

Hospitalizations for Coronary Heart Disease and Myocardial Infarction Among HIV-positive Patients in the HAART Era

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Abstract (as submitted)

Background: Concern persists that antiretroviral therapy (ART), particularly protease inhibitors (PI) may increase risk for coronary heart disease (CHD) among HIV+ patients. We previously reported (CROI 2001) no difference in CHD hospitalization rates among HIV+ patients regardless of PI exposure. Now with up to 5.5 years of follow-up (FU), we report updated hospitalization rates for CHD and myocardial infarction (MI). We also report prevalence of classic CHD risk factors.

Methods: Hospital events for CHD (ICD9 410-414, primary discharge diagnosis) including MI were identified among HIV+ males (cases) and among a sample of males not known to be HIV+ (controls). All persons studied were aged 35-64 years and members of the Kaiser Permanente Northern California HMO. FU began 1/1/96 and ended at the earliest of member termination or 6/30/01. For cases, FU in person-years (PY) was assigned by treatment exposure category separately as any ART vs. no ART, and as any PI vs. no PI. In each comparison, cases could contribute PY to both categories. Cases and controls with prior CHD events were excluded. Age-adjusted (1990 US census) CHD and MI event rates were calculated. Risk factors were obtained from electronic medical records.

Results: 4159 cases contributed 14,823 PY of FU (median 4.1); 40K controls contributed 190K PY of FU. There were 72 CHD events (47 MIs) among cases. Age-adjusted CHD rates, pre- vs. post- any ART (5.7 vs. 6.8 events/1000 PY) and pre- vs. post-PI (6.2 vs. 6.7), were similar, as were MI rates pre- vs. post-PI (4.4 vs. 4.3). In cases vs. controls, CHD rates were higher (6.5 vs. 3.8 events / 1000 PY, P=.003) and the difference in MI rates approached significance (4.3 vs. 2.9, P=.07). Differences in proportions with classic CHD risk factors were mixed (cases vs. controls): hyperlipidemia 21% vs. 16%, smoking 19% vs. 10%, hypertension 18% vs. 25%, and diabetes 7% vs. 9%.

Conclusions: After 5.5 years we find no effect of treatment type on CHD or MI hospitalization rates among HMO-enrolled HIV+ men. However, the rates are higher among HIV+ vs. HIV- men. This may be due to chronic infection or to other co-factors not studied here. Longer follow-up is needed and risk reduction management is warranted in all patients with multiple CHD risks.

Background

Since protease inhibitors (PIs) are associated with elevated lipid levels, concern has been expressed about the possible increased risk of coronary heart disease (CHD) associated with their use in the treatment of HIV infection (1,2). Several published case reports have described myocardial infarctions in HIV-infected patients receiving PI therapy (3,4). However, in other studies involving larger numbers of patients (5,6), no increased short-term risk has been found for CHD in HIV-positive patients started on PI therapy compared to HIV-positive patients never started on PI-containing regimens.

In February 2001 we also reported an increased rate of hospitalizations for CHD among male HIV-positive patients compared to a cohort of age-matched males not known to be HIV-positive (6). We theorized that the increased rate of CHD might be a consequence of chronic infection with HIV or other infectious agents.

Aims

- Estimate the CHD (and separately MI) hospitalization rate among HIV-positive Kaiser Permanente of Northern California (KPNC) members, stratifying by exposure to PIs, and separately stratifying by exposure to antiretroviral therapy (ART) in general.
- Compare the estimated rate of CHD (and separately MI) events among all HIV-positive members to that of age- and gender-matched HIV-negative (presumed) controls.
- Continue to evaluate the prevalence of classic CHD risk factors (hypertension, hypercholesterolemia, diabetes, and smoking) among HIV-positive patients and HIV-negative (presumed) controls.

Methods

Study Population and Period of Observation

- HIV-positive members of KPNC were identified from a KPNC-maintained HIV database.
- A presumed HIV-negative control group was generated from the general KPNC membership data system by drawing a 10% random sample of KPNC members age- and sex-matched to HIV-positive cases, and not present in the HIV database.
- To be eligible, cases and controls had to be active KPNC members for ≥12 months prior to the start of follow-up and to have no known history of CHD.
- Follow-up began 1/1/1996 or at HIV diagnosis (for cases), whichever came later, and continued through the earliest of a CHD hospital event, Health Plan termination, death, or 6/30/2001.

