (94.9)	N/A
No. of Non-NRTIs (%)	760 (48.1)	N/A

HIV cohort includes all patients diagnosed with HIV disease by ICD code. Non-HIV cohort includes all patients not diagnosed with HIV disease by ICD code. N/A, Not applicable.

<sup>a</sup> Other includes American Indian, Asian, Hispanic Black, Middle-Eastern, and patients classified as "Other" in hospital demographic record.

<sup>b</sup> Percentage use in each class is determined from the number of patients in whom data on ARV use is recorded (n = 1,578).

7.06) (Fig. 1A). The unadjusted RR was 1.53 (95% CI 1.32–1.75;  $P < 0.0001$ ). This increase in AMI rates in HIV compared with non-HIV patients remained significant when the data were adjusted for age, gender, race, hypertension, diabetes, and dyslipidemia, with a RR of 1.75 (95% CI 1.51–2.02;  $P < 0.0001$ ) in a combined regression model. Smoking was not included in the model due to limited data. In addition to HIV disease, risk factors for AMI included male gender (RR 1.72; 95% CI 1.68–1.77;  $P < 0.0001$ ), older age (RR 17.24 for ages 75–84 *vs.* 18–34; 95% CI 15.87–18.52;  $P < 0.0001$ ), African-

American race (RR 1.44 compared with Caucasians; 95% CI 1.38–1.50;  $P < 0.0001$ ), diabetes (RR 1.98; 95% CI 1.93–2.04;  $P < 0.0001$ ), hypertension (RR 1.62; 95% CI 1.57–1.66;  $P < 0.0001$ ), and dyslipidemia (RR 3.03; 95% CI 2.93–3.13;  $P < 0.0001$ ) in a combined model.

We also assessed the effects of individual covariates in the model. With the addition of age and gender into the model, the RR was 2.45 ( $P < 0.0001$ ). With race added to age and gender, the RR was 2.09 ( $P < 0.0001$ ). Cardiac risk factors were next tested individually in the model after adjustment for demographic covariates. The RR for AMI based on HIV status was 2.01 ( $P < 0.0001$ ) in a model adjusted for demographic covariates and hypertension. The RR for AMI was 1.89 ( $P < 0.0001$ ) adjusting for demographic covariates and diabetes, and also 1.89 ( $P < 0.0001$ ) adjusting for demographic covariates and dyslipidemia. The inclusion of hypertension attenuated the RR by 4%, whereas the inclusion of either diabetes or dyslipidemia attenuated the RR by 10%. Among the cardiac risk covariates tested individually in the model, the RR for AMI was largest for dyslipidemia (RR 4.5), followed by diabetes (RR 3.3), and then hypertension (RR 3.0) (all  $P$  values  $< 0.0001$ ). The same analysis was performed with Cox modeling with similar results.

The difference in AMI rates was more pronounced in women. In gender-stratified models, the unadjusted rates per 1000 PY were higher for the HIV group in the comparison of women (12.71 *vs.* 4.88 for HIV compared with non-HIV women), but not in men (10.48 *vs.* 11.44 for HIV compared

**TABLE 2.** Cardiac risk factors in HIV and non-HIV cohorts

	HIV (n = 3,851)		Non-HIV (n = 1,044,589)	
	n	Proportion	n	Proportion
Hypertension	818	21.2 <sup>a</sup>	165,665	15.9
Females	211	18.0 <sup>a</sup>	80,619	13.1
Males	607	22.7 <sup>a</sup>	85,046	19.9
Diabetes	443	11.5 <sup>a</sup>	68,565	6.6
Females	145	12.4 <sup>a</sup>	34,096	5.5
Males	298	11.1 <sup>a</sup>	34,469	8.1
Dyslipidemia	896	23.3 <sup>a</sup>	184,291	17.6
Females	262	22.4 <sup>a</sup>	92,411	15.0
Males	634	23.7 <sup>a</sup>	91,880	21.5

HIV cohort includes all patients diagnosed with HIV disease by ICD code. Non-HIV cohort includes all patients not diagnosed with HIV disease by ICD code. ICD codes used were 401 and all subtypes for hypertension, 250 and all subtypes for diabetes, and 272 and all subtypes for dyslipidemia.

