Progression of Atherosclerosis as Assessed by Carotid Intima-Media Thickness in Patients With HIV Infection

Priscilla Y. Hsue, MD; Joan C. Lo, MD; Arlana Franklin, RDMS; Ann F. Bolger, MD; Jeffrey N. Martin, MD; Steven G. Deeks, MD; David D. Waters, MD

Background—HIV-infected patients may be at increased risk for coronary events. The purpose of this study was to identify predictors of carotid intima-media thickness (IMT) in HIV patients at baseline and to measure IMT progression over 1 year.

Methods and Results—We measured blood lipids, inflammatory markers, and IMT in 148 HIV-infected adults (mean age, 45±8 years) and in 63 age- and sex-matched HIV-uninfected control subjects. The mean duration of HIV infection was 11 years, and the median duration of protease inhibitor treatment was 3.3 years. Mean baseline IMT was 0.91±0.33 mm in HIV patients and 0.74±0.17 mm in control subjects ($P=0.0001$). Multivariable predictors of baseline IMT in HIV patients were age ($P<0.001$), LDL cholesterol ($P<0.001$), cigarette pack-years ($P=0.005$), Latino race ($P=0.062$), and hypertension ($P=0.074$). When the control group was added to the analysis, HIV infection was an independent predictor of IMT ($P=0.001$). The rate of progression among the 121 HIV patients with a repeated IMT measurement at 1 year was 0.074±0.13 mm, compared with −0.006±0.05 mm in 27 control subjects ($P=0.002$). Age ($P<0.001$), Latino race ($P=0.02$), and nadir CD4 count ≤200 ($P=0.082$) were multivariable predictors of IMT progression.

Conclusions—Carotid IMT is higher in HIV patients than in age-matched control subjects and progresses much more rapidly than previously reported rates in non-HIV cohorts. In HIV patients, carotid IMT is associated with classic coronary risk factors and with nadir CD4 count ≤200, suggesting that immunodeficiency and traditional coronary risk factors may contribute to atherosclerosis. **(*Circulation*. 2004;109:1603-1608.)**

Key Words: AIDS ■ atherosclerosis ■ carotid arteries ■ risk factors

At the end of 2003, an estimated 40 million people were infected with HIV worldwide, and ≈40 000 new cases of HIV were occurring each year in the United States.[1] The introduction of highly active antiretroviral therapy (HAART) in the mid- to late 1990s dramatically reduced HIV-associated morbidity and mortality.[2,3] For example, among patients with HIV infection treated at Veterans Affairs facilities in the United States, all-cause mortality decreased between 1995 and 2001 from 21.3 to 5.0 deaths per 100 patient-years.[3]

However, HAART induces deleterious metabolic effects such as dyslipidemia and insulin resistance and is associated with lipodystrophy and central fat accumulation.[4] Compared with untreated HIV patients, those receiving HAART have endothelial dysfunction[5] and more coronary artery calcification.[6] In 1998, severe premature coronary disease was first reported in patients receiving protease inhibitors,[7] but controversy still exists as to whether the rate of coronary events is increased in HIV patients and whether the increase is caused by HAART. Some studies report increased rates of coronary events in HIV patients or in HIV patients receiving HAART,[8,9] but others do not.[3] In the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group,[9] combination antiretroviral therapy was associated with a 26% increase in the rate of myocardial infarction per year of exposure to antiretroviral drugs. Traditional coronary risk factors are often present for decades before the onset of myocardial infarction. That an increase in risk can be detected only 6 years after the introduction of protease inhibitors suggests that the level of risk after long-term use may be very high.

Measurement of carotid artery intima-media thickness (IMT) with high-resolution B-mode ultrasound is a well-accepted, noninvasive method of assessing atherosclerosis and tracking its progression. Carotid IMT measurements correlate well with pathological measurements[10] and are potent predictors of myocardial infarction and stroke, even after adjustment for other risk factors.[11–13] Progression of

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From the Divisions of Cardiology, Endocrinology, and Infectious Diseases, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco.

