

Risk of Cardiovascular Disease in HIV-infected Adults with Immune Reconstitution

P. Williams¹, J. Wu¹, S. Cohn², S. Koletar³, A. McCutchan⁴, R. Murphy⁵, and J. Currier⁶ for the ACTG 362 Team

¹Harvard Sch of Publ Hlth, Boston, MA, USA; ²Univ of Rochester Med Ctr, NY, USA; ³Ohio State Univ, Columbus, USA; ⁴Univ of California, San Diego, USA; ⁵Northwestern Univ, Chicago, IL, USA; and ⁶Univ of California, Los Angeles, USA

Paige Williams, Ph.D.
Harvard School of Public Health
Center for Biostatistics in AIDS Research
655 Huntington Avenue
Boston, MA 02115
Tel: (617) 432-3872
Fax: (617) 432-2832
Email: paige@dsdc.harvard.edu



ABSTRACT

Background: Risk of atherosclerosis among AIDS patients with a history of severe immunosuppression and long-term antiretroviral treatment is not well documented.

Methods: This study examined the actual and predicted incidence of verified CVD in 643 subjects with HAART-induced immune reconstitution. We sustained increase in CD4 cells from <50 to >100 cells/mm³ who were enrolled between 1997-1999 in a multicenter randomized study of stopping zidovudine prophylaxis for MAC disease. In 1999, 433 subjects agreed to remain in long term observational follow-up for evaluating risks of CVD and metabolic syndrome. Coronary heart disease (CHD) risk factors and lipid profiles were collected at entry to observational follow-up and every 32 weeks thereafter.

Incidence rates (IRs) and 95% confidence intervals (CIs) for CVD were calculated by calendar year and overall based on the Poisson distribution. Estimates of 10-year CHD risk were based on Framingham scoring, and compared between groups using Wilcoxon ranksum tests. Cox proportional hazard models were used to evaluate risk factors for development of CVD, both among all subjects using baseline values, and among the 433 long-term subjects using CVD risk factors.

Results: Median follow-up was 4.8 and 5.6 years, and median treatment with HAART was 5.6 and 6.3 years (max=8.8 years) for the 643 original and 433 long-term subjects, respectively. CVD developed in 18/643 (IR=7.2 per 1000 person years, 95% CI: 4.3-11.3), with no significant increase over calendar time (p=0.19). These 18 subjects experienced 20 atherosclerotic CVD events, including 10 myocardial infarctions and 3 with symptomatic CHD. Those randomized to zidovudine had a marginally significant decrease in risk of CVD (HR=0.45, p=0.099). Of the 433 long-term subjects, metabolic syndrome (defined by NCEP ATP III criteria) was observed in 89 (21%). Framingham scoring predicted 10% of subjects to have >20% 10-year CHD risk, with significantly higher predicted risk for males (p<0.03) and marginal association with observed CVD (p=0.087). For the long-term subjects, a multivariate Cox model indicated significant increases in the risk of CVD for those with higher BMI (HR=1.18, p=0.003), increased age (HR=1.08, p=0.006), and total cholesterol (HR=1.007, p=0.015).

Conclusions: These findings suggest a higher rate of CVD than has been previously reported from cohorts with shorter durations of follow-up. Interventions targeted to those at increased risk for CVD are warranted in patients receiving HAART.

BACKGROUND

There is growing concern that the metabolic complications associated with HIV and antiretroviral therapy (ART) may lead to accelerated cardiovascular disease (CVD). In particular, patients infected with HIV may present with premature atherosclerosis^{1,2} and with metabolic abnormalities³. Genetic variants of chemokines may influence progression of HIV disease and atherosclerosis⁴, and cardiovascular risk factors may also be associated with antiretroviral therapy^{5,6}. However, the risk of atherosclerosis among AIDS patients with a history of severe immunosuppression and long-term antiretroviral treatment is not well documented. We examined actual and predicted incidence of cardiovascular disease among 643 subjects enrolled in ACTG 362.