<sup>a</sup> Statistically significant comparison of HIV and non-HIV proportions, with  $\chi^2$  ( $P < 0.0001$ ).

**TABLE 3.** Myocardial infarction rates as determined by ICD coding

Age group (yr)	HIV			Non-HIV		
	PY (n) [%]	AMI (n)	Rate per 1000 PY (95% CI)	PY (n) [%]	AMI (n)	Rate per 1000 PY (95% CI)
18–34	6,452 (1,378) [38]	30	4.65 (3.00–6.30) <sup>a</sup>	1,212,521 (366,945) [34]	1,070	0.88 (0.83–0.94)
35–44	6,815 (1,591) [40]	69	10.13 (7.79–12.46) <sup>a</sup>	799,406 (207,401) [22]	2,669	3.34 (3.21–3.46)
45–54	2,775 (650) [16]	52	18.74 (13.85–23.62) <sup>a</sup>	678,358 (172,792) [19]	5,128	7.56 (7.36–7.76)
55–64	599 (155) [4]	20	33.39 (19.73–47.04) <sup>a</sup>	454,552 (123,830) [13]	6,719	14.78 (14.44–15.13)
65–74	219 (56) [1]	17	77.68 (46.86–108.49) <sup>a</sup>	364,570 (102,704) [10]	8,921	24.47 (23.98–24.96)
75–84	23 (4) [0]	1	43.63 (–30.43–117.68)	43,704 (21,568) [1]	1,594	36.47 (34.75–38.20)

HIV cohort includes all patients diagnosed with HIV disease by ICD code. Non-HIV cohort includes all patients not diagnosed with HIV disease by ICD code.

<sup>a</sup> Nonoverlapping 95% CIs (lower 95% CI of HIV cohort and upper 95% CI of non-HIV cohort).

with non-HIV men) (Table 4 for age breakdown). The RRs of AMI, comparing HIV with non-HIV, were 2.98 (95% CI 2.33–3.75;  $P < 0.0001$ ) for women and 1.40 (95% CI 1.16–1.67;  $P = 0.0003$ ) for men, adjusting for age, race, hypertension, diabetes, and dyslipidemia.

Individual covariates were also assessed in gender-stratified models. Among men, the RR increased to 1.73 (95% CI 1.40–2.06;  $P < 0.0001$ ) with adjustment for age alone, and was then attenuated to 1.44 (95% CI 1.20–1.72,  $P < 0.0001$ ) with adjustment for race and cardiovascular risk factors (hypertension, diabetes, and dyslipidemia). Of women, the RR increased to 5.74 (95% CI 4.49–7.22;  $P < 0.0001$ ) with adjustment for age alone, and was then attenuated to 3.12 (95% CI 2.44–3.93,  $P < 0.0001$ ) with adjustment for race and cardiovascular risk factors (hypertension, diabetes, and dyslipidemia).

#### Risk factors for AMI in stratified models of HIV and non-HIV

We stratified on the basis of HIV status to determine risk factors for AMI within the HIV and non-HIV groups. Among the HIV-infected patients, dyslipidemia was the cardiac risk factor most significantly associated with AMI, controlling for age, race, gender, and other cardiac risk factors (RR 3.65; 95% CI 2.59–5.19;  $P < 0.0001$ ). Hypertension (RR 1.23; 95% CI 0.90–1.68;  $P = 0.20$ ) and diabetes (RR 1.33; 95% CI 0.95–1.85;  $P = 0.09$ ) were also associated with AMI within the HIV group, but these associations did not reach statistical significance. African-American race was a significant predictor of AMI among HIV patients, with a RR of 1.43 (95% CI 1.01–2.00;  $P = 0.04$ ). Among the non-HIV patients, dyslipidemia was also the cardiac risk factor most significantly associated with AMI, controlling for age, race, gender, and other cardiac risk factors (RR 3.02; 95% CI 2.92–3.12;  $P < 0.0001$ ). Hypertension (RR 1.62; 95% CI 1.58–1.67;  $P < 0.0001$ ) and diabetes (RR 1.99; 95% CI 1.93–2.04;  $P < 0.0001$ ) were significantly associated with AMI in the non-HIV group.