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Correspondence to David D. Waters, MD, Room 5G1, Division of Cardiology, San Francisco General Hospital, 1001 Potrero Ave, San Francisco, CA 94110. E-mail dwaters@medsfgh.ucsf.edu

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carotid IMT can be measured reliably over time[14] and has been used as an end point in clinical trials in which treatment reduced both carotid IMT progression and cardiovascular events.[15]

In the present study, we measured lipids, inflammatory markers, and carotid IMT in a cohort of HIV-infected adults. We also assessed coronary risk factors and HIV disease characteristics. Our goals were to identify predictors of carotid IMT and to measure the progression rate of carotid IMT over 1 year.

Methods

Patient Selection

Patients were recruited mainly from the University of California, San Francisco Study of the Consequences of the Protease Inhibitor Era (SCOPE) cohort. The cohort consists of 3 categories: untreated HIV-infected patients, treated patients with detectable viremia, and treated patients who have achieved full viral suppression. SCOPE participants are not selected on the basis of any cardiovascular or metabolic criteria but are well characterized with regard to their HIV disease and are being followed up longitudinally. Control subjects of the same age and sex distribution were selected mainly from among subjects answering advertisements to participate in clinical trials. The University of California, San Francisco Committee on Human Research approved the study, and all patients provided written informed consent.

Risk Factor Assessment

At the baseline visit, each patient underwent an in-depth assessment, including a detailed interview and structured questionnaire covering sociodemographic characteristics, HIV disease history, other comorbid conditions, health-related behaviors, medication exposure, and family history. In the fasting state, blood was drawn to measure total and HDL cholesterol, triglycerides, and lipoprotein(a) by use of immunoprecipitation analysis, high-sensitivity C-reactive protein (hs-CRP, Dade Behring), fibrinogen, and glucose. LDL cholesterol was calculated except in hypertriglyceridemic patients, in whom it was measured directly. Lipoprotein(a) could not be calculated in 15 patients with marked hypertriglyceridemia. Waist-to-hip ratio was measured, and patients were assessed for changes in fat distribution.

Carotid IMT Measurements

Carotid B-mode ultrasound recordings were obtained from each patient using the standardized protocol of the Atherosclerosis Risk in Communities (ARIC) Study.[11,16,17] Briefly, patients lay supine in a dark quiet room, and blood pressure was recorded at the beginning and end of the study. The right and left carotid arteries were examined with the head in the midline position tilted slightly upward. A 10-MHz linear-array probe was used with the GE VividFive Imaging System. The probe was manipulated so that the near and far walls were parallel to it and lumen diameter was maximized in the longitudinal plane. Landmarks were identified, and high-resolution, high-frame-rate images were recorded digitally in a cine-loop format for subsequent measurement without data degradation.

Carotid IMT was measured in 12 predefined segments (6 per side) by a highly experienced vascular technician blinded to the patients' clinical features, including HIV status. At baseline, 61 of 1776 segments (3.4%) could not be measured; at follow-up, 14 of 1452 segments (0.96%) could not be measured. No values were imputed for missing segments. The technician did all recordings and all measurements in this study to maximize reproducibility. She was blinded to the first study when she read the follow-up study but then checked the 2 studies together to be certain that measurements were made at the same points. To assess measurement reproducibility, the scans of 16 randomly selected patients were remeasured. In each of the 16, the mean score for the 12 segments was identical for the first and second measurements when rounded to 0.01 mm. The difference between paired measurements for the 187 segments was 0.049 ± 0.053 mm, and the correlation coefficient was 0.99. To assess the reproducibility of rescanning and remeasurement, 15 patients underwent a second scan within 1 month of the first. The correlation coefficient for the comparison of blinded measurements was 0.996.

A carotid plaque was considered to be present when carotid IMT was >0.15 mm at any site.

Follow-Up Studies

Of the 148 HIV-infected patients who were enrolled in the study, 4 died of noncardiac causes during the first year of follow-up, and 5 underwent coronary bypass surgery for new-onset or worsening angina or after a non–Q-wave infarction. Carotid IMT measurements were repeated on 121 patients at 1 year, and 21 were lost to follow-up. The clinical features of the 121 patients with follow-up studies do not differ from those of the entire cohort.