Data Collection

- Hospital admissions with a primary discharge diagnosis of CHD (ICD9 codes 410 - 414, includes MI) were extracted from KPNC inpatient data systems and from databases that track any hospitalizations that occur at non-KPNC facilities.
- The medical records of patients with CHD events were reviewed to confirm the event and to assess the presence of risk factors.
- Evidence and dates of PI use were obtained from databases containing prescriptions filled at KPNC pharmacies.
- CHD risk factor data on HIV-positive cases and HIV-negative controls were extracted from the KPNC electronic outpatient diagnosis system.

Analysis

- For HIV-positive cases, person time and CHD hospital events, including MI, were assigned as non-PI or PI depending on whether they occurred before or after first PI use.
- Separately, person time and these same events were assigned as prior to any ART or after any ART.
- The age-adjusted (1990 census) CHD (and MI) hospital event rate and 95% confidence interval (CI) were calculated for all HIV-positive cases (as a whole, and separately for the two PI exposure categories and for the two ART exposure categories), and for the HIV-negative controls.
- Among HIV-positive cases, the PI CHD (and MI) event rate was compared to the non-PI event rate. Also among HIV-positive cases, the ART CHD event rate was compared to the no-ART event rate. Finally, the CHD (and MI) event rate among HIV-positive patients as a whole, was compared to that of the HIV-negative controls.
- HIV-positive cases were compared to HIV-negative controls with respect to the prevalence of each of four CHD risk factors using the Chi-Square test.

Results

Patients

- Overall, for the CHD event analysis, 4159 HIV-positive male cases contributed a total of 14,823 person-years (PY) of observation (median: 4.1, mean: 3.6). Over 25% of cases had the full 5.5 years of follow-up.
- This includes 3858 patients contributing 6793 PY of non-PI observation (median: 1.0, mean: 1.8) and 2633 patients contributing 8030 PY of PI observation (median: 2.8, mean: 2.6).
- 39,877 HIV-negative male controls provided 189,682 PY of observation for the CHD event analysis.

Results cont.

CHD and MI Events

- Among HIV-positive cases, a total of 72 CHD hospital events were identified, including 47 MIs (Table 1).
- Among HIV-negative controls, 700 CHD events were identified, including 526 MIs (Table 1).
- Among HIV-positive cases, the age-adjusted CHD event rate was similar in the PI and non-PI groups, and in the ART and non-ART groups (Table 2). However, the CHD rate among HIV-positive cases overall was significantly higher (by a factor of 1.7) than that of HIV-negative controls (p=.003).
- Among HIV-positive cases, the age-adjusted MI event rate was similar in the PI and non-PI groups (Table 3). The MI rate among HIV-positive cases overall was also higher (by a factor of 1.5) than that of HIV-negative controls, although this difference only approached significance (p=.07).

CHD Risk Factors

- CHD risk factor data were available on 2526 (61%) of HIV-positive patients and 23,541 (59%) of HIV-negative controls.
- The prevalence rates of smoking and hyperlipidemia were higher among HIV-positive cases than among HIV-negative controls, whereas the prevalence rates of hypertension and diabetes were lower among HIV positive cases (Table 4). The clinical significance of these statistically different rates is unclear.
- With the exception of smoking, which may be underreported, the observed prevalences of CHD risk factors among cases and controls were comparable to national estimates (Table 4).
- Risk factors for CHD were common among HIV-positive patients hospitalized for CHD: hypertension (27%), diabetes mellitus (16%), hypercholesterolemia (72%), and current smoker (29%).