#### Effect of smoking on the association of HIV and AMI

Smoking data were available in 854, or 22%, of HIV patients, of whom 57% were current or prior smokers, and 38% were current smokers. Among women with HIV, approximately 51% were current or prior smokers, and 33% were current smokers. Of men with HIV, approximately 62% were current or prior smokers, and 41% were current smokers. Among the non-HIV group, smoking data were available in 111,296, or 11% of patients, of whom 40% were current or prior smokers, and 18% were current smokers. For non-HIV

women, approximately 37% were current or prior smokers, and 16% were current smokers. For non-HIV men, approximately 48% were current or prior smokers, and 22% were current smokers.

Among non-smokers, the rates of AMI in HIV *vs.* non-HIV were 7.08 *vs.* 2.64% ( $P < 0.0001$ ). Of smokers, the rates of AMI in HIV *vs.* non-HIV were 7.80 *vs.* 6.15% ( $P = 0.13$ ). The common odds ratio estimate for risk of AMI (HIV *vs.* non-HIV) by Mantel-Haenszel analysis was 1.7 controlling for smoking (95% CI 1.3–2.2, HIV *vs.* non-HIV).

#### Validation subset and sensitivity analysis

We conducted a sensitivity analysis to reflect the possibility of misclassification bias, as outlined in *Patients and Methods*. The hazard ratio estimate over the 20 iterations resulted in an empirical mean hazard ratio of 1.69 (SD 0.14).

## Discussion

Prior studies examining myocardial infarction rates among HIV patients have been limited by several factors, including the absence of a reference population. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study provided important information regarding the duration-related association of ARV therapy with AMI rates among HIV patients (11). However, neither the DAD study nor another large study that prospectively evaluated the effect of PIs on the development of AMI (10) included control groups for comparison in prospective analyses. Our study included comparative data and specifically assessed whether AMI rates are elevated in HIV patients compared with a non-HIV reference population. In contrast to the DAD study, the purpose of this study was not to determine the relationship of AMI rates to ARV use because detailed information on the longitudinal use of ARVs could not be captured from the database but, rather, to compare myocardial infarction rates between HIV and non-HIV patients, followed at two large U.S. hospitals.

The rate of AMI per 1000 PY was higher among HIV patients in this study than in the DAD study, but our study included older patients as well and was from a U.S. population, with potentially different AMI rates and cardiovascular risk factors than the European-based population of the DAD study. Furthermore, the background rate among the entire reference population was similar to that seen in other large U.S. databases, including the Framingham Heart Study, suggesting that this study reliably captured AMI events across the two large hospitals for which we have data. Importantly, the RR of AMI in

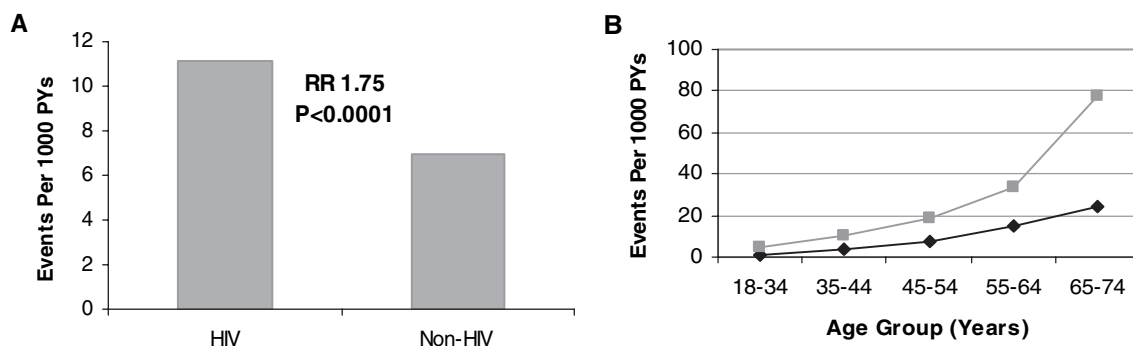


FIG. 1. A, Myocardial infarction rates and corresponding adjusted RR. Bars indicate crude rates of AMI events per 1000 PY as determined by ICD coding. RR and associated *P* value are shown above the bars. RR was determined from Poisson regression analysis adjusting for age, gender, race, hypertension, diabetes, and dyslipidemia. Associated 95% CIs for RR shown are 1.51–2.02. B, Myocardial infarction rates by age group. Light line indicates patients diagnosed with HIV disease. Dark line indicates patients not diagnosed with HIV disease. Data shown include both genders. Rates represent number of events per 1000 PY as determined by ICD coding. For associated 95% CIs, see Table 3.