Statistical Analyses

Intergroup differences were assessed by use of the *t* test for continuous variables and the χ^2 test for categorical variables; the Wilcoxon test was used for such variables as lipoprotein(a) and hs-CRP that were not normally distributed.

Stepwise regression analyses were performed to determine prognostic factors for baseline IMT and change at 12 months in IMT. The stepwise analysis method added variables 1 by 1 to the model, with the variable with the smallest probability value significant at the 0.05 level added into the model. At each step of the model building, the stepwise method deleted any variable already included in the model that did not have a value of $P<0.15$. The stepwise process ended when none of the variables outside the model had a value of $P<0.05$ and every variable in the model had a value of $P<0.15$ or when the variable to be added to the model was the one just deleted from it. For the analyses of HIV subjects, the variables used as the starting point for the stepwise analysis included in the stepwise regression analyses were age, sex, duration of HIV infection, CD4 nadir ≤ 200, diabetes, hypertension, history of coronary artery disease, hyperlipidemia, LDL cholesterol, cigarette pack-years, HDL cholesterol, lipodystrophy, race, total cholesterol, triglycerides, and duration of use of protease inhibitors. For the analyses of all subjects, duration of HIV infection, CD4 nadir, and duration of protease inhibitors were replaced by an indicator of HIV status (HIV subject/control subject).

Results

Patient Characteristics

The 148 HIV-infected patients enrolled in the study had a mean age of 45 ± 8 years; 123 were male; 81 were white; 46 were black; and 14 were Latino. A history of hepatitis C infection was present in 50 patients. The mean duration of HIV infection was 11 ± 4.5 years, and the median nadir CD4 count was 106 cells/mm^3. For the 116 patients taking protease inhibitors, the median duration of treatment with these drugs was 3.3 years. There were 47 patients on a ritonavir-containing regimen and 115 patients with a history of D4T exposure. Sixty-two patients had evidence of fat redistribution (lipodystrophy) on examination.

Coronary risk factors and laboratory values in HIV patients and age- and sex-matched control subjects are compared in Table 1. HIV patients were more likely to be current smokers and to have a history of hypertension. Total cholesterol levels were similar in the 2 groups, and HIV patients had marginally lower LDL cholesterol levels. However, their HDL cholesterol levels were lower, and their triglyceride levels were higher. Among HIV patients, the 36 nonsmokers and 112 smokers had similar HDL cholesterol levels (39 ± 15 and

TABLE 1. Baseline Coronary Risk Factors and Laboratory Values in HIV Patients and Control Subjects

	HIV Patients (n=148)	Control Subjects (n=63)	P
Age, y	45±8	43±9	0.09
Sex, male/female, n	123/25	52/11	0.92
Body mass index, kg/m^2	25.4±4.2	25.9±4.5	0.38
Waist-to-hip ratio	0.94±0.07	0.89±0.08	<0.01
History of coronary disease, n (%)	8 (5)	1 (2)	0.21
Coronary risk factors, n (%)			
Current smoking	82 (55)	16 (25)	<0.01
Diabetes	9 (6)	1 (2)	0.16
Hypertension	34 (23)	5 (8)	0.01
Hyperlipidemia	43 (29)	11 (17)	0.08
Family history	23 (16)	13 (21)	0.37
Current medications, n (%)			
Cholesterol-lowering drug	25 (17)	6 (10)	0.39
Antihypertensive drug	32 (22)	3 (5)	0.003
Laboratory values, mg/dL			
Total cholesterol	186±49	190±49	0.55
HDL cholesterol	40±15	51±15	<0.01
LDL cholesterol	103±39	116±46	0.05
Triglycerides	228±186	118±82	<0.01
Lipoprotein(a)	13	11	0.56
Glucose	90±27	88±13	0.54
hs-CRP, mg/L	1.6	0.8	<0.01
Fibrinogen	324±89	285±54	<0.01

40±15 mg/dL, respectively). The 116 HIV patients taking protease inhibitors had higher triglyceride levels than did the 32 protease inhibitor–naive patients (248±192 versus 156±143 mg/dL; $P=0.013$).

HIV patients also had significantly higher levels of fibrinogen and hs-CRP.