ACTG 362 enrolled subjects with HAART-induced immune reconstitution (a sustained increase in CD4 cells from <50 to >100 cells/mm³) to evaluate whether prophylaxis for MAC could be discontinued. Subjects were randomized in a 1:1 ratio to receive either zidovudine (continue MAC prophylaxis) or placebo. After a median of 16 months of follow-up, only 2 MAC endpoints were observed and randomized study treatment was discontinued in October 1999.

At that time, 433 of the 643 subjects (77% of those still on study) agreed to continue observational follow-up under a new protocol version, for the primary objectives of evaluating cardiovascular disease and metabolic complications.

OBJECTIVES

To examine the development of verified atherosclerotic CVD in 643 subjects with HAART-induced immune reconstitution, to evaluate predicted incidence of CHD in 433 of these subjects who participated in observational follow-up using models developed from the Framingham Heart Study, to evaluate prevalence of metabolic syndrome, and to evaluate incidence of hypercholesterolemia in this study population.

METHODS

Data Collection and CVD Event Verification

At entry to the ACTG 362 observational follow-up initiated in 1999, subjects reported height, weight, family history of cardiovascular events and/or deaths, history of hypertension and/or diabetes, and smoking status. In addition, lipid measures (including total cholesterol, LDL, and triglycerides), waist-hip measurements, weight, new diabetes diagnosis, and blood pressures were collected at entry to observational follow-up and every 32 weeks thereafter.

Cardiovascular events reported from the onset of the parent study, which opened in 1997, were reviewed and verified by the study chair as atherosclerotic CVD, non-atherosclerotic CVD, or not a CVD event. In this analysis, we focus only on those events reported as atherosclerotic CVD.

Definitions and Statistical Methods

- Incidence rates (IRs) and 95% confidence intervals (CIs) for CVD were calculated by calendar year and overall based on the Poisson distribution.
- Cox proportional hazard models were used to evaluate risk factors for development of CVD, both among all subjects using entry characteristics (Tables 1 & 2) and among the 433 long-term subjects using entry and CVD risk factors (Tables 1, 2, 4, 5).
- Estimates of 10-year CHD risk were based on Framingham scoring, as reflected by published scoring systems (NCEP ATP III⁷). This approach uses age, sex, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, treatment for hypertension, and diabetes history to define risk scores and corresponding 10-year CHD risk estimates. Estimated CHD risks were compared between groups using Wilcoxon ranksum tests.
- Metabolic syndrome was defined using NCEP ATP III criteria of having at least 3 of the following: fasting triglycerides>150mg/dL, waist circumference >102cm (male) or 88cm (female), BP ≥ 130/85, fasting glucose≥110, and HDL<40 (male) or <50 (female).
- Incidence of hypercholesterolemia was defined as total cholesterol ≥240mg/dL among subjects without hypercholesterolemia at entry to long-term observation.

RESULTS

Table 1: Demographic Characteristics of Study Participants at Study Entry

	Total (N=643)	Long Term Observation (N=433)
Gender		
Male	560 (87%)	386 (89%)
Female	83 (13%)	47 (11%)
Age in years		
Median	40	40
Over 55	41 (6%)	32 (7%)
Race/Ethnicity		
White	370 (58%)	273 (63%)
Black	131 (20%)	80 (19%)
Hispanic	117 (18%)	63 (15%)
Other	25 (4%)	17 (4%)
Previous/Current HIV Drug History		
Yes	89 (16%)	62 (14%)

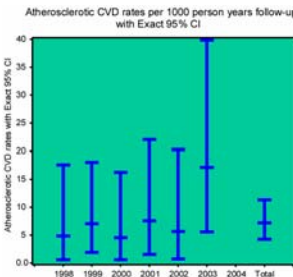
Table 2: Health Characteristics of Study Participants

