Declining Relative Risk for Myocardial Infarction Among HIV-Positive Compared with HIV-Negative Individuals with Access to Care

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Abstract

Concerns remain for an increased myocardial infarction (MI) risk among HIV-infected individuals. We conducted a cohort study evaluating MI risk from 1996 to 2011 by HIV status. The adjusted MI rate ratio for HIV status declined over time, reaching 1.0 (95% CI: 0.7-1.4) in 2010-2011, the most recent study period.

Introduction

As the prognosis for HIV-positive (HIV+) individuals in developed countries has dramatically improved with the availability of potent, more convenient, and better-tolerated ART regimens, life expectancy is anticipated to approach that of the general US population.[1] Consequently, medical care for this population is focusing more intently on control and prevention of age-related comorbidities, such as cardiovascular disease (CVD).

We and others have described an approximately 40-80% higher risk of myocardial infarction among HIV+ compared with HIV-negative (HIV-) populations during the antiretroviral therapy (ART) era.[2-5] Over time, with greater emphasis on CVD risk reduction, as well as increased use of more lipid friendly and less toxic antiretrovirals, one could expect a reduction in the risk of CVD outcomes, including myocardial infarction (MI). Thus, we investigated incidence rates of MIs over time among a large cohort of HIV+ and demographically matched HIV- individuals.

Methods

We conducted a cohort study using data from 1996 to 2011 on HIV+ and HIV-members of Kaiser Permanente (KP) Southern California (KPSC) and Kaiser Permanente Northern California (KPNC) health plans, which collectively provide comprehensive medical care to more than 6 million members. The eligible population included HIV+ and demographically-matched HIV- adults (≥18 years of age) who were health plan members between 1996-2011 for KPNC and 2000-2011 for KPSC. HIV+ subjects were restricted to those in care, defined as subjects with ≥1 recorded CD4 count measurement during

follow-up. HIV- subjects were frequency-matched 10:1 to HIV+ subjects by calendar year, age (5-year age groups), sex, and medical center. The start of follow-up was the earliest date on or after 1/1/1996 (1/1/2000 for KPSC) when a subject met all eligibility criteria (i.e., age≥18, active membership, in care). Subjects were followed until diagnosis of an MI, death, loss to follow-up, or December 31, 2011.

The primary data sources for this study were the KP maintained HIV registries and the electronic medical record (EMR), which include information on medications, diagnoses, laboratory tests, and vital status. The main outcome was a discharge diagnosis of an MI (ICD-9: 410.x), which has >95% positive predictive value in KP [6]. The primary exposures were HIV status and calendar time (1996-99, 2000-03, 2004-07, 2008-09, 2010-11). Study methods were described in more depth previously [4].

We first computed incidence rates (per 100,000 person-years) and unadjusted rate ratios (RR) by HIV status and calendar time. Next, we estimated adjusted RRs using Poisson models adjusting for fixed variables including sex, race/ethnicity (white, black, Hispanic, other, unknown), census-based socioeconomic status (quintiles), ever smoking, overweight/obese and alcohol/drug abuse diagnoses, and time-dependent variables including attained age (<40, 40-49, 50-64, 65+ years), prior diabetes, prior hypertension, and prior lipid-lowering therapy use. Next, we evaluated changes over time in HIV disease characteristics, and prescriptions for lipid-lowering and hypertension therapy. Finally, for years 2008-09 and 2010-11, for which complete data were available, we calculated Framingham risk scores. Differences by HIV status assessed by chi-square or t-test statistics.

Results

We identified 24,768 HIV+ and 257,600 HIV- subjects contributing 119,587 person-years (mean 4.8 years/subject) and 1,506,676 person-years (mean 5.8 years per subject), respectively. The HIV+ and HIV- groups were similar in terms of sex (91% men for both groups), age at baseline (mean 41 years for HIV+ and 40 for HIV-), age at end of follow-up (mean 49 years for HIV+ and 50 for HIV-), and baseline diabetes (3% prevalence for each group), hypertension (8% for HIV+ and 9% for HIV-), and receipt of lipid-lowering therapy (6% for each). HIV+ members were more likely black (18% vs. 10%), white (56% vs. 45%), less likely Hispanic (21% vs. 28%), and more likely to have smoked (45% vs. 31%), have a drug abuse (16% vs, 5%) or alcohol abuse diagnosis (11% vs. 7%).

There were 320 MIs among HIV+ (268 cases/100,000 person-years) and 2,483 MIs among HIV- (165 cases/100,000 person-years), corresponding with an unadjusted RR of 1.6 (95% CI: 1.5-1.8) and an adjusted RR of 1.4 (95% CI: 1.2-1.6) (Table). The unadjusted RR for HIV status declined from 2.0 (95% CI: 1.5-2.8) in 1996-1999 to 1.2 (95% CI: 0.9-1.6) in 2010-2011 (Table). Similarly, the adjusted RR for HIV status declined from 1.8 (95% CI: 1.3-2.6) in 1996-1999 to 1.0 (95% CI: 0.7-1.4) in 2010-2011 (Table).

