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Abnormal Glucose Metabolism among Older Men with or At-Risk for HIV

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Abstract

Objectives—To determine factors associated with diabetes, insulin resistance, and abnormal glucose tolerance in older men with or at-risk for HIV.

Methods—Diabetes was assessed by self-report in 643 men ≥49 years old with- or at-risk for HIV. In a subset of 216 men without previously-diagnosed diabetes (including 90 HIV-uninfected men; 28 HIV-infected, antiretroviral-naïve men; 28 HIV-infected men taking non-protease inhibitor-containing HAART; and 70 HIV-infected men taking protease inhibitor-containing HAART), an oral glucose tolerance test with insulin levels was performed. HIV serology, CD4+ count, weight, height, and waist circumference were measured. Antiretroviral use, drug use, family history of diabetes, physical activity and sociodemographic data were obtained using standardized interviews.

Results—Of 643 participants, 116 (18%) had previously-diagnosed diabetes. With the oral glucose tolerance test, 15/216 men (7%) were found to have undiagnosed diabetes and 40 (18%) impaired glucose tolerance. Factors independently associated with previously-diagnosed diabetes included use of non-protease inhibitor-containing HAART, methadone treatment, positive CAGE test for alcoholism, obesity, and family history of diabetes. Factors independently associated with greater insulin resistance included waist circumference and heroin use. Factors independently associated with abnormal glucose tolerance (impaired glucose tolerance or diabetes) included age ≥55 years and Hispanic ethnicity.

Conclusions—HIV-infected men with diabetes risk factors should undergo screening for diabetes regardless of HAART use. Interventions targeting modifiable risk factors, including overweight and physical inactivity, are warranted. The potential impact of opiate and alcohol abuse on glucose metabolism should be recognized in clinical care, and addressed in future research studies of HIV-infected persons.

Keywords

diabetes mellitus; insulin resistance; metabolic complications of HIV infection; antiretroviral therapy; opiate use

Introduction

Since the advent of highly active antiretroviral therapy (HAART), increased frequencies of insulin resistance and its clinical correlates, impaired glucose tolerance (IGT) and diabetes, have been reported among HIV-infected individuals [1-3]. Epidemiologic studies have

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demonstrated an increased risk for these disorders associated with protease inhibitor (PI) use [4,5], which has been attributed to both a direct effect on insulin sensitivity by PIs [6], and HAART-associated changes in fat distribution [7]. However most studies of glucose metabolism in HIV-infected individuals have lacked a demographically and behaviorally similar HIV-negative comparison group, and have included few drug users or adults beyond the fifth decade of life. One study that included both men with and men without HIV infection found that HAART use was associated with an increased risk of incident diabetes, but the study was limited in that fasting glucose levels, rather than glucose tolerance tests, were used to diagnose diabetes, and data on family history and physical activity were not available [8]. Two recent studies of glucose tolerance in midlife HIV-infected and at-risk women found that classic diabetes risk factors, rather than HIV or HAART, were associated with diabetes and abnormal glucose tolerance [9,10]. The factors associated with abnormal glucose tolerance and insulin resistance among midlife and older HIV-infected men are not known.

The objective of this study was to determine the associations of HIV, HAART and other factors, including drug and alcohol abuse, with prevalent diabetes in a cohort of men ≥ 49 years old with or at-risk for HIV. In addition we performed an oral glucose tolerance test (OGTT) with insulin levels among a subset of men without a prior diagnosis of diabetes to identify factors associated with insulin resistance and abnormal glucose tolerance.

Methods

Study participants

We performed a cross-sectional analysis of factors associated with previously-diagnosed diabetes among 643 men participating in the Cohort of HIV at-risk Aging Men's Prospective Study (CHAMPS), an ongoing longitudinal study of selected medical outcomes in men ≥49 years old with- or at-risk for HIV. Participant recruitment and study design have been described in detail elsewhere [11]. Briefly, between August 2002 and December 2003, men aged 49 or older who either had documented HIV infection or were at risk for HIV through injection drug use or high risk sexual behavior were enrolled from the community in the Bronx, NY. CHAMPS participants are followed with semi-annual research visits, at which a standardized interview is administered, blood is obtained for HIV serology and T-lymphocyte studies, and weight, height, and waist circumference are measured.

Interview data

Interview data, including medical history, antiretroviral use, family history, sociodemographic characteristics, and drug use behaviors were collected at research visits. At each visit, participants were asked whether they had been diagnosed with diabetes (or "high blood sugar"), age at diabetes diagnosis, and whether they had taken medication for diabetes. Participants were administered the CAGE questionnaire to screen for alcoholism [12], with a positive test defined as an affirmative response to ≥2 items [13]. Physical activity was defined as moderate or strenuous exercise for ≥20 minutes on >1 day per week.

Metabolic Substudy enrollment

Between March 2003 and July 2004, CHAMPS participants were screened for the Metabolic Substudy at research visits. To be enrolled, men had to meet criteria for one of the following enrollment groups: 1) HIV-uninfected; 2) HIV-infected and antiretroviral-naïve; 3) HIV-infected, currently taking HAART, and PI-naïve ("non-PI HAART"); or 4) HIV-infected and currently taking HAART including a PI ("PI-HAART"). Participants were ineligible if they reported a history of diabetes, were taking anti-diabetic medications, or had poor venous access. The study was approved by the Institutional Review Boards for the protection of human

subjects of Montefiore Medical Center and Albert Einstein College of Medicine. All participants provided written informed consent.

Oral glucose tolerance test

Following enrollment, Metabolic Substudy participants underwent an OGTT according to World Health Organization procedures [14] at the Einstein General Clinical Research Center. Participants were instructed to take their morning dose of medications with water and to report to the medical center after a 10-16h overnight fast. Seventy-five grams of dextrose in water was administered orally over <5 min. Blood samples were drawn immediately before and 120 min after ingestion of dextrose. Waist and hip circumference were measured.

