

ABSTRACT

Background: The risk of developing ischemic cardiovascular disease (CHD) is increasingly being evaluated in persons with HIV infection. There are few prospective data available on the risk of ischemic CHD in persons with HIV infection.

Objectives: To determine the risk of ischemic CHD in HIV-infected persons taking different antiretroviral regimens.

Methods: We prospectively collected fasting blood samples from HIV-infected persons taking different antiretroviral regimens; treatment naïve HIV-infected persons; and negative controls for cross-sectional analysis. Samples were tested for cholesterol, LDL, Triglycerides (TG), HDL, Lp(a), homocysteine, and fibrinogen. LDL was calculated unless the TG was > 400 and then was directly measured. Information was collected about ischemic CHD risk factors including: cigarette smoking, hypertension, a family history of premature CHD, exercise, diabetes mellitus and other cardiovascular disease risk equivalents. Body mass index and blood pressure were collected. The ATP3 Framingham score was used to measure cardiovascular risk.

Results: 111 (125) HIV-infected persons and 25 (49) controls were evaluated. The median age of the HIV+ cohort 41 years; 89% were male. The median CD4 count was 423 (284) cells/mm³ and 51% of antiretroviral treated subjects had undetectable viral loads. The median age of the HIV negative cohort was 39 (36) years; 40% (47%) were male. The median risk for progression of CHD in 10 years was 4% (range, <1%->30%) in the HIV infected cohort and was 1% (range, <1%-20%) in the HIV negative cohort (P<0.05). In the HIV-infected cohort, the median risk for progression of CHD in 10 years was 6% (range, <1%-30%) in PI treated subjects versus 3% (range, <1%-25%) in those not treated with PIs (P<0.02). 22% of the HIV infected cohort had a >10% risk for progression of CHD in the next 10 years indicating the need for risk reduction interventions.

Conclusions: There is a significant prevalence of risk for the progression of ischemic cardiovascular disease in persons with HIV infection.

Cardiovascular risk should be assessed in all persons with HIV infection and risk reduction efforts should be aggressively pursued. Longitudinal studies are needed to assess the change in cardiovascular risk over time.

INTRODUCTION

- There is concern about the risk for ischemic cardiovascular disease in persons with HIV infection.
- There have been published reports of myocardial infarctions in persons with HIV infection.
- Several metabolic complications (e.g., insulin resistance, hyperlipidemia) associated with the use of antiretroviral agents are likely to increase the risk for developing coronary atherosclerosis.
- There is a paucity of prospective information on the estimated risk for developing ischemic cardiovascular disease in persons with HIV infection.
- The objective of this study was to prospectively evaluate the risk for ischemic cardiovascular disease in HIV-infected persons based upon published validated measures used in HIV seronegative adults.

STUDY DESIGN

- Prospective evaluation of a convenience sample of HIV-infected persons attending a University-based Infectious Diseases Clinic in the United States.
- Prospective evaluation of HIV uninfected controls.
- Collection of medical history of risk for coronary artery disease including family history of premature heart disease, hypertension, diabetes mellitus, and cigarette smoking status.
- Collection of antiretroviral medication use history, prior opportunistic illnesses, and CD4+ lymphocyte count and plasma HIV RNA values at the time of enrollment.
- Subjects were excluded if they had a prior history of coronary artery disease, cerebrovascular disease, and peripheral vascular disease or were actively using lipid-lowering agents.
- Cardiovascular risk was estimated using the Framingham Point Scoring System (Age, Total cholesterol, Smoking status, High density lipoprotein and Systolic blood pressure) that provides a 10-Year Risk Percentage.
- Major risk factors for Heart Disease include: cigarette smoking, hypertension, low HDL cholesterol, family history of premature cardiovascular disease and older age.

METHODS

- 8-12h fasting lipids – LRC-validated enzymatic method.
- LDL was calculated. If the TG was >400 mg/dL then the LDL was directly measured using an enzymatic method.
- HDL – Direct enzymatic colorimetric assay.
- Triglycerides – Spectrophotometry.
- Glucose – Colorimetric hexokinase assay.
- Fibrinogen – Photo-optical clotting technique.
- Total L-homocysteine - IMx assay based on fluorescence polarization immunoassay (FPIA).
- Lipoprotein (a) – Immunoturbidimetric measurement.
- C-reactive protein – Nephelometry.

Laboratory Test	Normal Values
Total Cholesterol (TC)	0-200 mg/dL
Low density lipoprotein (LDL)	0-100 mg/dL
High density lipoprotein (HDL)	40-99 mg/dL
Triglyceride (TG)	0-150 mg/dL
Glucose	70-105 mg/dL
Fibrinogen	224-412 mg/dL
Homocysteine	5-15 umol/L
Lp(a)	0-35 mg/dL
C-reactive protein (CRP)	0- 2.5 mg/L

Table 1 – Baseline characteristics

	<i>HIV+</i>	<i>HIV-</i>	<i>P value</i>
Median age	41 years	36 years	0.008
Gender			
Male	112 (90%)	23 (47%)	<0.001
Female	13 (10%)	26 (53%)	
Ethnicity/Race			
White	81 (65%)	37 (76%)	<0.001
African-American	44 (35%)	7 (14%)	
Other	-	5 (10%)	
Premature heart disease in family	40 (32%)	11 (22%)	0.21
Hypertension	41 (33%)	11 (22%)	0.18
Cigarette smoking			
Current	43 (34%)	9 (18%)	<0.001
Prior	52 (42%)	6 (12%)	
Diabetes mellitus	4 (3%)	0	0.21
Median Body mass index	23.9 kg/m ²	27.2 kg/m ²	<0.001
Median CD4+ lymphocytes	284 cells/mm ³	-	
Median HIV RNA level	< 400 copies/mL	-	

