Immunodeficiency and Risk of Myocardial Infarction Among HIV-Positive Individuals With Access to Care

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Background: We sought to clarify the association of HIV infection and immunodeficiency on myocardial infarction (MI) risk.

Methods: We conducted a cohort study from 1996 to 2009 of HIV-positive (HIV^+) and demographically matched HIV-negative (HIV^-) Kaiser Permanente California health plan members. Rate ratios (RRs) were obtained from Poisson regression models comparing MI incidence rates between HIV^+ (overall and stratified by recent and nadir CD4 count, and recent HIV RNA levels) and HIV^- subjects, adjusting for age, sex, calendar era, race/ethnicity, census-based socioeconomic status, smoking, alcohol/drug abuse, overweight/obesity, diabetes, hypertension, and lipid-lowering therapy. Among HIV^+ subjects, we also evaluated the independent association of CD4, HIV RNA, and antiretroviral therapy (ART) use.

Results: The study population included 22,081 HIV^+ and 230,069 HIV^- subjects. The crude MI incidence rate per 100,000 person-years was 283 and 165 for HIV^+ and HIV^- subjects, respectively, with an adjusted RR of 1.4 [95% confidence interval (CI): 1.3 to 1.6]. Compared with HIV^- subjects (reference), MI rates were similar for HIV^+ subjects with recent CD4 $\geq$500 cells per microliter (RR = 1.18; 95% CI: 0.96 to 1.45) and those with nadir CD4 $\geq$500 cells per microliter (RR = 0.85; 95% CI: 0.55 to 1.33). Among HIV^+ subjects, nadir CD4 was the only HIV-specific factor associated with MIs (RR per 100 cells = 0.88; 95% CI: 0.81 to 0.96), whereas recent CD4 and HIV RNA, prior ART use, and duration of protease inhibitors and nonnucleoside reverse transcriptase inhibitors were not associated with MIs.

Conclusion: HIV^+ subjects with recent or nadir CD4 $\geq$500 cells per microliter had similar MI rates compared with HIV^- subjects. Lower nadir CD4, in particular, seems to be independently associated with MIs. These results strengthen recommendations for earlier ART initiation.

Key Words: HIV/AIDS, myocardial infarction, immunodeficiency, epidemiology

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INTRODUCTION

The prognosis for HIV-positive (HIV^+) individuals in developed countries has dramatically improved because of the availability of potent and better-tolerated combination antiretroviral therapies (ARTs).[1] In contrast to the pre-ART era, today's HIV^+ individuals generally have longer, more productive lives.[1] Thus, medical care for this population is increasingly focused on the management and control of non–AIDS-related morbidity, including cardiovascular disease (CVD), liver disease, and certain cancers.[2]

CVD is among the leading causes of death in developed countries but is uncommon in individuals younger than 50 years of age. It is anticipated that by the year 2015, the average age for HIV^+ individuals in the United States will reach 50 years[3]; thus an increased emphasis on the prevention and management of CVD is necessary, especially for myocardial infarction (MI), the major manifestation of CVD. Several large cohort studies, including our own, have described an increased risk of MI among HIV^+ individuals compared with HIV-negative (HIV^-) individuals.[4–8] Shortly after the widespread availability of combination ART, reports emerged demonstrating an excess risk of CVD in ART-treated patients, particularly those receiving protease inhibitors (PIs).[9–16]

Besides exposure to ART, possible explanations for increased MI rates in HIV^+ individuals include the higher prevalence of traditional CVD risk factors such as smoking, hyperlipidemia, and the metabolic syndrome.[8] Chronic immune activation and immunodeficiency may also contribute to accelerated atherosclerosis and higher MI rates.[17] Thus, the etiology of CVD in HIV^+ individuals is complex, with

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few settings having the necessary large sample size, internal HIV$^-$ control group, and longitudinal data required to disentangle the many contributing factors.[5]

