

Clinical Features of Acute Coronary Syndromes in Patients With Human Immunodeficiency Virus Infection

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Background—Patients with HIV infection exhibit increased rates of coronary events; however, the clinical features of acute coronary syndromes (ACS) in HIV-infected patients have not been well defined.

Methods and Results—Between 1993 and 2003, 68 HIV-infected patients were hospitalized with ACS. We compared the clinical features and outcome of these patients with those of 68 randomly selected control patients with ACS without HIV. HIV patients were on average more than a decade younger than controls and more likely to be male and current smokers and to have low HDL cholesterol. They were less likely than controls to have diabetes or hyperlipidemia, and their TIMI (Thrombolysis In Myocardial Infarction) risk scores on admission were significantly lower. At coronary angiography, the number of vessels with >50% stenosis was 1.3 ± 1.0 in HIV patients and 1.9 ± 1.2 in controls ($P=0.007$). Restenosis developed in 15 of 29 HIV patients who underwent percutaneous coronary intervention compared with 3 of 21 controls (52% versus 14%, $P=0.006$).

Conclusions—HIV patients with ACS are younger and more likely to be males and current smokers and to have low HDL cholesterol levels compared with other ACS patients. Their TIMI risk scores are lower, and they are more likely to have single-vessel disease; however, their restenosis rates after percutaneous coronary intervention are unexpectedly high. (*Circulation*. 2004;109:316-319.)

Key Words: risk factors ■ restenosis ■ coronary disease ■ angina ■ infection

At the end of 2002, an estimated 42 million people were infected with HIV worldwide, and $\approx 40\,000$ new cases 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. 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.²

In 1998, severe premature coronary disease was first reported in HIV patients receiving HAART, specifically protease inhibitors.³ 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.^{4,5}

There are several possible explanations for an increase in coronary events in HIV patients. Protease inhibitors induce deleterious metabolic effects such as dyslipidemia and insulin resistance.⁶ An alternate explanation is that HIV disease is atherogenic itself. HIV disease is associated with accelerated T-cell proliferation, heightened T-cell activation, and high

levels of inflammatory markers, immunologic perturbations that persist even after the introduction of effective antiretroviral therapy.⁷ T lymphocytes and inflammatory cytokines both play key roles in atherogenesis.⁸ Thus, immunodeficiency and immune reconstitution may accelerate atherosclerosis.

Because the pathogenesis of acute coronary syndromes (ACS) may differ in HIV patients, their clinical features and response to treatment may differ as well. The purpose of this study is to compare the clinical features of a series of HIV patients with ACS to patients with ACS without HIV infection.

Methods

Patient Selection

The medical record database of San Francisco General Hospital from 1993 to 2003 was searched to identify patients with the diagnosis of ACS, either acute myocardial infarction or unstable angina. Myocardial infarction was diagnosed in patients with compatible symptoms with elevated troponin I measurements. In 30 patients diagnosed before the introduction of troponin measurements, elevations of creatine kinase (CK)-MB and the ratio of CK-MB to total CK were used. Patients with evolving ST-segment elevation >0.1 mV in

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Clinical Features of HIV Patients and Controls With ACS

	HIV Patients (n=68)	Controls (n=68)	<i>P</i>
Age, y	50±8	61±11	<0.001
Male/female, n	61/7	42/26	<0.001
Coronary risk factors			
Family history	24	16	0.12
Diabetes	9	28	<0.001
Hypertension	36	41	0.39
Hyperlipidemia	17	28	0.045
Current cigarette smoking	46	28	0.003
Prior coronary disease	19	28	0.11
Prior renal disease	10	9	0.81
Medication before admission, n			
Aspirin	22	27	0.37
β-Blocker	19	17	0.86
ACE inhibitor	13	18	0.31
Calcium channel blocker	11	9	0.63
Cholesterol-lowering drug	13	18	0.39
Admission physical findings			
Systolic blood pressure, mm Hg	140±29	155±38	0.01
Diastolic blood pressure, mm Hg	78±21	82±20	0.27
Heart rate, bpm	85±20	87±23	0.61
STEMI, n			
TIMI risk score for STEMI	2.2±1.2	3.4±1.9	0.017
Non-STEMI, n			
Peak troponin I in MI patients, mg/mL	14±27	14±25	0.95
Unstable angina, n			
TIMI risk score for unstable angina and non-STEMI	1.6±1.3	3.3±1.6	<0.001
Admission laboratory values			
Total cholesterol, mg/dL	197±63	205±59	0.51
LDL cholesterol, mg/dL	121±54	117±40	0.65
HDL cholesterol, mg/dL	35±12	41±9	0.005
Triglycerides, mg/dL	262±278	218±185	0.36

STEMI indicates ST-elevation myocardial infarction; MI, myocardial infarction.

2 contiguous leads were categorized as having ST-elevation myocardial infarction and those without this criterion as having non-ST-elevation MI. Unstable angina was diagnosed in patients hospitalized with worsening angina or new-onset angina at rest without troponin I elevations. For each HIV patient with myocardial infarction or unstable angina, we selected the first available non-HIV patient with either of these diagnoses as a control.

Patients were categorized as having diabetes, hypertension, or hyperlipidemia when they were being treated for 1 of these conditions or when the condition had been diagnosed. The TIMI (Thrombolysis In Myocardial Infarction) risk score for ST-elevation myocardial infarction⁹ and the TIMI risk score for unstable angina/non-ST-elevation myocardial infarction¹⁰ were calculated for each of these subsets of patients. Coronary angiography and percutaneous coronary intervention (PCI) were performed with standard techniques according to standard clinical practice. The study was approved by the Committee on Human Research of the University of California, San Francisco.