HIV patients was approximately 2-fold increased over controls and, thus, likely to be clinically significant.

Several other studies that have included reference populations have used endpoints whose broad or composite nature may have decreased specificity. Two large studies that determined cases based on insurance claims from Medicaid and health maintenance organization data used coronary heart disease (CHD) as an endpoint (12, 13). When evaluated for AMI instead of CHD, one study showed only a trend toward higher rates in the HIV group (13). A second study demonstrated increased CHD incidence among younger patients ages 25–34 using one of five ICD codes for ischemic heart disease (12). A study of patients in the Veterans Affairs system, from an earlier time period (1993–2001), used five composite endpoints and showed decreased hospitalization rates but did not distinguish cardiovascular from cerebrovascular disease or AMI from CHD (14). In contrast, our data using the specific ICD code for AMI as opposed to CHD, demonstrate increased AMI rates for all age groups relative to the non-HIV cohort. A study based on data from the Women’s Health Initiative showed strong agreement between hospital discharge code of myocardial infarction and validation of events by study physicians for the diagnosis of myocardial infarction (15).

There was no difference in the overall unadjusted AMI rates in the comparison of HIV-infected with uninfected men. Among men, the RR became highly significant in a gender-stratified model after adjusting for age. With adjustment for all demographic and clinical variables, the RR of AMI remained highly significant in the comparison of male HIV *vs.* non-HIV groups. As expected, the RR was attenuated by approximately 17% when adjusting for hypertension, diabetes, and dyslipidemia. Both the unadjusted event rates and the adjusted RR were higher in the comparison of female HIV to non-HIV groups. In the gender-stratified model for women, adjustment for age increased the RR in a pattern similar to that of men. However, adjustment for hypertension, diabetes, and dyslipidemia attenuated the RR by 46% among women.

Prior studies have shown that women demonstrate increased cardiovascular disease risk indices associated with fat redistribution (16), but only limited information is available regarding the risk of cardiac events in HIV-infected women. Two major studies excluded women due to a small number of outcomes (10, 13). Data from a study based on California Medicaid claims suggested an increased AMI incidence among HIV-infected women ages 25–34 (12). In this study, we conducted both combined regression and gender-stratified models. In both male

TABLE 4. Myocardial infarction rates as determined by ICD coding among females and males

Age group (yr)	HIV			Non-HIV		
	PY (n) [%]	AMI (n)	Rate per 1000 PY (95% CI)	PY (n) [%]	AMI (n)	Rate per 1000 PY (95% CI)
<b>Females</b>						
18–34	2,604 (530) [48]	16	6.15 (3.18–9.11) <sup>a</sup>	812,106 (234,898) [37]	496	0.61 (0.56–0.66)
35–44	1,938 (418) [36]	20	10.32 (5.91–14.74) <sup>a</sup>	507,464 (124,254) [23]	1,092	2.15 (2.02–2.28)
45–54	631 (152) [12]	19	30.11 (17.45–42.78) <sup>a</sup>	419,114 (100,728) [19]	1,981	4.73 (4.52–4.93)
55–64	177 (41) [3]	5	28.19 (5.04–51.35)	253,864 (65,603) [11]	2,552	10.05 (9.67–10.43)
65–74	73 (22) [1]	9	122.47 (60.96–183.97) <sup>a</sup>	199,828 (53,582) [9]	3,931	19.67 (19.08–20.26)
75–84	7.0 (1) [0]	0	0.00 (0.00–0.00)	24,751 (11,708) [1]	765	30.91 (28.79–33.03)
<b>Males</b>						
18–34	3,848 (848) [34]	14	3.64 (1.75–5.53) <sup>a</sup>	400,415 (132,047) [30]	574	1.43 (1.32–1.55)
35–44	4,877 (1173) [43]	49	10.05 (7.29–12.80) <sup>a</sup>	291,942 (83,147) [22]	1,577	5.40 (5.14–5.67)
45–54	2,144 (498) [19]	33	15.39 (10.32–20.46)	259,244 (72,064) [19]	3,147	12.14 (11.72–12.55)
55–64	422 (114) [4]	15	35.57 (18.79–52.34)	200,688 (58,227) [15]	4,167	20.76 (20.16–21.37)
65–74	145 (34) [1]	8	55.03 (21.68–88.38)	164,741 (49,122) [12]	4,990	30.29 (29.49–31.09)
75–84	16 (3) [0]	1	62.12 (–37.29–161.53)	18,954 (9,860) [1]	829	43.74 (40.89–46.59)