METHODS

Subjects and Follow-Up

We conducted a cohort study from 1996 to 2009 of adult HIV$^+$ and HIV$^-$ subjects within the Kaiser Permanente (KP) Southern California (KPSC) and Kaiser Permanente Northern California (KPNC) health plans, 2 large integrated healthcare delivery systems providing comprehensive medical care to more than 6 million members. HIV$^+$ subjects were identified from HIV registries, described previously,[18,19] which include all known cases of HIV infection dating back to the early 1980s for KPNC and 2000 for KPSC. Data indicate that KP members are very similar to the California statewide population with respect to age, sex, and race/ethnicity[20]; moreover, demographics of the HIV$^+$ population are very similar to reported AIDS cases in California.[21]

The eligible population included HIV$^+$ and HIV$^-$ adults ($\geq$18 years of age) who were health plan members between 1996 and 2009 for KPNC and 2000 and 2009 for KPSC. HIV$^+$ subjects were further restricted to those in care, defined as subjects with $\geq$1 recorded CD4 count measurement during follow-up; most HIV$^+$ subjects (ie, >95%) met the in-care eligibility. The final study population consisted of all eligible HIV$^+$ subjects and a sample of HIV$^-$ subjects who were frequency-matched 10:1 to HIV$^+$ subjects by calendar year, age (5-year age groups), sex, and medical center (to account for care practice differences). Additionally, we identified the subset of HIV$^+$ subjects whose complete ART history was available. The start of follow-up for all subjects was assigned as the earliest date on or after January 1, 1996 (January 1, 2000 for KPSC) when a subject met all eligibility criteria. Subjects were followed until the earliest of an MI, death, lost to follow-up (ie, left health plan), or end of the study (December 31, 2009).

Measurements

The primary data sources for this study were the HIV registries and electronic medical records (EMRs), which include information on prescription medications, inpatient and outpatient diagnoses and visits, laboratory tests, membership dates, and vital status. The main outcome was a primary inpatient discharge diagnosis of an MI (*ICD-9*: 410.x); MI discharge diagnoses are generally made in KP after troponin and/or CK-MB confirmation. Other data extracted included age, sex, race/ethnicity, HIV exposure risk [eg, men who have sex with men (MSM), heterosexual, injection drug use (IDU)], duration of known HIV infection, dates of death, laboratory test results (CD4 count and HIV RNA levels), prescription fills (dispensed ART and lipid-lowering therapy), and clinical diagnoses corresponding with other traditional CVD risk factors, including alcohol or drug abuse, overweight/obesity, hypertension, diabetes mellitus, and tobacco use.

Race/ethnicity was known for 95% of HIV$^+$ subjects and 63% of HIV$^-$ subjects. The higher proportion of known race/ethnicity among HIV$^+$ individuals was due to a manual chart review conducted on all HIV registry patients. We imputed missing race/ethnicity using the Bayesian Improved Surname Geocoded (BISG) algorithm.[22,23] Briefly, the BISG algorithm computes a probability for belonging to each distinct racial/ethnic group based on surnames and year 2000 geocoded census block groups. Each participant with unknown race was then assigned a probable racial/ethnic affiliation based on a BISG probability cut-point of 0.75. A similar algorithm for imputing race/ethnicity was recently applied and validated in KPSC.[24] After imputation, race/ethnicity was assigned for 98% of HIV$^+$ subjects and 89% of HIV$^-$ subjects.

Next, we used 6 census block group variables to create a neighborhood socioeconomic status (SES) index based on the Diez-Roux neighborhood index.[25] The census variables used in the index included income (median household income; median value of housing units; percent of households with interest, dividend, or rental income), occupation (percent of employed residents with executive, managerial, or professional occupations), and education (percent of adult residents who completed high school; percent of adult residents who completed college). Previous research validating the index noted an association between the index and CVD-related outcomes.[26–28] Here, the score was categorized into quintiles with the first quintile representing the most disadvantaged areas and the fifth quintile representing the least disadvantaged areas.

The institutional review boards at KPNC and KPSC approved this study with a waiver of written informed consent.

Statistical Analysis

Several variables were fixed variables in analyses, including sex, race/ethnicity (white, black, Hispanic, Asian/Pacific other, unknown), and census-based SES (quintiles). Smoking, overweight/obese, and alcohol/drug abuse were also treated as fixed variables, set to "ever" if noted in the EMR at any point during follow-up; otherwise, these variables were set to "never."

