Prediction of Coronary Heart Disease Risk in HIV-Infected Patients with Fat Redistribution

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A metabolic syndrome has been described among human immunodeficiency virus (HIV)–infected patients receiving highly active antiretroviral therapy; the syndrome is characterized by fat redistribution, insulin resistance, and dyslipidemia. We compared the 10-year coronary heart disease (CHD) risk estimates for 91 HIV-infected men and women with fat redistribution with the risk estimates for 273 age-, sex-, and body mass index (BMI)–matched subjects enrolled in the Framingham Offspring Study. Thirty HIV-infected patients without fat redistribution were also compared with 90 age- and BMI-matched control subjects. The 10-year CHD risk estimate was significantly elevated among HIV-infected patients with fat redistribution, particularly among men; however, when they were matched with control subjects by waist-to-hip ratio, the 10-year CHD risk estimate did not significantly differ between groups. HIV-infected patients without fat redistribution did not have a greater CHD risk estimate than did control subjects. In addition, the CHD risk estimate was greatest in HIV-infected patients who had primary lipoatrophy, compared with those who had either lipohypertrophy or mixed fat redistribution. Therefore, although CHD risk is increased in HIV-infected patients with fat redistribution, the pattern of fat distribution and sex are potential important components in determining the risk in this population.

Recent reports have identified a metabolic syndrome among HIV-infected patients receiving combination antiretroviral therapy; the syndrome is characterized by fat redistribution (increased visceral fat and/or reduced subcutaneous fat), insulin resistance, dyslipidemia (increased triglyceride level and decreased high-density lipoprotein [HDL] cholesterol level), and hypertension

[1–4]. The etiology of these abnormalities is not known but may relate to specific effects of antiretroviral drugs on adipocyte metabolism with consequent metabolic abnormalities, and/or from direct effects of antiretroviral drugs on lipid or glucose metabolism [5, 6]. HIV infection may play a role independent of drug-related effects, but prior data do not demonstrate severe metabolic abnormalities in patients without fat redistribution [2]. Preliminary reports suggest increased rates of cardiovascular disease among HIV-infected patients [7, 8], but data from prospective, longitudinal cohort studies are not available.

The Framingham risk equation, which estimates 10-year coronary heart disease (CHD) risk, was developed on the basis of coronary events (including angina pectoris, myocardial infarction, and deaths due to CHD) that occurred during longitudinal follow-up of the Framingham cohort [9]. The equation includes age, total cholesterol level, HDL cholesterol level, blood pressure,

presence of diabetes, and smoking status, and it is a well-established tool to evaluate long-term CHD risk. In this study, the calculated 10-year CHD risk estimate in HIV-infected subjects who have fat redistribution is compared with the CHD risk estimate in sex-matched, age-matched, body mass index (BMI)–matched, and, in a substudy, waist-to-hip ratio (WHR)–matched subjects from the Framingham Offspring Study.

PATIENTS, MATERIALS, AND METHODS

HIV-infected patients with lipodystrophy. Ninety-one consecutive HIV-infected subjects (65 men and 26 women) who reported recent changes in body fat distribution were prospectively evaluated from December 1998 through November 1999 at the Clinical Research Center of the Massachusetts Institute of Technology (Cambridge, MA). Subjects were recruited using community-based advertisements seeking HIV-infected patients with fat redistribution or were referred by their physicians for evaluation of fat redistribution. Subjects were screened by telephone and asked whether they had experienced any of the following changes: (1) loss of fat in the face, (2) increased fat under the chin or back of the neck, (3) increased abdominal girth, (4) increased chest or breast fat, or (5) loss of fat in the arms or legs. Subjects who identified a change in fat distribution in ⩾1 body area were invited to participate, and fat redistribution was confirmed by physical examination of all subjects.

Subjects were excluded from the study if they had changed antiretroviral medications ⩽6 weeks before presentation; had a history of diabetes mellitus or previous treatment with an antidiabetic agent; reported use of testosterone, estrogen, growth hormone, or other steroids in the 6 months before presentation; were active alcohol or substance abusers; or were not aged 18–60 years. Metabolic and dietary data for a subsample of the subjects who participated in this evaluation were reported elsewhere [2, 10, 11], and a subsample of the patients subsequently enrolled in a study of metformin treatment for HIV-associated lipodystrophy [12, 13]. Here, we report previously unpublished data on 10-year CHD risk estimates determined using the Framingham CHD risk score [9]. Written informed consent was obtained from each subject before testing, in accordance with the Committee on Human Experimentation with Subjects of the Massachusetts Institute of Technology and the Subcommittee on Human Studies at Massachusetts General Hospital (Boston).