Carotid IMT Measurements

The mean carotid IMT measurement was 0.91±0.33 mm in HIV patients and 0.74±0.17 mm in control subjects ($P=0.0001$). A carotid plaque was detected in 67 of the 148 HIV patients and in 15 of the 63 control subjects (45% versus 24%; $P=0.0034$).

As shown in Table 2, multivariate predictors of thicker carotid IMT among the HIV patients were age ($P<0.001$), LDL cholesterol ($P<0.001$), cigarette pack-years ($P=0.005$), Latino race ($P=0.062$), and hypertension ($P=0.074$). Duration of use of protease inhibitors did not predict carotid IMT. When both HIV patients and control subjects were combined in the analysis, HIV infection was an independent predictor of thicker IMT ($P=0.001$), as were age ($P<0.001$), LDL cholesterol ($P<0.001$), cigarette pack-years ($P=0.001$), and Latino race ($P=0.024$).

Progression of Carotid IMT

Among the 121 HIV patients with follow-up measurements at 1 year, carotid IMT measured 0.93±0.32 mm at baseline and 1.00±0.41 mm at 1 year. Carotid IMT thus progressed by a mean of 0.074±0.13 mm ($P<0.001$). In 45 of the 121 patients, mean carotid IMT progressed by ≥0.10 mm. New plaques developed in 12 of the 64 patients who did not have plaque at the baseline examination. Predictors of IMT progression by multivariate analysis (Table 2) were age ($P<0.001$), Latino race ($P=0.02$), and CD4 nadir ≤200 cells/mm^3 ($P=0.082$).

TABLE 2. Variables Correlating With Baseline Carotid IMT and Progression of IMT by Univariate and Stepwise Regression Analyses in HIV Patients

Analysis and Predictive Variables	Parameter Estimate	Standard Error	P
Baseline IMT, univariate analysis			
Age	0.002	0.0003	<0.001
Pack-years	0.0006	0.0001	<0.001
LDL	0.0003	0.00007	<0.001
HIV duration	0.002	0.0006	0.003
Hypertension	0.018	0.006	0.005
Latino race	−0.022	0.009	0.019
Hyperlipidemia	0.016	0.006	0.008
Total cholesterol	0.00014	0.00005	0.015
History of coronary disease	0.032	0.012	0.007
Lipodystrophy	0.013	0.006	0.025
Baseline IMT, stepwise analysis			
Age	0.002	0.0003	<0.001
LDL	0.0002	0.0001	<0.001
Pack-years	0.0003	0.0001	0.005
Latino race	−0.0133	0.0071	0.062
Hypertension	0.0091	0.0051	0.074
IMT progression, univariate analysis			
Age	0.0005	0.00015	0.002
HIV duration	0.0006	0.0003	0.040
Latino race	−0.0085	0.0043	0.050
Hyperlipidemia	0.006	0.0028	0.033
IMT progression, stepwise analysis			
Age	0.0005	0.0001	<0.001
Latino race	−0.0087	0.0037	0.020
CD4 nadir ≤200 cells/mm^3	−0.0043	0.0024	0.082

Among the 27 control subjects who underwent follow-up measurements at 1 year, carotid IMT measured 0.71±0.14 mm at baseline and 0.70±0.15 mm at 1 year, a change of −0.006±0.05 mm ($P=0.53$). The rate of carotid IMT progression was thus much faster in HIV patients than in control subjects (0.074±0.13 versus −0.006±0.05 mm; $P=0.002$).

Discussion

The findings of this study indicate that HIV-infected patients have greater carotid IMT compared with age- and sex-matched control subjects. The mean carotid IMT of control subjects in our study was similar to and the mean carotid IMT of HIV patients was much greater than that previously reported for subjects this age.[18,19] Furthermore, the rate of progression of

carotid IMT in HIV patients, a mean of 0.074 mm/y, is several-fold higher than the rate of ≈0.01 mm/y reported in previous studies of non–HIV-infected subjects[18,19] and is much higher than the rate of progression in our non-HIV control subjects.