The remaining analytical variables were time-dependent, including current age (<40, 40–49, 50–64, 65+ years), calendar era (1996–1999, 2000–2004, 2005–2009), prior diagnosis of diabetes (yes/no), prior diagnosis of hypertension (yes/no), and prior lipid-lowering therapy (yes/no). Among HIV$^+$ subjects, we also considered prior ART use (any/none), years known HIV$^+$ ($\geq$10, 5–9.9, <5 years), HIV exposure risk (MSM, IDU, heterosexual, unknown), recent and nadir CD4 counts (continuous and categorized as <200, 200–499, $\geq$500 cells/μL), and recent HIV RNA levels (continuous and categorized as $\geq$10,000, 500–9999, <500 copies/mL). Nadir CD4 count was defined as the lowest recorded CD4 during KP membership. Finally, in the subset of HIV$^+$ subjects with complete ART history, we computed the cumulative duration of PIs and nonnucleoside reverse transcriptase inhibitors (NNRTIs) used during follow-up. With the exception of CD4 count and HIV RNA levels that were updated at 6-month intervals, all other time-dependent variables were updated continuously (ie, updated on day the variable changed).

We first compared demographics and other potential confounders between HIV$^+$ and HIV$^-$ subjects using Pearson χ^2 test for categorical variables and Kruskal–Wallis test for continuous variables. Rate ratios (RRs) for HIV status were obtained from Poisson models with adjustment for age, sex, race/ethnicity, calendar era, census-based SES, smoking, drug/alcohol abuse, diabetes, hypertension, use of lipid-lowering therapy, and obesity. Then, we examined MI rates by HIV status with HIV$^+$ subjects stratified by recent CD4 count (<200, 200–499, ≥500 cells/μL), nadir CD4 (same levels), and HIV RNA levels (<500, 500–9999, and ≥10,000 copies/mL). A *P*-value was obtained from the likelihood ratio test of equality across strata.

Next, among HIV$^+$ subjects only, multivariable Poisson models were constructed to evaluate the independent associations of recent and nadir CD4 count, recent HIV RNA level, prior ART, HIV risk group, years known HIV$^+$, and the other demographic and clinical variables listed above. In the subset of HIV$^+$ subjects with complete ART history, we further examined the association of PI and NNRTI duration in models adjusting for baseline (but not recent or nadir) CD4, baseline HIV RNA, and other covariates described above.

Analyses were performed with SAS (version 9.1; SAS Institute Inc., Cary, NC). All statistical tests are 2-sided, and statistical significance was defined as $P < 0.05$.

RESULTS

The study population included 22,081 HIV$^+$ and 230,069 HIV$^-$ subjects who contributed 99,090 person-years (mean, 4.5 years/subject) and 1,253,550 person-years (mean, 5.4 years/subject) of follow-up, respectively. The HIV$^+$ and HIV$^-$ groups were similar with respect to matching parameters of age and sex (Table 1). HIV$^+$ subjects, compared with HIV$^-$ subjects had higher percentage smoking history (43.3% vs. 29.0%; $P < 0.001$) and alcohol/drug abuse history (20.3% vs. 8.4%; $P < 0.001$). The prevalence of diabetes, overweight/obesity, use of lipid-lowering therapy, and hypertension at study entry were comparable by HIV status. A higher percentage of HIV$^+$ subjects were whites and blacks, whereas a higher percentage of HIV$^-$ subjects were Hispanics and Asian/Pacific Islanders ($P < 0.001$). HIV$^-$ subjects were equally distributed in census-based SES quintiles, whereas HIV$^+$ subjects had a modestly higher percentage in the lowest SES quintile ($P < 0.001$). The HIV exposure risk factor among HIV$^+$ subjects was predominantly MSM (74.5%), followed by heterosexual transmission (16.4%) and IDU (7.1%). At study entry, HIV$^+$ subjects were known to be HIV$^+$ for a mean 3.6 years, had mean 400 cells per microliter CD4$^+$ T cells, mean 55,272 HIV RNA copies per milliliter, 39.4% had a history of clinical AIDS, and 48.7% had prior ART. By the end of follow-up, most (79.8%) had received ART.