Table 1. Distribution of CHD hospitalization diagnoses by HIV status and in HIV-infected patients by PI- and ART-exposure status

Hospitalization Diagnoses	Number of Patients Hospitalized					
	HIV-Positive ¹		Cases vs. Controls		HIV-Positive ¹	HIV-Negative ²
	PI-Exposure No	PI-Exposure Yes	ART-Exposure No	ART-Exposure Yes		
ICD-9 Description						
410 Acute myocardial infarction	19	28	9	38	47	526
411 Other acute and sub-acute forms of ischemic heart disease	1	4	0	5	5	117
412 Old myocardial infarction	0	0	0	0	0	0
413 Angina pectoris	1	0	1	0	1	26
414 Other forms of ischemic heart disease	7	12	3	16	19	31
Total	28	44	13	59	72	700

CHD = coronary heart disease (ICD-9 410-414)
PI = protease inhibitor; ART = antiretroviral therapy
¹ Males, age 35-64, known HIV-positive
² Males, age 35-64, not diagnosed HIV-positive

Table 2. Age-adjusted¹ CHD hospitalization rates by study group

Study Group	Age-adjusted rate (per 1000 person-years)	95% Confidence Interval
All HIV-positive cases ²	6.5 *	(4.7, 8.3)
No PI exposure	6.2	(3.5, 8.9)
PI exposure	6.7	(4.4, 9.1)
No ART exposure	5.7	(2.1, 9.3)
ART exposure	6.8	(4.7, 8.8)
HIV-negative controls ³	3.8 *	(3.5, 4.1)

CHD = coronary heart disease (ICD-9 410-414)
PI = protease inhibitor, ART = antiretroviral therapy
* Difference is significant, p=.003
¹ Adjusted to 1990 United States population
² Males, age 35-64, known HIV-positive
³ Males, age 35-64, not diagnosed HIV-positive

Table 3. Age-adjusted MI hospitalization rates by study group

Study Group	Age-adjusted rate (per 1000 person-years)	95% Confidence Interval
All HIV-positive cases ¹	4.3 *	(2.8, 5.8)
No PI exposure	4.4	(2.0, 6.7)
PI exposure	4.3	(2.4, 6.1)
HIV-negative controls ²	2.9 *	(2.7, 3.2)

MI = myocardial infarction (ICD-9 410)
PI = protease inhibitor
* Difference is not significant, p=.07
¹ Males, age 35-64, known HIV-positive
² Males, age 35-64, not diagnosed HIV-positive

Table 4. Prevalence of Established CHD risk factors by study group

CHD Risk Factors	KPNC Data			U.S. National Data
	HIV-positive Cases ¹ (n=2526)	HIV-negative Controls ² (n=23,5414)	P value (HIV-positive versus HIV-negative)	
Hypertension	18.0%	24.5%	<.0001	24% ³
Hyperlipidemia	21.5%	16.0%	<.0001	17% ³
Diabetes mellitus	7.2%	8.8%	<.002	5% ³
Current smoker	18.8%	9.5%	<.0001	26% ⁴

CHD = coronary heart disease (ICD-9 410-414); KPNC = Kaiser Permanente Medical Care Program of Northern California
¹ Males, age 35-64, known HIV-positive, visited Health Plan in last 12 months of observation period, risk based on outpatient clinical notes
² Males, age 35-64 years, not diagnosed HIV-positive, visited Health Plan in last 12 months of observation period, risk based on outpatient clinical notes
³ Data for men, age 20-74 years, from the NHANES III (1988-94) study of the CDC/NCHS
⁴ Data for men, age 18 and older, from the 1995 National Health Interview Study (NHIS) of the CDC/NCHS

Conclusions

- Neither PI therapy, per se, or ART therapy in general, increase the risk for CHD (or MI) hospitalization among HIV-positive individuals in the relative short term.
- We continue to demonstrate a significantly (p=.003) higher rate of CHD hospitalizations among HIV-positive patients compared to HIV-negative controls (6.5 vs. 3.8 events per 1000 PY).
- We also found a higher (p=.07) rate of MI hospitalizations among HIV-positive patients compared to HIV-negative controls (4.3 vs. 2.9 events per 1000 PY).
- We continue to find that the differences in CHD and MI hospitalization rates between HIV-positive and HIV-negative patients do not appear to be attributable to the moderate and opposing differences in classic risk factors.
- It is postulated that HIV, alone or in conjunction with other infectious agents (7,8), may be implicated in the pathogenesis of CHD.

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