Because increasing carotid IMT is an independent predictor of stroke and myocardial infarction in other populations,[11–13] the findings of this study suggest that the rate of vascular events is likely to increase substantially in HIV patients. The pathogenesis of accelerated atherosclerosis in HIV patients has not been adequately studied, and the degree to which classic coronary risk factors are responsible, as opposed to HIV-related factors and factors related to treatment, is not known. Additional studies with longer follow-up are needed to determine the cause of accelerated atherosclerosis in HIV patients.

Coronary Risk Factors in HIV Patients

The burden of coronary risk factors in HIV patients in our study was higher than in control subjects (Table 1) and is higher than in the general population. Specifically, more than half of the HIV patients were current smokers, and one quarter had hypertension. Their HDL cholesterol levels were much lower and their triglyceride levels much higher than in control subjects. Biochemical markers of atherosclerotic risk, specifically hs-CRP and fibrinogen, were also higher in our HIV patients. To what extent the lipid abnormalities are related to either their underlying HIV disease or HAART cannot be answered by this study.

In HIV patients not treated with HAART, HDL cholesterol levels are low and triglyceride levels are high.[20,21] The high triglyceride levels may be a result of decreased triglyceride clearance, which has been correlated with higher interferon-α levels.[20] Smoking also reduces HDL cholesterol levels,[22] but in our HIV patients, nonsmokers had mean HDL cholesterol levels that were almost identical to those of smokers. HAART regimens that include a protease inhibitor increase total cholesterol and triglyceride levels.[5,23–25] Treatment with protease inhibitors has been linked to peripheral insulin resistance and impaired glucose tolerance.[25,26] In our study, the HIV patients receiving protease inhibitors had higher triglyceride levels than both HIV patients without protease inhibitors and control subjects.

In large, cross-sectional studies, increased carotid IMT has been associated with the classic risk factors for atherosclerosis.[16] Progression of carotid IMT in these populations is also related to risk factors.[27] Age, LDL cholesterol, and cigarette pack-years were strong predictors and hypertension was a weak predictor of baseline carotid IMT by multivariable analysis in our HIV patients. The high prevalence of current smoking (55%) and low prevalence of diabetes (6%) in our HIV cohort may explain why cigarette pack-years but not diabetes was a strong predictor of carotid IMT. Duration of smoking was the strongest predictor of severe carotid atherosclerosis in a study of non-HIV patients.[28]

HIV as an Independent Predictor of Atherosclerosis and Atherosclerosis Progression

In the combined population of HIV patients and control subjects, the presence of HIV infection was a strong predictor of increased carotid IMT by multivariable analysis ($P=0.001$). Of note, this effect of HIV was independent of all other classic coronary risk factors, including age, sex, smoking, hypertension, lipid abnormalities, and diabetes. Furthermore, nadir CD4 count ≤200 cells/mm^3 correlated with progression of IMT. A nadir CD4 count ≤200 cells/mm^3 is commonly used as an indicator of profound immunodeficiency.

Why might HIV infection and a low nadir CD4+ T cell count be associated with accelerated atherosclerosis independently of other factors? Two independent lines of investigation may provide a conceptual framework for addressing this issue. First, progressive HIV disease is associated with accelerated T-cell proliferation, heightened T-cell activation, and high levels of inflammatory markers.[29–32] These immunologic perturbations persist even after the introduction of effective antiretroviral therapy.[33] Indeed, in a recent analysis by our group, persistent levels of immune activation were observed even after years of treatment-mediated viral suppression. The level of immune activation in this study was independently associated with CD4+ T cell nadir.[34] Second, there is a general consensus that chronic low-grade inflammation contributes to accelerated atherosclerosis.[35] Several mechanisms for this observation have been proposed, including cytokine-mediated increases in atheroma and/or an increased risk for thrombosis.[36] This association between HIV infection, chronic inflammation, and accelerated atherosclerosis may underlie how HIV infection in general and a low CD4 nadir in particular predicts a greater IMT.