HIV$^+$ subjects had an MI incidence rate of 283 per 100,000 person-years (n = 280 MIs), whereas HIV$^-$ subjects had an incidence rate of 165 per 100,000 person-years (n = 2064 MIs). The corresponding unadjusted RR for HIV status was 1.72 [95% confidence interval (CI): 1.51 to 1.94], and the adjusted RR was 1.44 (95% CI: 1.27 to 1.64) (Table 2). The higher incidence rate for HIV$^+$ subjects compared with HIV$^-$ subjects was more apparent among ART-treated subjects with an adjusted RR of 1.47 (95% CI: 1.28 to 1.68); for ART-untreated subjects, the RR was 1.21 (95% CI: 0.86 to 1.69); (data not otherwise shown). In unadjusted models comparing results by age, the association of HIV status appeared to be modestly stronger in younger individuals, with RRs of 1.92 (95% CI: 1.55 to 2.40) and 1.65 (95% CI: 1.42 to 1.92) for those <50 years and ≥50 years of age, respectively. However, with the adjustment for other risk factors, results were similar in these age strata with adjusted RRs of 1.34 (95% CI: 1.07 to 1.68) and 1.40 (95% CI: 1.20 to 1.64), respectively (data not otherwise shown).

TABLE 1. Subject Characteristics

Characteristics	HIV$^+$	HIV$^-$	*P**
Number of subjects	22,081	230,069	
Total years follow-up (mean/subject)	99,090 (4.5)	1,253,550 (5.4)	
Year of enrollment			<0.001
1996–1999	26.8	28.1	
2000–2004	43.6	43.2	
2005–2009	29.6	28.6	
Age, yrs			<0.001
<24	4.0	4.9	
25–29	8.0	9.0	
30–34	15.6	15.7	
35–39	20.9	20.6	
40–44	19.3	18.8	
45–49	14.5	14.0	
50–54	8.9	8.6	
55–59	4.8	4.6	
60–64	2.3	2.3	
≥65	1.5	1.5	
Men, %	90.6	90.5	0.67
Race/ethnicity†, %			<0.001
White	55.9	45.8	
Black	18.0	9.7	
Hispanic	21.1	28.2	
Asian/Pacific Islander	4.2	14.9	
Other	0.8	1.6	
% Unknown race/ethnicity of total	1.8	11.5	
2000 census-based SES			<0.001
Quintile 1 (low SES)	22.8	19.7	
Quintile 2	20.7	19.9	
Quintile 3	19.9	20.0	
Quintile 4	17.4	20.3	
Quintile 5 (high SES)	19.2	20.1	
Ever history of smoking, %	43.3	29.0	<0.001
Ever alcohol/drug abuse diagnosis, %	20.3	8.4	<0.001
Ever overweight/obese, %	39.0	44.3	<0.001
Prior diabetes, %	2.9	2.7	0.19
Prior lipid-lowering therapy use, %	5.0	4.8	0.299
Prior hypertension	7.3	8.1	<0.001

*Based on Pearson χ^2 test for categorical variables and Kruskal–Wallis test for continuous variables.

†Race/ethnicity was estimated for 3.3% of HIV$^+$ and 26.2% of HIV$^-$ subjects using a previously described method[22,23] that combines census block geocoding and surnames.

TABLE 2. RRs* (95% CI) for MI Comparing HIV+ (Overall and Stratified by Recent and Nadir CD4 Count, and Recent HIV RNA) With HIV− Subjects