Table 2 – Laboratory and other values*

	<i>Male</i>			<i>Female</i>		
	<i>HIV+</i>	<i>HIV-</i>	<i>P</i>	<i>HIV+</i>	<i>HIV-</i>	<i>P</i>
Age (yrs)	41.5	30	<0.001	33	39	0.08
TC (mg/dL)	201	188	0.15	212	194	0.38
HDL (mg/dL)	39	45	0.005	51	57	0.16
LDL (mg/dL)	115	118	0.92	108	127	0.38
TG (mg/dL)	189	105	<0.001	278	84	0.002
Glucose (mg/dL)	89	84	0.07	89	87	0.91
Lp(a) (mg/dL)	17	16	0.18	21	16	0.44
CRP	0.4	0.33	0.55	0.4	0.8	0.07
HCY (umol/dL)	9.6	9.8	0.52	7.2	7.0	0.98
Fibrinogen(mg/dL)	299	248	0.005	304	345	0.22
Risk factors	2.0	1.0	<0.001	1.0	1.0	0.64
10 yr CVD risk	5.0%	<1%	<0.001	<1%	<1%	0.86

*Values represent medians.

Table 3 – *Comparison of HIV-infected persons on protease inhibitor containing regimens versus other HIV-infected subjects.

	PI regimen	Non-PI regimen/naïve	P-value
N	84 (68%)	40 (32%)	-
TC	203 mg/dL	197 mg/dL	0.46
HDL	36 mg/dL	44 mg/dL	0.03
LDL	115 mg/dL	115 mg/dL	0.60
TG	200 mg/dL	188 mg/dL	0.41
Glucose	90 mg/dL	87 mg/dL	0.55
Fibrinogen	337	267	<0.001
CD4+ count	344 cells	490 cells	0.02
HIV RNA level	< 400	< 400	0.78
Risk factors	2	2	0.15
10 yr CVD risk	6.0%	3.0%	0.02

***There were no significant differences in homocysteine levels, CRP levels, Lp(a) levels, cigarette smoking rates, gender, and ethnicity/race or family history of premature heart disease. All values in the table represent median values.**

Table 4 – Comparison of CVD risk by regimen

	Lopinavir/r	Nelfinavir	P-value
N	18	16	-
10 year risk	3.5%	5.5%	0.54
	Lopinavir/r	Efavirenz	
N	18	20	-
10 year risk	3.5%	3.0%	0.54
	Lopinavir/r	Indinavir	
N	18	19	-
10 year risk	3.5%	6.0%	0.27
	Indinavir	Nelfinavir	
N	19	16	-
10 year risk	6.0%	5.5%	0.63
	Indinavir	Efavirenz	
N	19	20	-
10 year risk	6.0%	3.0%	0.04
	Nelfinavir	Efavirenz	
N	16	20	-
10 year risk	5.5%	3.0%	0.15

***Values represent medians**

RISK FACTOR ASSESSMENT

- **25% of HIV negative controls had 2 or more major risk factors for ischemic cardiovascular disease.**
- **Only 6% of HIV negative controls had > 10% risk of cardiovascular disease by Framingham point scores.**
- **58% of HIV-infected patients had 2 or more major risk factors for ischemic cardiovascular disease.**
- **26% of HIV-infected patients had > 10% risk of cardiovascular disease by Framingham point scores.**
- **18% of HIV-infected patients met criteria for the “metabolic syndrome” even in the absence of waist measurements.**
- **Multivariate analysis of factors (cigarette smoking, hypertension, family history, protease inhibitor use, NRTI duration of exposure, NNRTI duration of exposure, PI duration of exposure, HIV RNA level and CD4+ count) found that only a higher CD4+ lymphocyte count was independently associated with a lower risk of ischemic cardiovascular disease (OR=0.998, 95% CI, 0.997-0.999, P=0.003). Thus, for every 100-cell decline in CD4+ lymphocyte count there is a corresponding 20% increase in cardiovascular risk.**

SUMMARY

- **The risk for ischemic cardiovascular disease was greater in HIV+ versus HIV- men.**
- **The prevalence of cigarette smoking was higher in HIV+ persons compared to HIV- controls.**
- **Triglyceride and fibrinogen levels were generally higher, whereas HDL levels were generally lower in HIV+ persons compared to HIV- controls (mostly men).**
- **The risk for ischemic cardiovascular disease was greater in HIV+ persons taking protease inhibitor-based regimens compared to treatment naïve persons and those taking NNRTI-based regimens.**
- **Over half of all HIV+ persons had 2 or more major risk factors for ischemic cardiovascular disease.**
- **Approximately one-quarter of HIV+ persons had high enough risk to merit intervention by ATP 3 guidelines.**
- **18% of HIV+ persons met criteria for the “metabolic syndrome” that carries an extremely high risk for developing ischemic cardiovascular disease.**

CONCLUSIONS

- **Dyslipidemia is a common problem in HIV+ persons.**
- **Major risk factors for ischemic cardiovascular disease are common in persons with HIV infection.**
- **Some of these risk factors are modifiable (cigarette smoking, hypertension) and should be aggressively treated.**
- **The risk for ischemic cardiovascular disease appears to be higher in persons with HIV infection and particularly in those taking protease inhibitors.**
- **Larger, prospective longitudinal studies are needed to determine changes in ischemic heart disease risk over time and whether specific regimens present a greater risk.**
- **The use of proven life-saving antiretroviral regimens should continue in persons with advanced HIV infection despite concerns over the potential risk for ischemic cardiovascular disease until safer, effective regimens are developed.**