Both immunodeficiency and immune reconstitution may be atherogenic. T lymphocytes, of which CD4-positive cells constitute the major population, play a key role in atherogenesis.[37,38] Activation of CD4-positive cells appears to promote atherosclerosis through elaboration of proinflammatory cytokines, including tumor necrosis factor and interleukins.[39] T-cell lymphocytes are also involved in the arteriosclerosis that develops in immune-suppressed patients after cardiac transplantation.[40]

Previous Studies

Carotid B-mode ultrasound has been used in other studies to assess atherosclerosis in HIV patients. Maggi et al[41] reported that carotid plaques were more common in 55 patients receiving protease inhibitors than in 47 protease inhibitor–naive patients. In a larger series, investigators from the Swiss HIV Cohort Study found that carotid and femoral artery plaques were associated with classic coronary risk factors and not with protease inhibitor use.[42] Neither of these studies reported carotid IMT. Seminari et al[43] found that carotid IMT was increased in 28 HIV patients receiving protease inhibitors compared with measurements in 15 protease inhibitor–naive patients and 16 HIV-negative subjects. Chironi et al[44] reported that 36 HIV patients receiving protease inhibitors had carotid IMT equal to that of non-HIV subjects with similar lipid and glucose disturbances; both groups had increased carotid IMT compared with control subjects without lipid and glucose abnormalities. In another study of 423 HIV-infected patients, conventional risk factors but not lipodystrophy or HAART were independent predictors of increased carotid IMT.[45] However, measurements in this study

were made at only 1 site in the common carotid artery free from plaque, and the median value for carotid IMT was only 0.54 mm.

Differences in measurement techniques and a lack of statistical power in the smaller studies may account for the contradictory results in these reports. As in our population, classic coronary risk factors, specifically age, LDL cholesterol, and smoking, were associated with increased carotid IMT in the larger studies.[42,45] Serial measurements of carotid IMT were not done in any of these studies, so our finding of markedly accelerated progression of carotid IMT in HIV patients is new.

The relative contribution of protease inhibitors to the accelerated atherosclerosis in HIV patients is difficult to assess from the available literature. The metabolic abnormalities induced by these drugs are certain to be atherogenic; however, the contribution of protease inhibitors could be relatively minor compared with the atherogenic effects of immunodeficiency or immune reconstitution. Interestingly, protease inhibitor treatment itself, triglycerides, and HDL cholesterol were not independent predictors of increased carotid IMT in our study or the 2 larger previous studies.[42,45]

Study Limitations

This study has several limitations. A statistical association between a risk factor and a measure of atherosclerosis does not prove that the risk factor directly promotes atherogenesis. Carotid IMT reflects the cumulative effects of risk factors acting over many years, whereas we measured risk factors at 1 point in time only. Thus, blood cholesterol and triglyceride levels or blood pressure measured at baseline may not accurately represent lifetime exposure. The study may be underpowered to detect weak relationships; several risk factors thought to be important, such as HDL cholesterol, triglyceride, and hs-CRP levels or use of protease inhibitors, were not independent predictors of carotid IMT or progression. Finally, the findings in our HIV patients from an urban public health clinic may not necessarily apply to other HIV-infected populations.

Clinical Implications

HIV-infected patients carry a high burden of risk factors for coronary disease, have increased carotid IMT compared with age-matched control subjects, and exhibit rapid progression of carotid IMT. They are therefore at high risk for coronary events. Our findings and data accumulating from other sources suggest that it would be reasonable to count HIV infection itself as a coronary risk factor, just like smoking, hypertension, hypercholesterolemia, or diabetes. Although randomized trials have not been done to demonstrate that treatment of risk factors reduces events in HIV-infected patients, it seems reasonable to extrapolate from other populations and to recommend aggressive control of risk factors. Smoking is particularly important because of its high prevalence. Hypertension should be treated. LDL cholesterol should be reduced to low levels, and hypertriglyceridemia should be controlled. If lipids are difficult to control, antiretroviral medication that may be contributing to lipid elevation should be reviewed and changed to medication with fewer lipid effects. Until further data are available, treating to the National Cholesterol Education Panel guidelines for patients with established vascular disease or diabetes seems prudent.

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Priscilla Y. Hsue, Joan C. Lo, Arlana Franklin, Ann F. Bolger, Jeffrey N. Martin, Steven G. Deeks and David D. Waters

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