	HIV Status (HIV− Reference)			*P*
Unadjusted	1.72 (1.51–1.94)			<0.001
Adjusted	1.44 (1.27, 1.64)			<0.001
	Recent CD4, cells/μL (HIV− Reference)			
	<200	**200–499**	**≥500**	***P*†**
Unadjusted	1.96 (1.46–2.63)	1.92 (1.61–2.28)	1.42 (1.16–1.74)	0.0482
Adjusted	1.76 (1.31–2.37)	1.59 (1.34–1.90)	1.18 (0.96–1.45)	0.030
	Nadir CD4, cells/μL (HIV− Reference)			
	<200	**200–499**	**≥500**	***P*†**
Unadjusted	2.28 (1.93–2.69)	1.50 (1.23–1.81)	0.82 (0.53–1.28)	<0.001
Adjusted	1.74 (1.47–2.06)	1.30 (1.07–1.58)	0.85 (0.55–1.33)	0.002
	Recent HIV RNA, copies/mL (HIV− Reference)			
	≥10,000	**500–9999**	**<500**	***P*†**
Unadjusted	1.46 (1.11–1.93)	1.44 (1.04–2.00)	1.87 (1.61–2.17)	0.1398
Adjusted	1.66 (1.26–2.20)	1.37 (0.98–1.90)	1.41 (1.21–1.64)	0.54

*Unadjusted and adjusted RRs from Poisson regression models with terms for HIV status/CD4/HIV RNA (HIV− reference group). Adjusted model additionally adjusted for age, sex, race/ethnicity, calendar era, SES, smoking, overweight, alcohol/drug abuse, diabetes, hypertension and lipid-lowering therapy.

†*P*-value from the likelihood ratio test of equality across strata.

As shown in Table 2, HIV+ subjects with recent CD4 <200 cells per microliter had an adjusted RR = 1.76 (95% CI: 1.31 to 2.37) for MIs compared with HIV− subjects, whereas no association was observed comparing HIV+ subjects with CD4 ≥500 cells per microliter with HIV− subjects (RR = 1.18, 95% CI: 0.96 to 1.45) (*P*-trend = 0.03). Similarly, HIV+ subjects with nadir CD4 <200 cells per microliter had an adjusted RR = 1.74 (95% CI: 1.47 to 2.06) compared with HIV− subjects, but those with nadir CD4 ≥500 per microliter had an adjusted RR = 0.85 (95% CI: 0.55 to 1.33) (*P* = 0.002). Stratification by recent HIV RNA levels did not reveal any significant differences (*P* = 0.54).

Table 3 presents results of the multivariable analysis of risk factors for MI among HIV+ subjects. Higher nadir CD4 count was the only HIV-related factor independently associated with MIs, whereas recent CD4, recent HIV RNA, and prior ART were not significant. Traditional CVD risk factors were also associated with MIs, including older age, male sex, smoking, prior diabetes, prior hypertension, and prior lipid-lowering therapy. In addition, a higher risk of MI was noted in earlier years and for whites (compared with blacks and Hispanics), whereas census-based SES was not associated with MI.

As shown in the Figure 1, along with the unadjusted results presented in Table 4, there was a trend for increased MI incidence rates with longer duration of PI-based ART, although it was no longer significant in adjusted models (Table 4). For NNRTIs, the rates appeared to have a U-shape that increased initially and then decreased with longer duration. However, the wide CIs with longer duration (particularly at 4 and 5 years) indicate this result should be interpreted with caution. Poisson models did not support an association of NNRTIs and MIs.

DISCUSSION

Our current findings demonstrate a 44% increased risk of MIs among HIV+ subjects compared with HIV− subjects from the same healthcare setting, independent of traditional CVD risk factors such as smoking, male sex, older age, hyperlipidemia, and hypertension. We also documented that HIV-associated immunodeficiency, but not HIV RNA levels, or longer duration PIs or NNRTIs contributed to this higher risk. Importantly, we observed that HIV+ subjects with recent or nadir CD4 ≥500 cells per microliter did not have excess MI risk compared with HIV− subjects.

