810

Contribution of Immunodeficiency to Coronary Heart Disease: Cohort Study of HIV-infected and HIV-uninfected Kaiser Permanente Members

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1. ABSTRACT

Background: As the prognosis for people living with HIV has improved, greater attention has been directed towards monitoring the long term complications from treatment and infection. Our objective was to evaluate whether coronary heart disease (CHD) rates have approached rates in the general population. **Methods:** We matched adult HIV+ members of Kaiser Permanente (KP) California health plan to HIV- members (1:10 ratio) on age, sex, medical center and year of start of follow-up. We searched hospitalization records to identify members with documented CHD (ICD-9: 410x-411x, 413x-414x). The cohort was followed from first KP enrollment after 1996 until the earliest of CHD event, death, KP disenrollment, or 12/31/2008. CHD rates among HIV+ members stratified by ART use, recent and lowest KP-recorded CD4 were compared to rates among HIV- KP members. Adjusted rate ratios (RRs) for any CHD diagnosis and for MIs were obtained from Poisson regression models adjusting for age, sex, race, tobacco use, alcohol/drug abuse, obesity, diabetes, and use of lipid lowering and hypertension therapy. An additional analysis of only HIV+ individuals examined the effects of ART use, recent HIV RNA, and recent and lowest recorded CD4 on CHD. **Results:** 20,775 HIV+ and 215,158 HIV- members contributed 90,961 and 1,133,444 person-years, respectively. HIV+ had 399 CHD events (447/100,000 py) including 248 MIs. HIV- had 3,463 CHD events (311 cases/100,000 py) including 1,825 MIs, for an adjusted CHD RR of 1.2 (95% CI: 1.1-1.4; p<0.001), and an adjusted MI RR of 1.4 (95% CI: 1.3-1.7; p<0.001). HIV+ patients on ART and CD4>500 had similar CHD risk compared with HIV-. In the HIV+ only model, the only significant HIV-related factor associated with an increased risk of CHD was lowest KP-recorded CD4<=200 (RR=1.3 [95% CI: 1.0-1.6, p=0.022). **Conclusions:** Adjusting for traditional risk factors, HIV+ individuals have a statistically significant increased risk for cardiovascular complications. However this association is not seen for patients with relatively preserved CD4, possibly supporting earlier initiation of ART.

2. BACKGROUND / OBJECTIVES

- Limited data regarding independent effect of HIV immunodeficiency on risk of coronary heart disease (CHD)
- Objectives were:
  1. To determine whether HIV+ subjects have increased risk of CHD compared with HIV- subjects that is independent of traditional CHD risk factors
  2. To assess whether CHD risk varies by CD4 among HIV+

3. METHODS

- **Setting:** Kaiser Permanente (KP), integrated CA health systems
- **Study design and population**
  - Cohort study, 1996-2008
  - HIV+ and HIV- matched by age, sex, year, medical center
- **Data sources:** KP HIV registries, clinical databases
- **Outcome:**
  - CHD: ICD-9 410x-411x, 413x-414x
  - Myocardial infarction (MI): ICD-9 410x
- **Analysis**
  - Followed until event, left health plan, death, or 12/31/08
  - HIV-infected follow-up split into 6-month intervals with recent/lowest recorded CD4 measured at start of interval
  - Rate ratios (RR) from Poisson models adjusting for CHD risk factors; HIV+ model also evaluated HIV-related factors

4. RESULTS

Baseline characteristics

Parameter	HIV+	HIV-
N	20,775	215,158
Baseline year, %		
1996-1999	29	30
2000-2003	41	40
2004-2008	31	30
Mean age	41	40
Race/ethnicity (% among known)		
White	55	46
Black	19	12
Hispanic	22	27
Other	5	16
Unknown race/ethnicity, %	6	43
Ever smoking, %	43	28
Ever alcohol/drug abuse, %	20	8
Ever obese/overweight, %	38	42
Diabetic, %	3	3
Medication use, %		
Anti-hypertension	13	11
Lipid-lowering	5	4
Antiretrovirals	47	n/a
HIV risk group (% among known)		n/a
Men who have sex with men	75	
Injection drug use	7	
Other	18	
Unknown risk group, %	21	
Mean years known HIV+	3.5	n/a
Mean CD4, cells/μl	400	n/a
Mean log HIV RNA, cp/ml	4.7	n/a

CHD Incidence rates

	HIV-infected			HIV-uninfected		
	N	PY	Rate[1]	N	PY	Rate[1]
CHD	399	89,190	447	3,463	1,114,169	311
MI	248	89,875	276	1,825	1,124,405	162

PY, person-years
[1] cases per 100,000 person-years

5. RESULTS (CONT)

Rate ratios of CHD by HIV status

	Unadjusted			Adjusted[1]		
	RR	(95% CI)	P	RR	(95% CI)	P
CHD	1.4	(1.3-1.6)	<0.001	1.2	(1.1-1.4)	<0.001
MI	1.7	(1.5-1.9)	<0.001	1.4	(1.3-1.7)	<0.001

CHD, Coronary heart disease; MI, myocardial infarction; RR, rate ratio
[1] Adjusted for age, sex, race, tobacco use, alcohol/drug abuse, obesity, diabetes, and use of lipid-lowering and anti-hypertensive therapy