Statistical Analysis

Differences between HIV patients and controls were assessed with χ^2 tests for binary variables and *t* tests for continuous variables. The *t* tests used the Satterthwaite approximation for unequal variances.

Results

Clinical Features

The clinical characteristics of HIV patients with ACS and control patients with ACS are listed in the Table. The mean age of the HIV patients was 50 years, compared with 61 years in the control group. Almost all of the HIV patients were men, but more than one third of the controls were women. The risk factor profiles of the 2 groups were different: diabetes and hyperlipidemia were significantly more common in controls, and current smoking was the predominant risk factor in HIV patients. HIV patients had significantly lower HDL cholesterol levels, a mean of 35 mg/dL. Myocardial infarction was slightly more common in controls, and unstable angina was more common in HIV patients. TIMI risk score on admission was lower in HIV patients.

The mean duration of HIV infection was 8.5±5.3 years, and 36 of the 68 HIV patients were receiving HAART at the time of onset of their ACS. The median nadir CD4 count in

the HIV patients was 153 cells/mm³. The median current CD4 count was 341 cells/mm³, and the median viral load was 1683 copies/mL. Eight of the 68 HIV patients had been diagnosed as having lipodystrophy, and 32 had previously had an opportunistic infection.

Compared with the other 35 HIV patients, the 33 receiving protease inhibitors were more likely to have a history of hyperlipidemia (13 versus 4, $P=0.008$) and to be taking cholesterol-lowering drugs (11 versus 2, $P=0.004$). Their LDL cholesterol and triglyceride levels tended to be higher than the levels in HIV patients not taking protease inhibitors, but the differences were not statistically significant.

Angiographic Features

Coronary angiography was performed on 56 of the 68 HIV patients and 61 of the control patients. Coronary disease was more extensive in controls, with a mean of 1.9 ± 1.2 vessels involved compared with 1.3 ± 1.0 vessels in the HIV patients ($P=0.007$). More patients in the control group were referred for coronary bypass surgery (16 versus 6, $P=0.032$).

PCI was done on 29 HIV patients and 21 controls; a stent was included in the procedure in 22 HIV patients and 11 controls. Restenosis was subsequently detected in 15 HIV patients and 3 controls (52% versus 14%, $P=0.006$). Among patients with stents, the restenosis rate was 11 of 22 in the HIV group and 2 of 11 in controls (50% versus 18%, $P=0.078$).

Discussion

This study shows that HIV patients who develop ACS differ in several ways from other ACS patients. HIV patients are more than a decade younger, with a mean age of only 50 years. They are more likely to be male, to be current smokers, and to have low HDL cholesterol levels. The prevalence of diabetes was lower in HIV patients than in controls.

As might be expected given their younger age and other clinical features, HIV patients with ACS had less extensive coronary disease at angiography than did controls. They therefore frequently underwent PCI; however, their rate of clinical restenosis over the ensuing year was 52%, significantly higher than the rate of restenosis in the control patients who underwent PCI. HIV infection was an independent predictor of restenosis in the combined population.

Previous Studies

Coronary disease has been described previously in patients with HIV infection; a recent literature search identified 129 patients from 25 reports.¹¹ The mean age of these patients was 42 years, and 91% of them were men. Myocardial infarction was the initial presentation in most of these patients, but data on their clinical features and outcomes are limited. Ambrose et al¹² subsequently described a series of 51 HIV patients with ACS from 1 hospital, collected between 1996 and 2000. Although that study did not include a control group, the clinical features of their HIV patients with ACS were very similar to those of the patients in the present study: the mean age was 48 years, nearly all were men, and 55% were current smokers. It is therefore likely that the clinical features of HIV

patients with ACS that we are describing are not specific to our institution.

None of the previous reports include follow-up of a sufficiently large number of HIV patients undergoing coronary intervention to ascertain whether PCI yields good long-term results in this patient group. In a preliminary report, the restenosis rate among 30 HIV patients who received stents and had follow-up angiography was 74%.¹³ Half of these patients had diabetes; in 18, the treated lesion was type C, and in 6, it was a total occlusion. These adverse features may account for the higher restenosis rate than that found in HIV patients in the present study.

HIV Infection and Restenosis

Patients with higher levels of inflammatory markers, such as C-reactive protein, at the time of PCI have higher restenosis rates.¹⁴ HIV patients without ACS in the present study had higher levels of C-reactive protein than did age and sex-matched controls.¹⁵ Chronic low-level inflammation in HIV patients may therefore contribute to their high rate of restenosis. By inducing adhesion molecule expression on endothelial cells¹⁶ and LDL cholesterol uptake by macrophages,⁷ C-reactive protein may contribute directly to atherogenesis and restenosis.

Clinical Implications

The introduction of HAART has dramatically reduced mortality and morbidity in patients with HIV infection; however, several reports from databases and observational cohorts indicate that the rate of ACS is increasing in HIV patients. The present study shows that HIV patients with ACS are relatively young men who smoke and have low HDL cholesterol. Although their TIMI risk scores are lower and they have less extensive coronary disease than other patients with ACS, PCI in this group is associated with high restenosis rates. Whether this complication will be prevented by drug-eluting stents is not yet known. The long-term outcome of HIV patients with ACS is also not known. Although the value of preventive measures such as smoking cessation and cholesterol lowering have not been documented specifically in HIV patients, it appears reasonable to institute such measures in patients at risk.

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