The increased risk of MIs among HIV+ patients was established early in the ART era, including an early report from our cohort.[6] However, it was unclear how much of the increased risk was influenced by confounding factors, including smoking, socioeconomic factors, and access to medical care. Here, we evaluated MI risk in a large population of HIV+ and HIV− subjects identified from the same healthcare setting, thus reducing disparities with respect to access to care. We also adjusted for smoking, race/ethnicity, and census-based SES to further adjust for potential key confounders. A similar recent study on this topic included HIV+ and HIV− individuals from the Veterans Aging Cohort Study (VACS) Virtual Cohort.[5] They reported an adjusted hazard ratio for MIs of 1.48, which is remarkably similar to our RR of 1.44. The similarity of these findings is notable, given the uniform access to care for both the VACS and KP systems. Similar to our finding and that of the VACS,[5] the incidence of acute MI in the French-Hospital Database on HIV cohort was increased among HIV+ individuals compared with age- and sex-standardized rates in the general population of France (standardized morbidity ratio of 1.5).[15] Data from the Partners Healthcare System in Boston also demonstrated an increased

TABLE 3. Risk Factors for MI Among HIV+ Subjects

	RR*	95% CI	*P*
Prior ART	1.26	0.83 to 1.91	0.28
Recent CD4 (per 100 cells/μL)	1.03	0.97 to 1.10	0.30
Nadir CD4 (per 100 cells/μL)	0.88	0.81 to 0.96	0.006
Recent HIV RNA (per 1 log)	1.03	0.97 to 1.08	0.38
HIV risk			
IDU vs. MSM	0.68	0.36 to 1.31	0.25
Heterosexual vs. MSM	1.28	0.85 to 1.91	0.23
Unknown vs. MSM	0.94	0.67 to 1.31	0.70
Years known HIV+			
≥10 vs. <5 yrs	0.92	0.67 to 1.27	0.60
5–9.9 vs. <5 yrs	1.05	0.77 to 1.45	0.75
Female sex	0.53	0.28 to 0.98	0.044
Age, yrs			
≥65 vs. 18–39	11.87	6.29 to 22.42	<0.001
50–64 vs. 18–39	5.94	3.35 to 10.56	<0.001
40–49 vs. 18–39	3.20	1.80 to 5.71	<0.001
Race/ethnicity			
Black vs. white	0.60	0.41 to 0.87	0.008
Hispanic vs. white	0.62	0.41 to 0.93	0.020
Other vs. white	0.95	0.51 to 1.75	0.86
Unknown vs. white	0.78	0.11 to 5.66	0.81
2000 census-based SES			
Quintile 1 vs. quintile 5 (high SES)	1.17	0.80 to 1.72	0.41
Quintile 2 vs. quintile 5 (high SES)	1.05	0.72 to 1.53	0.78
Quintile 3 vs. quintile 5 (high SES)	1.08	0.76 to 1.55	0.66
Quintile 4 vs. quintile 5 (high SES)	0.77	0.52 to 1.14	0.19
Year of enrollment			
2000–2004 vs. 1996–1999	0.76	0.51 to 1.14	0.18
2005–2009 vs. 1996–1999	0.42	0.27 to 0.64	<0.001
Ever smoked	2.21	1.66 to 2.93	<0.001
Ever overweight/obese	0.82	0.64 to 1.05	0.12
Ever alcohol/drug abuse	1.26	0.96 to 1.64	0.096
Prior diabetes	1.53	1.10 to 2.12	0.011
Prior hypertension	1.99	1.51 to 2.61	<0.001
Prior lipid-lowering therapy	1.61	1.21 to 2.13	<0.001

*RRs obtained from Poisson regression models adjusted for all variables listed.

risk for acute MI among HIV+ individuals compared with HIV− individuals with a more elevated RR of 1.75.[8]

Some studies have demonstrated that the association of HIV status and MI risk may vary by age. A large study using California Medicaid claims data by Currier et al[4] showed significantly increased unadjusted CVD incidence rates only for HIV+ men of ≤34 years of age and HIV+ women ≤44 years. Triant et al[8] also reported somewhat larger relative differences in MI incidence rates by HIV status in younger age strata. The recent VACS[5] study, however, did not demonstrate much difference in crude MI incidence rates by age. Here, we did observe a stronger unadjusted RR by HIV status for those <50 years compared with ≥50 years of age, but similarly elevated adjusted RRs. Thus, previously reported differences by age might be explained by a higher prevalence of CVD risk factors among younger HIV+ individuals.