HIV cohort includes all patients diagnosed with HIV disease by ICD code. Non-HIV cohort includes all patients not diagnosed with HIV disease by ICD code.

<sup>a</sup> Nonoverlapping 95% CIs (lower 95% CI of HIV cohort and upper 95% CI interval of non-HIV cohort).

and female models, including age, race, and common cardiac risk factors, HIV status was a significant predictor of AMI, but the RR of AMI was higher in women (RR 2.98) than in men (RR 1.40), possibly because of altered inflammatory marker profiles (16), significant changes in body composition in this group, and relative shift from gynoid to android fat distribution (7), or other factors. Indeed, our data suggest that the rates of some common cardiac risk factors, such as diabetes, may be relatively greater in women.

Age and race were significant independent risk factors for AMI. The risk of AMI increased with age in both the HIV and non-HIV groups, and increased AMI rates were seen for all ages in the comparison of HIV and non-HIV patients. These data suggest that cardiovascular disease will likely become an increasing problem for HIV-infected patients as the population lives longer and ages. Race was also significant in the overall model as an independent predictor of AMI. AMI risk was significantly increased among African-Americans relative to Caucasians and in Hispanics relative to Caucasians. Among HIV patients, African-American race was significant as a predictor of AMI. Prior data suggest that there is an association between race and cardiovascular disease, with higher median rates of cardiovascular events (defined as AMI, angina, CHD, or stroke) compared with the national average for African-American women, and lower rates for Hispanic women and men and African-American men (17). Racial differences between the HIV and non-HIV groups were accounted for in Poisson regression modeling, which showed a significant RR of 1.75 for AMI in the HIV group relative to the non-HIV group.

Metabolic changes are common in HIV-infected patients and likely play a role in the development of atherosclerosis, possibly in concert with other cardiac risk factors. Our study demonstrates increased rates of traditional comorbidities, including hypertension, diabetes, and dyslipidemia, seen at rates of 21.2, 11.5, and 23.3 per 100 persons in the HIV cohort, respectively. An increased rate of dyslipidemia has been well documented in smaller studies of HIV-infected populations, and may relate to effects of HIV as well as ARV therapy (18, 19). Among the Swiss HIV cohort, classification of hypercholesterolemia was seen in approximately one third of patients on PIs (8). The dyslipidemia rate of 23.3 per 100 persons seen in our study was determined from a large HIV cohort not selected for PI use, providing further evidence for the widespread prevalence of dyslipidemia in this population. Dyslipidemia was an independent risk factor for AMI in separate models of HIV and non-HIV, and in the fully adjusted model of the combined groups (RR 3.03; 95% CI 2.93–3.13;  $P < 0.0001$ ), controlling for age, gender, race, hypertension, and diabetes.

In this study we also demonstrate increased rates of diabetes and hypertension in the HIV compared with the non-HIV cohort. Increased risk factors were seen in both the male and female comparisons, in gender-stratified analyses. A recent study showed a 14% prevalence rate of diabetes in HIV-infected men using ARV therapy compared with 5% in seronegative men (3). Our data confirm and extend these data, showing an approximate 2-fold increase in diabetes rates in HIV-infected patients relative to non-HIV patients. Only limited data are available regarding hypertension rates. Another group demonstrated elevated rates of hypertension in a small study of HIV-infected patients (20). Our data add further emphasis to

the potential role played by this and other cardiac risk factors. Both diabetes and hypertension were independent risk factors for AMI in the fully adjusted model of the combined groups (RR 1.98, 95% CI 1.93–2.04,  $P < 0.0001$  for diabetes; and RR 1.62, 95% CI 1.57–1.66,  $P < 0.0001$  for hypertension). Sensitivity analyses suggested that diabetes and dyslipidemia, more than hypertension, contributed to the increase in AMI rates in the HIV group.