The mean Framingham risk score in 2008-2009 comparing HIV+ and HIV- subjects, respectively, was 9.6% and 9.9% (P<0.001), and in 2010-2011, 9.5% and 10.0% (P<0.001). Regarding components of the score for 2010-2011, HIV+ subjects were less likely than HIV- subjects to have total cholesterol>200 mg/dl (30% vs. 39%; p<0.001), but more likely to have HDL<40 mg/dl (39.4% vs. 26.2%; p<0.001), have hypertension

(28.5% vs. 26.2%; p<0.001), and have smoked (48.7% vs. 34.0%; p <0.001). Similar results were observed for 2008-2009 (data not shown).

Prescriptions for lipid-lowering therapy increased for HIV+ subjects from 5.5% in 1996-1999 to 31.5% in 2010-2011, while for HIV- subjects it increased from 3.7% to 24.3%. Similarly, prescriptions for hypertension therapy increased for HIV+ subjects from 17.2% in 1996-1999 to 34.6% in 2010-2011, while for HIV- subjects it increased from 13.6% to 31.2%. By the end of 2010-2011, the HIV+ group was predominantly on ART (90%), with a mean CD4 of 605, mean nadir CD4 (i.e., lowest in KP) of 303, and with 88% having HIV RNA levels<500 copies/ml. This represents a substantial improvement compared with the earliest period (1996-1999), with 66% on ART by the end of the period, with a mean CD4 of 391, mean nadir CD4 of 242 and with 65% having HIV RNA levels<500 copies/ml.

Discussion

In this large cohort, we found that HIV+ individuals no longer had an elevated risk for MIs in 2010-2011 compared with a matched population of HIV- individuals. There was evidence of similar or even superior CVD risk profiles for HIV+ subjects, with Framingham risk scores which were lower for HIV + subjects compared with HIV- subjects since at least 2008. HIV+ subjects also had similar increases over time compared with HIV- subjects in the use of lipid-lowering and hypertension therapy.

In our large integrated care setting of insured patients, these results may be explained by access to care, and broadly disseminated CVD risk reduction efforts, such as the implementation of health prompts that appear during all clinic visit registrations,

including reminders for cholesterol and blood pressure monitoring, diabetes follow-up, and smoking cessation. In addition, one of the first reports documenting an increased risk of CVD was among KP HIV patients [7], and may have resulted in early awareness and enhanced attention to CVD risk reduction interventions in this population. Such early and sustained improvements in care would have been necessary to result in the observed equal MI rates by HIV status in the most recent era. Several other large cohorts (Partners[5], VACS[2] and French[3]) have reported increased incidence rates for MIs for HIV+ compared with HIV- control populations but have not reported results by calendar era.

An additional explanation for the reduction in MI events over time is the greater use of ART regimens with reduced association with CVD events, as reflected in national treatment guidelines [8] and mirrored within KP. Additionally, changes in HIV disease management over time, including earlier initiation of ART [8] may have also contributed to the converging MI incidence rates by HIV status, since emerging findings from our group and others indicate that lower recent and/or nadir CD4 was associated with a higher risk of MIs [2,4,9-11]. This association is potentially a result of the link between immunodeficiency, chronic inflammation and accelerated atherosclerosis [12].

The major strengths of our study are the use of a large, well-characterized population of HIV+ subjects and matched HIV- subjects from the same integrated health care system. With a comprehensive EMR, and highly valid MI ascertainment, missed MI events were unlikely. Limitations included lack of detail on risk factors, such as smoking, and current recreational drug use, and no information on other risk factors such as family history of CVD. An additional limitation is sample size, requiring larger studies to

confirm whether a small excess MI risk remains in recent years for HIV patients. Lastly, the majority of our subjects were men and results may not be as generalizable to women, nor to populations without access to care since KP patients were highly treated with well-controlled disease.

In conclusion, we found that the previously reported excess risk of MI among HIV+ patients no longer exists in our setting in recent years. The reasons for the convergence in incidence rates by HIV status may include greater use of CVD-friendly antiretroviral medications, increased emphasis on CVD risk reduction in this population, and the emerging profile in the modern ART era of a highly successfully treated HIV patient population. Although encouraging, it remains plausible that underlying inflammation associated with HIV continues to contribute to subclinical disease, including accelerated atherosclerosis. Nevertheless, our findings lend support to the concept that increased MI risk for HIV patients is largely reversible with continued emphasis on primary prevention in combination with early initiation of ART to preserve immune function.

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Table. MI incidence rates and rate ratios for HIV status

Calendar year	Incidence rate / 100,000py		Rate ratio* (95% CI)	
	HIV+	HIV-	Unadjusted	Adjusted
1996-2011	268	165	1.6 (1.5-1.8)	1.4 (1.2-1.6)
1996-1999	276	136	2.0 (1.5, 2.8)	1.8 (1.3, 2.6)
2000-2003	324	162	2.0 (1.6, 2.5)	1.7 (1.4, 2.1)
2004-2007	270	178	1.5 (1.2, 1.9)	1.3 (1.0, 1.6)
2008-2009	245	167	1.5 (1.1, 2.0)	1.3 (0.9, 1.7)
2010-2011	195	165	1.2 (0.9, 1.6)	1.0 (0.7, 1.4)

* Reference is HIV-. Adjusted models also include terms for age, sex, year, census-based socioeconomic status, race/ethnicity, hypertension, smoking, diabetes, alcohol/drug abuse, overweight/obesity, and lipid-lowering therapy