Examination protocol. Each subject provided a medical history and underwent a physical examination to confirm the presence of fat redistribution. As reported elsewhere [2], fat redistribution was scored by a single investigator on the basis of facial fat loss, increased neck fat (anterior or posterior), increased trunk or chest fat, and decreased leg and arm fat.

Patients were subsequently categorized as having primary lipoatrophy (with no evidence of increased abdominal fat), primary lipohypertrophy (i.e., increased abdominal fat, with or without increased neck fat, and no evidence of peripheral fat atrophy), or mixed lipodystrophy (i.e., both increased abdominal fat and peripheral fat atrophy). Blood pressure, weight, height, BMI (defined as weight in kilograms divided by height in meters squared), and the circumferences of the waist (at the umbilicus), hip, midarm, and midthigh were determined. After a 12-h overnight fast, blood glucose, total cholesterol, and HDL cholesterol levels were determined. Antiretroviral therapy was characterized by current use of a protease inhibitor (PI), nucleoside reverse-transcriptase inhibitor (NRTI), or nonnucleoside reverse-transcriptase inhibitor.

HIV-infected control subjects without lipodystrophy. Thirty HIV-infected patients (18 men and 12 women) without clinical evidence of fat redistribution were also evaluated. None of the subjects had experienced fat redistribution of the face, neck, arms, legs, or trunk; this was confirmed by physical examination of all subjects. The remaining inclusion and exclusion criteria and means of patient evaluation were identical to those used for HIV-infected patients with lipodystrophy.

Framingham Offspring Study control subjects. Control subjects for both HIV-infected subjects with lipodystrophy ($n = 273$) and HIV-infected subjects without lipodystrophy ($n = 90$) were selected from the Framingham Offspring Study, a population-based observational study of risk factors for cardiovascular disease described elsewhere [14, 15]. Control subjects ($n = 2959$) were eligible for matching if they did not have diagnosed diabetes mellitus, were not receiving estrogen replacement therapy, and had complete information available on all analytic covariates. We matched each HIV-infected subject to 3 control subjects by sex, age (within 4 years), and BMI (within 2). In a secondary analysis, we matched each HIV-infected subject to at least 1 and up to 3 control subjects by sex, age (within 4 years), BMI (within 2), and WHR (within 0.1 units). Seven HIV-infected subjects could not be matched by these criteria; therefore, they were excluded from secondary analyses. Data on control subjects were obtained from January 1991 through September 1995, during the fifth Framingham Offspring Study examination cycle. As did HIV-infected patients, control subjects provided a standardized medical history and underwent physical examination, including measurement of height; weight; blood pressure; the circumferences of the waist (at the umbilicus), midthigh, and midarm; and fasting glucose, total cholesterol, and HDL cholesterol levels.

Calculation of 10-year CHD risk estimate. Ten-year CHD risk estimates were calculated in accordance with the equations of Wilson et al. [9] with use of sex-specific risk calculations based on age, total and HDL cholesterol levels, systolic and diastolic blood pressure, presence of diabetes (defined as a fast-

Table 1. Ten-year coronary heart disease (CHD) risk assessment for HIV-infected subjects with fat redistribution syndrome, compared with age-, sex-, and body mass index (BMI)–matched control subjects from the Framingham Offspring Cohort.