Our results suggest that immunodeficiency is a key MI risk factor. We found an increased risk of MI among HIV+ subjects with low CD4 (eg, <200) compared with HIV− subjects, but no increased risk among HIV+ subjects with recent or nadir CD4 ≥500 cells per microliter compared with HIV− subjects. In contrast, the VACS study[5] reported a similarly elevated MI risk for HIV+ Veterans with CD4 <200 and ≥200 cells per microliter, compared with HIV− Veterans. However, these results are not directly comparable to ours since they did not evaluate more preserved CD4 (ie, CD4 ≥500) or nadir CD4. There are other emerging data supporting immunodeficiency as a risk factor for MIs.[29–31] Triant et al[31] demonstrated an elevated MI risk for individuals with CD4 <200 cells per microliter, which they found comparable in magnitude to the other traditional CVD risk factors examined. In the HIV Outpatient Study cohort, CD4 <500 cells per microliter was associated with increased risk for CVD and was equal in magnitude to smoking or high LDL cholesterol.[30] Like our study, Lang et al[29] also identified nadir CD4 count as a key risk factor.

That nadir CD4 acts as a risk factor for MIs is biologically plausible because atherosclerosis is considered a consequence of a chronic inflammatory process in which monocytes, T and B cells, and their associated mediators contribute to its development.[17] Hsue et al have provided key insights into the possible underlying mechanism among HIV+ patients from the San Francisco General Hospital, including associations of lower nadir CD4 with specific adverse CVD effects, including higher left ventricular mass,[32] increasing intima–media thickness,[33] and lower brachial artery flow-mediated dilation.[34] The strong observed associations for nadir CD4 and MI risk likely reflect the fact that it is a better surrogate than recent CD4 for increased duration of immunosuppression and HIV-associated inflammation. Alternatively, any potential direct toxic effects of specific ART such as PI-based ART may have masked protective effects of recent CD4. However, a sensitivity analysis that excluded those treated with PIs indicated that recent CD4 was still not protective against MIs (data not shown).

Higher HIV RNA levels, a marker of immune activation among HIV patients,[35] have been evaluated as a risk factor for MI, but with mixed results. Similar to our findings, some have reported that baseline[12,30] or recent[36] HIV RNA levels are not associated with MI risk. However, 1 case–control study[29] and another study of CVD deaths[37] reported an association with higher recent HIV RNA levels. Differences might be explained by variable case definitions or ascertainment, covariates included in models, or chance. For at least our study and Triant et al,[31] HIV RNA levels were not associated with MI in models that also considered CD4. We also noted similarly elevated MI incidence rates for HIV+ subjects stratified by HIV RNA levels (<500, 500–9999, or ≥10,000 copies/mL) compared with HIV− subjects, providing further evidence of a lack of an association of HIV RNA levels on MI risk. This is consistent with the data from the VACS study[5] that also noted similar hazard ratios for HIV+ Veterans stratified by HIV RNA levels (<500 or ≥500 copies/mL), compared with HIV− Veterans.

Here, we found that longer duration of PIs, but not NNRTIs, increased the risk for MIs in unadjusted models, but not in adjusted models. Thus, the observed unadjusted

TABLE 4. ART Class Duration and Risk of MI

	RR*	95% CI	*P*
Unadjusted results			
Per year PI use	1.14	1.04 to 1.26	0.006
Per year NNRTI use	1.03	0.91 to 1.17	0.61
Adjusted results			
Per year PI use	1.01	0.90 to 1.14	0.83
Per year NNRTI use	0.95	0.82 to 1.10	0.47

*Unadjusted and adjusted RRs for PI (or NNRTI) duration from Poisson regression models. Adjusted model additionally adjusted for age, sex, race/ethnicity, calendar era, SES, smoking, overweight, alcohol/drug abuse, diabetes, hypertension, and lipid-lowering therapy, CD4 count at baseline, HIV RNA levels at baseline, prior ART use, HIV risk, and years known HIV$^+$.