Relatively little is known about the risk of smoking and cardiovascular disease in HIV patients. Among non-HIV groups, numerous cohort studies demonstrate increased rates of CHD for smokers, with RRs among current smokers as opposed to never-smokers ranging from 1.3–3.5 (21). The DAD study (11) suggested that smoking was an independent risk for AMI in HIV patients but did not perform a comparison with control patients, controlling for smoking use. The estimated common odds ratio obtained from the analysis by smoking status in patients for whom smoking data were available in our study was comparable with that obtained using the multivariate Poisson regression model approach. However, due to database constraints, smoking data were available in only a subset of the patients and, thus, could not be added to the overall model. It is possible that increased smoking rates in the HIV group contribute to the increased rate of AMI in the HIV group. Other factors not measured, including inflammation (22, 23), direct effects of the virus, or ARV therapy (4, 24, 25), may also contribute to the increased risk of AMI demonstrated in the HIV group.

This study investigates AMI events in both HIV and non-HIV patients followed longitudinally at two large U.S. hospitals. Furthermore, adequate women were studied to develop gender-stratified models, showing that HIV status was a relatively greater predictor of AMI among women than men. Background comparison rates for AMIs in the entire cohort of over 1 million are similar to those reported in other large outpatient databases (26), suggesting that the database reliably captured AMI events. The relatively long and similar duration of follow-up between HIV and non-HIV groups and exclusion of all patients with a single isolated encounter, or initial encounter being an AMI, ensures that rates were determined in patients receiving longitudinal follow-up in the system, rather than patients acutely referred in for AMI assessment and treatment.

The study was limited by the constraints of the database. Overall rates of ARV use were similar to other large cohorts, but we could not investigate the contribution of ARV drugs to myocardial infarction rates in HIV-infected patients because specific data on duration of ARV use were not available through the database. Rather, the primary purpose of the study was to investigate myocardial infarction rates and major cardiac risk factors among patients with HIV disease in comparison with a large non-HIV cohort, controlling for common cardiac risk factors, age, race, and gender. Smoking data were assessed in a subanalysis among patients for whom these data were available, demonstrating that the higher AMI risk remained in HIV patients despite higher smoking rates. However, due to a lack of uniformly available data, this information was not able to be included in the overall regression model. Use of ICD coding to define AMI is standard in large epidemiological studies but is subject to misclassification bias. We performed a sensitivity analyses based on data obtained from a validation subset to

determine the effect of possible misclassification bias. The hazard ratio in the sensitivity analysis, testing a 50% maximum misclassification rate, was 1.69, compared with 1.75. In addition, hypertension and dyslipidemia could only be included as dichotomous rather than quantitative traits because we were limited to the use of ICD codes in the study, and this may have limited the strength of the covariate analysis. Thus, it is not possible to know whether the differences between HIV and non-HIV after adjustment are due to HIV *per se* or the limited nature of covariate information in the database.

In summary, our data from a large cohort of HIV-infected patients demonstrate increased AMI rates and cardiovascular risk factors compared with a non-HIV population, particularly among women. The AMI event rate was approximately 2-fold elevated in the HIV cohort, and this difference was seen over multiple age ranges. Relative myocardial infarction rates were greater among women, in comparison with the non-HIV cohort, and this gender-specific difference may account in part for the overall differences we observed. Determining the mechanisms of increased cardiovascular disease and cardiac risk factor rates in HIV-infected women is an important area of future research. Cardiac risk modification strategies are also particularly needed and will be an important component of the long-term care of this population.

### Acknowledgments

We thank Dr. Shawn Murphy, Vivian Gainer, and Jeanne Guerin in the collection of data from the Research Patient Data Registry; Nancy Wong for help with the statistical programming; and Dr. Christopher Cannon for assistance with the study design and review of the manuscript.

Received October 6, 2006. Accepted April 12, 2007.

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This work was supported by National Institutes of Health Grants RR-01066, DK-59535, and DK-49302, and the Mary Fisher Clinical AIDS Research and Education Fund.

S.K.G. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure Statement: None of the authors have any disclosures to make.

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