Characteristic or laboratory value	All subjects			Men			Women		
	HIV infected (n = 91)	Control (n = 273)	P	HIV infected (n = 65)	Control (n = 195)	P	HIV infected (n = 26)	Control (n = 78)	P
Age, years	43.2 ± 0.9	43.7 ± 0.5	.54	44.6 ± 1.0	45.0 ± 0.5	.75	39.5 ± 1.6	40.6 ± 0.8	.54
BMI	26.2 ± 0.5	26.4 ± 0.3	.70	26.3 ± 0.6	26.6 ± 0.3	.68	26.0 ± 0.9	26.0 ± 0.5	.94
Body circumference, cm									
Waist	94.8 ± 1.1	91.0 ± 0.8	.01	94.6 ± 1.3	94.2 ± 0.9	.83	95.5 ± 2.3	82.8 ± 1.3	.0001
Hip	97.6 ± 0.9	100.9 ± 0.5	.002	96.9 ± 1.0	100.5 ± 0.6	.003	99.4 ± 2.1	101.9 ± 1.1	.29
Thigh	50.7 ± 0.5	59.8 ± 0.3	.0001	51.0 ± 0.6	58.9 ± 0.4	.0001	50.0 ± 1.2	62.2 ± 0.7	.0001
Arm	31.4 ± 0.4	31.8 ± 0.2	.43	32.5 ± 0.5	32.3 ± 0.3	.78	28.9 ± 0.7	30.7 ± 0.4	.03
WHR	0.97 ± .006	0.90 ± .005	.0001	0.97 ± 0.006	0.94 ± 0.004	.0001	0.96 ± 0.01	0.81 ± 0.01	.0001
Total cholesterol, mg/dL	226 ± 6	193 ± 2	.0001	229 ± 8	191 ± 2	.0001	217 ± 7	197 ± 4	.01
HDL cholesterol, mg/dL	37 ± 1	49 ± 1	.0001	35 ± 1	46 ± 1	.0001	42 ± 3	56 ± 2	.0001
Fasting glucose, mg/dL	92.1 ± 1.3	93.3 ± 0.5	.43	94.1 ± 1.6	94.6 ± 0.6	.76	87.2 ± 2.2	89.9 ± 1.0	.28
Blood pressure, mm Hg									
Systolic	120 ± 1	119 ± 1	.32	122 ± 2	121 ± 1	.52	116 ± 3	112 ± 2	.22
Diastolic	76 ± 1	74 ± 1	.09	78 ± 1	76 ± 1	.08	72 ± 2	70 ± 1	.29
Current smoker, % of subjects	31	25	.29[a]	21	26	.42[a]	58	24	.002[a]
CHD risk assessment									
10-year risk, %	7.4 ± 0.6	5.3 ± 0.3	.002	9.0 ± 0.7	6.5 ± 0.3	.001	3.4 ± 0.8	2.2 ± 0.3	.19
10-year risk of ≥10%, percentage of subjects	29.1	12.8	.001[a]	38.7	17.4	.001[a]	4.2	1.3	.37[a]

NOTE. Data are mean ± SEM, unless otherwise indicated. P values were determined by Student's t test, unless otherwise indicated. HDL, high-density lipoprotein; WHR, waist-to-hip ratio.

[a] Determined by χ^2 test.

ing glucose level of >140 mg/dL), and smoking status. The equation estimates the 10-year risk for CHD events, including angina pectoris, myocardial infarction, and death due to CHD.

Biochemical and immunologic assays. Levels of glucose, total cholesterol, and HDL cholesterol were determined for HIV-infected subjects and control subjects with use of methods described elsewhere [2]. HIV RNA levels were determined using the Amplicor HIV-1 Monitor test (Roche Molecular Systems), which has a lower limit of detection of 400 copies/mL.

Statistical analysis. Comparisons of 10-year CHD risk estimates between HIV-infected and control subjects based on Framingham equations were made using Student's t test. The percentage of subjects who smoked and the percentage of subjects with a 10-year CHD risk estimate of ≥10% were compared between groups with the χ^2 test. Analyses were repeated after stratification by sex. CHD risk estimates, metabolic data, and anthropometric data were compared among the lipodystrophic HIV-infected patients according to PI exposure and by pattern of lipodystrophy (i.e., primary lipoatrophy, lipohypertrophy, and mixed lipodystrophy). PI exposure was categorized as current use versus no current use. Statistical analyses were performed with SAS software (SAS Institute). Statistical significance was determined using 2-tailed tests, and $P < .05$ indicated statistical significance. Results are presented as means ± SEMs, unless otherwise indicated.