Rate ratios of CHD by HIV status, ART use and CD4

		Recent CD4[1]			Lowest recorded CD4[1]		
		RR	(95% CI)	P	RR	(95% CI)	P
HIV+, ART+	CD4 ≥ 500	0.9	(0.8, 1.1)	0.38	0.8	(0.5, 1.3)	0.40
	CD4 201-499	1.4	(1.2, 1.6)	< 0.001	1.0	(0.8, 1.2)	0.82
	CD4 ≤ 200	1.7	(1.3, 2.2)	< 0.001	1.4	(1.3, 1.7)	< 0.001
HIV+, ART-	CD4 ≥ 500	1.3	(0.9, 1.9)	0.19	1.2	(0.7, 2.0)	0.51
	CD4 201-499	1.1	(0.7, 1.6)	0.75	1.3	(0.9, 1.9)	0.14
	CD4 ≤ 200	1.5	(0.7, 3.4)	0.29	1.0	(0.5, 2.0)	0.93
HIV- (reference)	*All RRs presented compare rates in HIV+ (within ART/CD4 category) with overall rate for HIV-uninfected subjects*						

ART, antiretroviral therapy; RR, rate ratio
[1] Adjusted for age, sex, race, tobacco use, alcohol/drug abuse, obesity, diabetes, and use of lipid-lowering and anti-hypertensive therapy. The following factors were time-varying in the analysis: ART, CD4, age, diabetes, lipid-lowering therapy, anti-hypertensive therapy; remaining factors were fixed variables.

Rate ratios of MI by HIV status, ART use and CD4

		Recent CD4[1]			Lowest recorded CD4[1]		
		RR	(95% CI)	P	RR	(95% CI)	P
HIV+, ART+	CD4 ≥ 500	1.1	(0.9, 1.5)	0.29	0.9	(0.5, 1.6)	0.67
	CD4 201-499	1.6	(1.3, 2.0)	< 0.001	1.2	(0.9, 1.5)	0.13
	CD4 ≤ 200	1.9	(1.4, 2.6)	< 0.001	1.8	(1.5, 2.1)	< 0.001
HIV+, ART-	CD4 ≥ 500	1.5	(0.9, 2.5)	0.08	1.0	(0.5, 2.1)	0.93
	CD4 201-499	1.2	(0.7, 2.1)	0.46	1.7	(1.1, 2.5)	0.016
	CD4 ≤ 200	0.8	(0.2, 3.4)	0.82	0.7	(0.2, 2.1)	0.52
HIV- (reference)	*All RRs presented compare rates in HIV+ (within ART/CD4 category) with overall rate for HIV-uninfected subjects*						

ART, antiretroviral therapy; RR, rate ratio
[1] Adjusted for age, sex, race, tobacco use, alcohol/drug abuse, obesity, diabetes, and use of lipid-lowering and anti-hypertensive therapy. The following factors were time-varying in the analysis: ART, CD4, age, diabetes, lipid-lowering therapy, anti-hypertensive therapy; remaining factors were fixed variables.

6. RESULTS (CONT)

Adjusted rate ratios of CHD among HIV-infected patients

Variable	RR[1]	(95% CI)	P
Antiretroviral therapy use	1.0	(0.7, 1.4)	0.92
Recent CD4≤200 vs. >200	1.2	(0.9, 1.6)	0.26
Lowest CD4≤200 vs. >200	1.3	(1.0, 1.6)	0.022
HIV RNA≥500 vs. <500	1.1	(0.9, 1.4)	0.51
Injection drug use vs. MSM	0.7	(0.4, 1.2)	0.18
Heter/other risk vs. MSM	1.1	(0.8, 1.6)	0.44
Unknown risk vs. MSM	1.0	(0.8, 1.3)	0.87
>10 yrs vs. <5 yrs HIV+	0.8	(0.7, 1.1)	0.19
5-9 yrs vs. <5 yrs HIV+	1.0	(0.8, 1.3)	0.98
Age 65+ vs. 18-39	12.3	(7.2, 20.8)	<0.001
Age 50-64 vs. 18-39	6.4	(4.0, 10.4)	<0.001
Age 40-49 vs. 18-39	2.7	(1.7, 4.4)	<0.001
Female sex	0.4	(0.2, 0.8)	0.004
Black vs. White	0.7	(0.5, 0.9)	0.021
Hispanic vs. White	0.7	(0.5, 1.0)	0.046
Other vs. White	1.1	(0.3, 4.5)	0.87
Ever tobacco use	1.9	(1.5, 2.4)	<0.001
Ever alcohol or drug abuse	1.3	(1.0, 1.6)	0.036
Ever overweight/obese	0.9	(0.7, 1.1)	0.23
Diabetes	1.5	(1.2, 2.0)	0.001
Anti-hypertensive therapy	1.9	(1.5, 2.3)	<0.001
Lipid-lowering therapy	1.9	(1.5, 2.4)	<0.001

MSM, men who have sex with men; RR, rate ratio
[1] Adjusted for all variables in Table. The following factors were time-varying in the analysis: ART, CD4, HIV RNA, Years HIV+, age, diabetes, lipid-lowering therapy, anti-hypertensive therapy; remaining factors were fixed variables.

7. STRENGHTS/LIMITATIONS

Strengths
- HIV+ and HIV- from same health system
- Large and population-based
- Adjustment for traditional CHD risk factors

Limitations
- Less generalizability to women, uninsured, racial/ethnic minorities
- Incomplete measurement of some risk factors
- No data on family history
- Less power for evaluating risk in untreated HIV

8. SUMMARY

- HIV infection confers higher independent risk of CHD
- HIV+ patients on ART and CD4>500 (recent or lowest) had similar CHD risk compared with HIV- individuals
- Lowest recorded CD4<200 (but not recent CD4, recent HIV RNA, any ART, HIV risk group) conferred independent increased risk of CHD in HIV+ patients

9. CONCLUSION

HIV-infected patients have a significant increased risk for cardiovascular complications. However, this association is not seen for treated patients with relatively preserved immune function. These findings support earlier initiation of antiretroviral therapy and aggressive risk factor management.

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