association for PI use was either because of confounding or was real and mediated entirely through factors affected by PI use, such as dyslipidemia. D:A:D researchers previously reported an association of MIs with PI-based ART and noted an attenuation (but not elimination as noted here) of the PI class effect with adjustment for time-updated lipid levels, hypertension, and diabetes diagnoses.[11] The reason for the difference is unclear, but may be due in part to use of different and more lipid-friendly PIs in recent years. The D:A:D and others have noted associations with specific PIs, including indinavir,[16] fosamprenavir,[16] lopinavir/ritonavir,[16,38] and some NNRTIs, such as efavirenz.[38] Previous studies have also noted an increased risk for abacavir,[39–41] a commonly prescribed NRTI, although this has been refuted in recent studies.[42,43] We did not attempt to analyze individual medications within antiretroviral drug classes because of the relatively limited accumulated person-time and events.

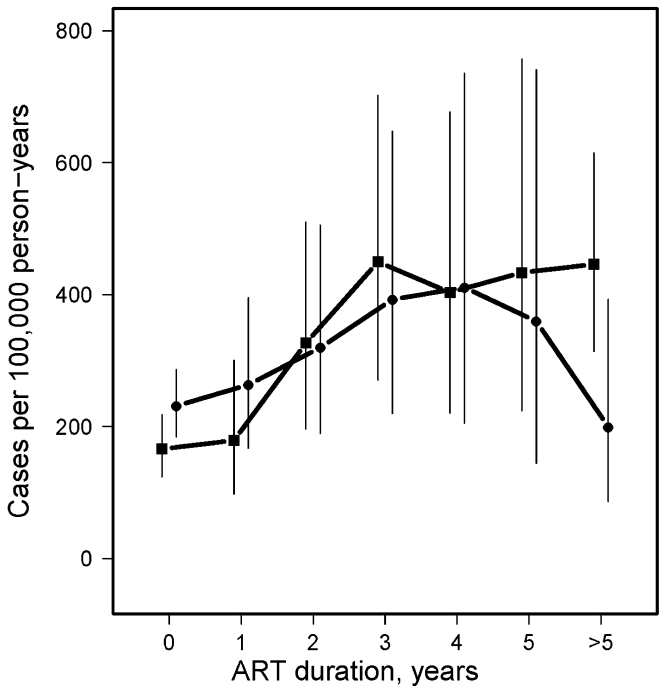

FIGURE 1. Association of cumulative use of PIs or NNRTIs on MI incidence rates. Squares represent incidence rates by duration PIs, and circles represent incidence rates by duration NNRTIs. Vertical lines are 95% CIs.

We acknowledge some study limitations. First, the CVD risk factors considered were obtained from routine clinical practice. Smoking, for example, was captured during outpatient visit encounters, and the level of detail recorded only allowed for broad categorizations (eg, ever or never smoked). We also did not capture actual drug or alcohol usage, instead relying on various coded diagnoses. Residual confounding by these risk factors cannot be excluded, although the misclassification is likely nondifferential by HIV status. There were also no available data on MI family history; however, because this variable is not expected to be associated with HIV status, it is not likely a strong confounder. Finally, as the majority of our HIV subjects were men, reflecting the epidemiology of HIV in California, our results may not be as generalizable to women.

The major strength of our study is the use of a large well-characterized population of HIV$^+$ and matched HIV$^-$ subjects from the same integrated healthcare system. Because the KP medical care program has a strong systems level emphasis on CVD prevention,[44] this study setting inherently controls for many ecologic, provider and system level factors. We also adjusted for census-based SES, thus further reducing potential biases introduced by potential variable access to care. Another strength of the study is the availability of a comprehensive EMR, resulting in few missed MI events. Finally, our study results will become increasingly generalizable in the United States with healthcare reform because it is anticipated that many previously uninsured Americans, including those with HIV, will receive their medical care in settings similar to KP.

In summary, we have demonstrated that HIV$^+$ subjects continue to have an elevated risk for MIs, even with adjustment for traditional CVD risk factors. We also observed that nadir CD4, but not recent CD4, was independently associated with MIs among HIV$^+$ individuals, suggesting the higher MI risk in this population may not be easily reversible. These findings argue for increased efforts to diagnose and treat HIV as early as possible, which if combined with aggressive traditional CVD risk factor management might result in a similar MI burden as the general population.

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