RESULTS

Demographic characteristics and 10-year CHD risk estimates for HIV-infected subjects with fat redistribution and for control subjects are shown in table 1. HIV-infected subjects with fat redistribution had a duration of infection of 7.2 ± 0.5 years, received 4.7 ± 0.3 years of antiretroviral therapy, and had a mean HIV RNA level of 6572 ± 2511 copies/mL. The 10-year CHD risk estimate was significantly increased among HIV-infected patients with fat redistribution, compared with that for control subjects from the Framingham Offspring Study: 7.4% ± 0.6% versus 5.3% ± 0.3%, for all subjects ($P = .002$); 9.0% ± 0.7% versus 6.5% ± 0.3%, for men ($P = .001$); and 3.4% ± 0.8% versus 2.2% ± 0.3%, for women ($P = .19$). The percentage of HIV-infected subjects with a 10-year CHD risk estimate of ≥10% was substantially elevated for HIV-infected subjects, compared with the percentage of Framingham control subjects: 29.1% vs. 12.8%, for all subjects ($P = .001$); 38.7% vs. 17.4%, for men ($P = .001$); and 4.2% vs. 1.3%, for women ($P = .37$). HIV-infected patients without evidence of fat redistribution (age, 39.4 ± 0.9 years; BMI, 24.0 ± 0.4 kg/m²; WHR, 0.90 ± 0.01; duration of HIV infection, 7.7 ± 0.7 years; duration of antiretroviral therapy, 3.0 ± 0.6 years; and HIV RNA level, 23,175 ± 9927 copies/mL) did not demonstrate elevated 10-year CHD risk estimate, compared with matched

Framingham control subjects (10-year CHD risk estimate, 4.1% ± 0.7% vs. 3.3% ± 0.3%, respectively; $P = .27$).

Framingham control subjects were then matched with HIV-infected subjects according to sex, age, BMI, and WHR, which revealed that the 10-year CHD risk estimate was not significantly elevated among HIV-infected patients with fat redistribution, compared with Framingham control subjects (7.6% ± 0.6% vs. 7.6% ± 0.4%; $P = .9$; table 2). Thirty percent of HIV-infected patients with fat redistribution had a 10-year CHD risk estimate of ≥10%, compared with 28% of the WHR-matched control subjects ($P = .7$). Matching by WHR did not change the results of the comparison between HIV-infected subjects without fat redistribution and Framingham control subjects; there was no difference in 10-year CHD risk estimates between the 2 groups (4.1% ± 0.7% vs. 3.4% ± 0.4% for 30 HIV-infected subjects vs. 58 control subjects; $P = .37$).

In subanalyses of HIV-infected subjects with fat redistribution, 10-year CHD risk estimates differed on the basis of pattern of fat redistribution (e.g., primary lipoatrophy vs. abdominal lipohypertrophy vs. mixed lipodystrophy; table 3). Anthropometric measurements confirmed that thigh circumference and arm circumference were lowest among patients with lipoatrophy, whereas waist circumference was highest among patients with abdominal lipohypertrophy. Subjects with primary lipoatrophy demonstrated the highest 10-year CHD risk estimate (9.2% ± 1.8%, compared with the abdominal lipohypertrophy group, 4.3% ± 0.7%; compared with the mixed lipodystrophy group, 7.6% ± 0.8%; $P = .043$, for overall comparison between the groups; $P < .05$, for the primary lipoatrophy group vs. the abdominal lipohypertrophy group; and $P < .05$, for the mixed lipodystrophy group vs. the abdominal lipohypertrophy group).

Ten-year CHD risk estimates were also stratified by the subjects' PI use, as shown in table 4. There was no difference in 10-year CHD risk estimates between patients currently receiving a regimen that contained a PI versus those not currently receiving a regimen that contained a PI.

DISCUSSION

In this study of HIV-infected patients experiencing fat redistribution, 10-year CHD risk estimates were significantly elevated, particularly among men. Furthermore, the percentage of patients with moderate risk (i.e., a 10-year CHD risk estimate of ≥10%) was more than double the percentage among control subjects. However, this difference did not persist when control subjects were further selected to match the increased WHR and central adiposity of the HIV-infected subjects. In contrast, HIV-infected patients without fat redistribution did not demonstrate an elevated 10-year CHD risk estimate, regardless of WHR

Table 2. Ten-year coronary heart disease (CHD) risk assessment for HIV-infected subjects with fat redistribution syndrome, compared with age-, sex-, body mass index (BMI)–, and waist-to-hip ratio (WHR)–matched control subjects from the Framingham Offspring Cohort.