	Total (N=643)	Long Term Observation (N=433)
Randomized Treatment Assignment		
Zidovudine	322 (50%)	227 (52%)
Placebo	321 (50%)	206 (48%)
Entry CD4 count (cells/mm³)		
Median	226	229
<200	240 (37%)	154 (36%)
200-299	208 (32%)	147 (34%)
300+	195 (31%)	132 (30%)
Entry HIV-1 Viral Load (copies/ml)		
500 copies or less	407 (63%)	279 (64%)
500-20,000	110 (17%)	71 (16%)
20,000+	96 (15%)	64 (15%)
Unknown/Missing	30 (5%)	19 (4%)
Lowest pre-entry CD4 (cells/mm³)		
Median	20	21
<200	10	10
200-299	4	4
300+	6	6
Duration on HAART at entry (weeks)		
Median	40	40

Observed CVD Events

A total of 18 of the 643 subjects developed atherosclerotic CVD (IR=7.2 per 1000 person years, 95% CI: 4.3-11.3). These 18 subjects experienced 20 atherosclerotic CVD events, including 10 myocardial infarctions and 3 with symptomatic CHD.

Figure 1: Yearly Incidence Rates of Atherosclerotic CVD



Based on a Poisson regression model, there was no significant trend over time in atherosclerotic CVD (p=0.19). However, the slight increase in 2003 may warrant future examination of such trends.

RESULTS

Table 3: Multivariate Cox Model for Predicting Incidence of CVD

Using both forward and backwards selection approaches for final multivariate Cox proportional hazards model, the predictors below were identified as having a significant association with time to first CVD event among the 433 long term observation subjects. For example, a subject with total cholesterol>240 would have a 32% higher risk of CVD than one with cholesterol=200.

Predictor	Hazard Ratio	95% confidence interval	p-value
Age (years)	1.082	(1.022-1.147)	0.006
Body Mass Index	1.190	(1.099-1.335)	0.005
Total Cholesterol	1.007	(1.001-1.013)	0.015

Among all 643 subjects, randomization to zidovudine had a marginally protective effect (HR=0.45, p=0.099), but this effect did not persist when adjusted for age.

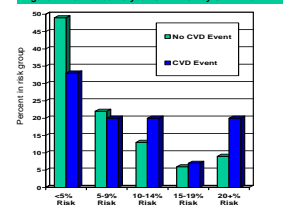
Table 4: Risk Factors for Cardiovascular Disease

	Long Term Observation (N=433)
Age Group (years)	
20-39	136 (31%)
40-49	208 (48%)
50-59	63 (15%)
60+	26 (6%)
Current Smoker	136 (31%)
History of Diabetes	39 (9%)
History of Hypertension	73 (17%)
Systolic Blood Pressure, mmHg	
<120	136 (31%)
120-129	71 (16%)
130-139	67 (15%)
140-159	63 (15%)
160+	3 (1%)
Missing/Unknown	93 (21%)
Family History of CVD (male or M)	
CVD event (maternal or paternal)	79 (18%)
CVD death (maternal or paternal)	33 (8%)
CVD event or death	85 (20%)
Body Mass Index (kg/m²)	
<25	220 (51%)
25-30	160 (37%)
30+	48 (11%)
Missing/Unknown	5 (1%)
Waist:Hip Ratio	
<0.90	79 (18%)
0.90-0.95	129 (30%)
0.95-1.00	134 (31%)
1.00+	89 (21%)
Missing/Unknown	2 (<1%)

Table 5: Lipid Profiles

	Total (N=643)
Total Cholesterol, mg/dL	
Median	211
<160	55 (9%)
160-199	106 (24%)
200-239	134 (31%)
240-279	78 (17%)
280+	41 (9%)
Unknown/Missing	24 (6%)
HDL Cholesterol, mg/dL	
Median	37
<40	237 (55%)
40-49	93 (21%)
50-59	38 (9%)
60+	25 (6%)
Unknown/Missing	40 (9%)
Fasting Triglycerides, mg/dL	
Median	234
<100	41 (9%)
100-200	91 (21%)
200-400	88 (23%)
400+	70 (16%)
Unknown/Missing	133 (31%)

Figure 2: Estimated 10-year CHD Risk by CVD Event



Overall, 10% of subjects were estimated to have 20% or greater risk of CHD within the next 10 years, and 29% of subjects were estimated to have 10% or greater 10-year CHD risk. There was a marginally significant difference between predicted risk for those with an observed CVD event versus those without (p=0.087); however, over 50% of those with CVD events were predicted to have low (<10%) 10-year CHD risk. In addition, all but one male (98%) had low estimated 10-year CHD risk, as compared to 6% of males (p<0.001).