Characteristic or laboratory value	WHR-matched subjects		
	HIV infected (n = 84)	Control (n = 168)	P
Age, years	43.5 ± 0.9	45.3 ± 0.6	.09
BMI	26.4 ± 0.5	26.7 ± 0.3	.6
Body circumference, cm			
Waist	95.0 ± 1.2	96.8 ± 0.8	.2
Hip	97.9 ± 1.0	99.8 ± 0.6	.1
Thigh	51.0 ± 0.6	58.5 ± 0.4	.0001
Arm	31.8 ± 0.4	32.1 ± 0.2	.5
WHR	0.97 ± .006	0.97 ± .004	.9
Total cholesterol, mg/dL	227 ± 6	202 ± 3	.0003
HDL cholesterol, mg/dL	38 ± 1	45 ± 1	.0001
Fasting glucose, mg/dL	92 ± 1	98 ± 1	.0004
Blood pressure, mm Hg			
Systolic	121 ± 1	124 ± 1	.1
Diastolic	77 ± 1	77 ± 1	.8
Current smoker, % of subjects	27	35	.2[a]
CHD risk assessment			
10-year risk, %	7.6 ± 0.6	7.6 ± 0.4	.9
10-year risk of ≥10%, percentage of subjects	30	28	.74[a]

NOTE. Data are mean ± SEM, unless otherwise indicated. *P* values were determined by Student's *t* test, unless otherwise indicated. HDL, high-density lipoprotein.

[a] Determined by χ^2 test.

matching. Of interest, the relative risk of CHD was most increased among patients with lipoatrophy. Furthermore, current PI use conferred no additional increase in the 10-year CHD risk estimate.

The mechanisms of fat redistribution in HIV-infected patients are not known and may relate to stimulatory effects of antiretroviral drugs on adipogenesis in certain fat depots, with effects that increase lipolysis and/or apoptosis in other depots. Increased visceral adiposity and reduced amounts of subcutaneous fat have been shown to independently predict hyperinsulinemia in this population [16] and have been associated with other metabolic abnormalities, including hypertension and dyslipidemia, as well as increased cardiovascular disease risk in HIV-uninfected patients [17–22]. In this study, when control subjects were matched to HIV-infected subjects according to WHR, the 10-year CHD risk estimate in the control subjects increased and was no longer different from that of the HIV-infected patients, suggesting important potential influences of

Table 3. Anthropometric and 10-year coronary heart disease (CHD) risk assessment data for HIV-infected subjects, according to pattern of fat redistribution.

Characteristic or laboratory value	Subjects with lipoatrophy (n = 15)	Subjects with lipohypertrophy (n = 15)	Subjects with mixed lipodystrophy (n = 61)
Percentage of cohort	16.5	16.5	67
Age, years	43.9 ± 2.3	39.0 ± 1.5[a]	44.0 ± 1.1[a]
BMI	23.0 ± 0.5[b,c]	29.2 ± 1.3[a,b]	26.3 ± 0.5[a,c]
Body circumference, cm			
Waist	85.4 ± 1.2[b,c]	105.2 ± 2.7[a,b]	94.6 ± 1.3[a,c]
Hip	91.4 ± 0.9[b,c]	106.6 ± 2.6[a,b]	97.0 ± 1.0[a,c]
Thigh	48.3 ± 0.9[b]	55.1 ± 1.8[a,b]	50.2 ± 0.6[a]
Arm	30.5 ± 0.9	33.4 ± 1.3	31.2 ± 0.5
WHR	0.93 ± 0.01[b,c]	0.99 ± 0.01[b]	0.97 ± 0.01[c]
Total cholesterol, mg/dL	227 ± 18	215 ± 10	228 ± 7
HDL cholesterol, mg/dL	31 ± 2[b]	38 ± 3[b]	39 ± 2
Fasting glucose, mg/dL	92 ± 5	92 ± 3	92 ± 1
Blood pressure, mm Hg			
Systolic	118 ± 3	118 ± 3	121 ± 2
Diastolic	76 ± 2	77 ± 2	76 ± 1
Current smoker, % of subjects	40.0	26.7	29.8
CHD risk assessment			
10-year risk, %	9.2 ± 1.8[b]	4.3 ± 0.7[a,b]	7.6 ± 0.8[a]
10-year risk of ≥10%, percentage of subjects	42.9[d]	0[d]	33.3[d]

NOTE. BMI, body mass index; HDL, high-density lipoprotein; WHR, waist-to-hip ratio.
[b] For lipoatrophy group vs. lipohypertrophy group, $P < .05$, by Student's t test.
[c] For lipoatrophy group vs. mixed lipodystrophy group, $P < .05$, by Student's t test.
[a] For lipohypertrophy group vs. mixed lipodystrophy group, $P < .05$, by Student's t test.
[d] For overall comparison between groups, $P = .003$, by χ^2 test.

central adiposity. In addition, recent data suggest that certain antiretroviral medications can have direct effects on glucose and lipid metabolism [5, 23], and these direct and indirect effects may simultaneously contribute to increased CHD risk.

We used the Framingham risk equation to determine 10-year CHD risk estimates. This equation was developed on the basis of coronary events that occurred during longitudinal follow-up of the Framingham cohort. The equation uses age, total cholesterol level, HDL cholesterol level, blood pressure, presence of diabetes, and smoking status data, and it is a well-established tool to evaluate CHD risk. Of note, the Framingham risk equation does not include WHR or a measure of central adiposity in the calculation of risk. Therefore, WHR matching would not, a priori, be expected to result in a matched CHD risk estimate. However, in this study, selection of control subjects with a similar degree of central adiposity brought the 10-year CHD risk estimate for control subjects to a level similar to that for HIV-infected subjects with fat redistribution.

One potential caveat for use of the Framingham risk equation is that the definition of diabetes includes a fasting plasma glucose level of >140 mg/dL. If we had used the more liberal World Health Organization definition of diabetes (i.e., fasting glucose level of >126 mg/dL or a 2-h postchallenge glucose level of >200 mg/dL), we might have expected an increase in the 10-year CHD risk because of inclusion of an increased number of patients with diabetes. Previous investigation of this population found that 7% of HIV-infected patients with lipodystrophy met the WHO criteria for diabetes [2]. Therefore, our data, which used the standard Framingham risk equation, may somewhat underestimate the 10-year risk of CHD in this population. In both patient and control groups, subjects with previously diagnosed diabetes were excluded; therefore, the overall CHD risk estimates made here are likely lower than those for a more inclusive population. HIV-infected subjects were selected for the presence of fat redistribution, and this sample may not reflect the larger population of HIV-infected patients who experience more-subtle changes in body fat distribution. Furthermore, a single determination of the presence of hyperlipidemia may not accurately reflect long-term lipid levels, which may vary over time with changes in health and medication regimens in HIV-infected patients.

Although the Framingham equation has been validated in

Table 4. Anthropometric and 10-year coronary heart disease (CHD) risk assessment for HIV-infected subjects with fat redistribution syndrome, according to protease inhibitor (PI) use.

Characteristic or laboratory value	Subjects currently using a PI (n = 63)	Subjects not currently using a PI (n = 28)	P
Age, years	42.8 ± 1.0	44.0 ± 1.7	.54
BMI	26.5 ± 0.6	25.4 ± 0.8	.28
Body circumference, cm			
Waist	95.4 ± 1.4	93.5 ± 2.1	.45
Hip	97.9 ± 1.1	97.0 ± 1.7	.66
Thigh	51.1 ± 0.6	49.8 ± 1.0	.29
Arm	32.1 ± 0.5	29.1 ± 0.8	.02
WHR	0.97 ± 0.007	0.96 ± 0.011	.39
Total cholesterol, mg/dL	231 ± 7	212 ± 11	.14
HDL cholesterol, mg/dL	37 ± 1	38 ± 3	.54
Fasting glucose, mg/dL	92.0 ± 1.7	92.4 ± 2.2	.88
Blood pressure, mm Hg			
Systolic	121 ± 2	119 ± 2	.57
Diastolic	77 ± 1	76 ± 2	.61
Current smoker, % of subjects	27.1	39.3	.26[a]
CHD risk assessment			
10-year risk, %	7.7 ± 0.7	6.4 ± 1.0	.35
10-year risk of ≥10%, percentage of subjects	32	22	.34[a]

NOTE. Data are mean ± SEM, unless otherwise indicated. P values were determined by Student's t test, unless otherwise indicated. BMI, body mass index; HDL, high-density lipoprotein; WHR, waist-to-hip ratio.