Prevalence of Metabolic Syndrome

Overall, metabolic syndrome was prevalent in 89 of 433 subjects (21%), with a significantly higher prevalence among females than males (38% vs 18%, p<0.003).

Incidence of Hypercholesterolemia

At entry to the long-term observation phase, 114 of 409 subjects with cholesterol data (28%) had prevalent hypercholesterolemia. Among the 279 without prevalent hypercholesterolemia and with follow-up cholesterol measurements, 97 (35%) developed hypercholesterolemia, for an incidence rate of 14.4 cases per 1000 person-years (95% CI: 11.7-17.6).

SUMMARY

During long-term follow-up of 643 subjects with immune restoration over a median of 4.8 years, the overall incidence of atherosclerotic CVD was 7.2 events per 1000 person years (95% CI: 4.3-11.3). This rate was slightly higher than has been reported in other studies, including the D:A:D study⁸, which reported a rate of 3.5 events per 1000 person-years overall and 5.5 per 1000 person-years among those with more than 5 years HAART exposure, and the Kaiser study⁹, which reported a rate of 6.6 events per 1000 person-years.

The subjects that developed CVD did not all present with traditional CHD risk factors; over half were estimated to have low risk (<10%) of a CHD event over the next 10 years based on Framingham scoring using such risk factors. However, in a subset of 433 subjects followed for long-term observation, prevalence of such CHD risk factors was high (26% with total cholesterol ≥240 mg/dL, 11% with BMI ≥ 30, 9% with history of diabetes, 17% with history of hypertension, and 20% with family history of CVD event or death). In addition, the prevalence of metabolic syndrome was 21% (38% in females), and the incidence of hypercholesterolemia was 14.4 events/1000 person years (95% CI: 11.7-17.6), suggesting that this group of subjects with long term exposure to HAART (median=5.3 yrs) warrants future monitoring for cardiovascular complications and events.

CONCLUSIONS

These findings suggest a higher rate of CHD than has been previously reported from cohorts with shorter durations of HAART therapy. Interventions targeted to those at increased risk for CVD are warranted in patients receiving HAART.

REFERENCES

- Maggi P, Serio G, Eplandi G, et al. Premature lesions of the carotid vessels in HIV-4-infected patients treated with protease inhibitors. *AIDS* 2000; 14:F123-F128.
- DePaïron M, Chessex S, Sudre P, et al. Premature atherosclerosis in HIV-infected individuals: focus on protease inhibitor therapy. *AIDS* 2001; 15:329-334.
- Hadigan C, Meigs JB, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus and lipodystrophy. *Clin Infect Dis* 2001; 32:130-139.
- Alonso-Villaverde C, Blai C, Parra S, et al. Atherosclerosis in patients infected with HIV is influenced by a mutant monocyte chemoattractant protein-1 allele. *Circulation* 2004; 220A-2209.
- Fris-Møller N, Sabin CA, Weber R, et al. Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; 349(21):1933-3030.
- National Cholesterol Education Program (NCEP). Third report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication No. 01-3670.
- Klein D, Hurley LB, Quesenberry CP Jr, et al. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? *J Acquir Immune Defic Syndr* 2002; 30:474-477.

ACKNOWLEDGMENTS

Supported in part by the Adult AIDS Clinical Trials Group funded by the National Institutes of Health and Infectious Diseases, National Institutes of Health, U01 AI05855. Thanks to Peter Bohlin for his graphics assistance.