[a] Determined by χ^2 test.

other populations of patients [24], the reliability of this equation to predict coronary events among HIV-infected patients with fat redistribution and multiple metabolic abnormalities remains unknown. Although preliminary studies suggest an increase in CHD risk [7, 8], Bozzette et al. [25] found no increase in the number of hospitalizations for cerebrovascular or cardiovascular events or in the mortality rate from 1993 through 2001 in a large cohort of HIV-infected patients. However, prospective, longitudinal follow-up studies conducted over a sufficient number of years have not been performed with HIV-infected populations. Nonetheless, we believe that our data provide a reasonable estimate of CHD risk that can be used to help target risk factor modification in this population, including treatment of high blood pressure, treatment of dyslipidemia, and smoking cessation. According to current National Cholesterol Education Program (NCEP) III guidelines, HIV-infected patients at increased risk for CHD because of modifiable risk factors should be treated with lifestyle modification and medication therapy, when appropriate [26].

The metabolic syndrome is characterized by abdominal obesity, dylipidemia, hypertension, and hyperglycemia; HIV-unin-fected individuals with this constellation of findings have an increased incidence of insulin resistance and CHD. In this study, a significant percentage of HIV-infected subjects met the Adult Treatment Panel of NCEP III criteria for the metabolic syndrome (46% of HIV-infected subjects vs. only 15% of the age- and weight-matched Framingham control subjects; $P = .001$, by χ^2 analysis) [27]. For HIV-uninfected patients, much attention has recently been focused on modifying cardiovascular risk factors in patients with the metabolic syndrome [28], and similar efforts to modify risk factors for CHD in HIV-infected patients with the metabolic syndrome may also be warranted. For example, a high percentage of HIV-infected patients smoked cigarettes (31% of all HIV-infected subjects with fat redistribution and 58% of female HIV-infected subjects). A reduction in the high smoking rates may reduce the CHD risk in this population.

Estimates of CHD risk were not significantly elevated among women with HIV infection and fat redistribution, compared with women in the control group. This observation may be related in part to the relatively smaller sample size and younger age of women in this study. In addition, there may be a pro-

tective effect of sex with respect to fat redistribution. Although the WHR was elevated, HIV-infected women did not differ from control subjects in hip circumference, suggesting a partial preservation of the gynoid fat distribution pattern. Further prospective studies with larger sample sizes are needed to determine the sex-specific effects of fat redistribution and metabolic abnormalities on CHD risk in men and women with HIV infection.

Ten-year CHD risk estimates were not elevated among current PI users, but this comparison may be limited because of the patients' prior exposure to these agents, which might affect fat redistribution, lipid level, and glucose level and, therefore, increase risk indirectly. Although it was not statistically significant, the increased proportion of smokers among persons not receiving PIs may have contributed to this lack of association between PI use and CHD risk. Mary-Krause et al. [8] demonstrated increased risk of CHD among PI users in a large French cohort, whereas no increased risk was seen among current PI users in the Kaiser-Permanente study [7]. Furthermore, use of other agents, such as NRTIs, may also increase the risk of CHD, but this study was not designed to ascertain the relative risk of NRTIs, because the vast majority of our patients were receiving such therapy. Further longitudinal studies are needed to determine whether use of PIs or any other antiretroviral agents or classes of agents confers increased CHD risk.

An unanticipated finding of this study was that 10-year CHD risk estimates were highest among HIV-infected subjects for whom anthropometric measurements confirmed a primarily lipoatrophic pattern of fat loss. It is well recognized that severe subcutaneous fat loss, like other conditions of lipodystrophy, may well predispose patients to insulin resistance, diabetes, and dyslipidemia [29]. A nonsignificant increased proportion of smokers and greater age among subjects with lipoatrophy may have contributed to this finding. However, our results suggest that subcutaneous fat loss in patients with HIV disease may substantially contribute to CHD risk. Although more-specific measurements of visceral and subcutaneous fat may correlate more tightly with CHD risk, anthropometry can be performed at all clinics and may be a valuable adjunct in the estimation of CHD risk in HIV-infected patients.

In conclusion, HIV-infected patients with fat redistribution demonstrate an increase in 10-year CHD risk estimates, but this risk does not differ from that of a population with a similar central pattern of fat distribution. Nearly one-third of the HIV-infected patients evaluated in this study have a ⩾10% risk of having CHD diagnosed in the next 10 years, as determined on the basis of the Framingham risk equation estimates. Further longitudinal follow-up studies are needed to determine the actual incidence of CHD and whether CHD risk reduction decreases morbidity in this population. Nonetheless, our data strongly suggest that modification of risk factors for CHD is warranted for HIV-infected patients with fat redistribution.

Acknowledgments

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