Assays

Fasting specimens for insulin determination were collected in iced, heparinized tubes. Plasma was separated within 20 min of collection and stored at −70°C until the day of the assay. Plasma insulin was measured by double antibody radioimmunoassay in the Hormone Assay Core of the Einstein Diabetes Research and Training Center (intrassay coefficient of variance [CV] 7.2%, interassay CV 9.4%; cross-reactivity with proinsulin 36.8%). Specimens for glucose determination were collected at 0 and 120 min in tubes with glycolytic inhibitors. Plasma glucose was measured by the hexokinase method.

Data analysis

The associations of previously-diagnosed diabetes with sociodemographic characteristics, drug and alcohol use, and clinical variables, including HIV serostatus, HAART use, and CD4 + count, were determined for the entire cohort. In this analysis, diabetes was defined by self-report of a diabetes diagnosis. Comparisons were performed using chi-square or Fisher's exact tests for categorical variables, and Student's t-test or Mann-Whitney test for continuous variables. Multivariate logistic regression analysis was performed to assess predictors of diabetes. Corresponding ORs and 95% CIs were computed.

For participants in the Metabolic Substudy, additional outcome measures were insulin resistance and abnormal OGTT (i.e., IGT or diabetes). Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR): (fasting insulin [μU/mL] × fasting glucose [mmol/L])/22.5 [15]. IGT and diabetes were determined using American Diabetes Association criteria, which define IGT as a fasting glucose level <126 mg/dL and a 120-min glucose level ≥140 mg/dL and <200 mg/dL during an OGTT; and diabetes as a fasting glucose level ≥126 mg/dL, or a 120-min glucose level ≥200 mg/dL [16].

Comparisons of anthropometric parameters, glucose and insulin levels, and insulin resistance for the enrollment groups and other factors of interest were performed using ANOVA or Kruskal-Wallis tests. For insulin resistance, analysis of covariance was performed to adjust the effect of possible confounding factors on the observed mean differences, using SAS software version 8.1 (Cary, NC). This analysis was based on the ranks of the dependent variable, as it was not normally distributed. Multivariate logistic regression analysis was performed to assess predictors of abnormal OGTT. In constructing multivariate models, we included enrollment group (HIV-uninfected; HIV-infected, antiretroviral-naïve; HIV-infected, taking non-PI HAART; and HIV-infected, taking PI-HAART), as well as factors whose univariate tests yielded a value of $p \leq .2$. SPSS software version 10.0 was used for all other analyses. Statistical significance was determined using 2-tailed tests with alpha =.05.

Results

Study participants

Participant characteristics are shown in Table 1. Of 643 participants, 364 (57%) were HIV-infected. Diabetes risk factors were common; 375 (58%) had a body mass index (BMI) ≥25 kg/m^2, 450 (70%) were not physically active, and of 624 participants with available data, 244 (39%) had a first-degree relative with diabetes. HIV-uninfected participants had a higher prevalence of obesity (BMI ≥30 kg/m^2) (27% vs. 13%, p <.0005) and abdominal obesity (waist circumference >102 cm) (27% vs. 13%, p<.0005) compared with HIV-infected men. Nearly half (47%) of the men had a positive CAGE test for alcoholism, and 35% reported either heroin or cocaine use in the last six months, with no difference by HIV status.

The majority (n=209, 57%) of HIV-infected participants were diagnosed with HIV >10 years ago, and most (n=326, 90%) were antiretroviral-experienced. Of 269 participants with a history of PI use, 160 (60%) had taken nelfinavir, 136 (51%) indinavir, 105 (39%) lopinavir/ritonavir, 75 (28%) ritonavir, 67 (25%) saquinavir, and 22 (8%) amprenavir. The median duration of PI use was 48.0 (IQR 24.0-72.0) months.

Prevalence of previously-diagnosed diabetes

Of 643 participants, 116 (18%) reported being told by a healthcare provider that they had diabetes. The median age at diagnosis was 51.0 years (range 14-67). Seventy percent (n=81) of men with diabetes were diagnosed within the last 5 years, and 84% (n=97) reported a history of taking anti-diabetic medication. There was no difference in diabetes prevalence by HIV status (16% for HIV-infected vs. 20% for uninfected, p=.24) or, among HIV-infected men, by PI use (18% for PI-experienced vs. 12% for PI-naive, p=.13).

Factors associated with previously-diagnosed diabetes

The factors associated with previously-diagnosed diabetes are shown in Table 2. After controlling for age, race/ethnicity, physical activity, HIV, and PI use, factors independently associated with previously-diagnosed diabetes included use of non-PI HAART (OR_{adj} 1.8, 95% CI 1.03, 3.0), current methadone treatment (OR_{adj} 6.7, 95% CI 3.8, 11.9), positive CAGE test for alcoholism (OR_{adj} 1.7, 95% CI 1.1, 2.7), BMI (reference: <25.0 kg/m^2; for 25.0-29.9 kg/m^2, OR_{adj} 1.4, 95% CI 0.8, 2.5; for ≥30.0 kg/m^2, OR_{adj} 3.3, 95% CI 1.8, 6.2), and family history of diabetes (OR_{adj} 3.5, 95% CI 2.2, 5.6). Substitution of waist circumference for BMI did not significantly alter the results (for waist circumference >102 cm OR_{adj} 2.3, 95% CI 1.3, 4.0).

Metabolic Substudy participants

Of 216 participants, 90 (42%) were HIV-uninfected; 28 (13%) were HIV-infected, antiretroviral-naïve; 28 (13%) were HIV-infected, taking non-PI HAART; and 70 (32%) were HIV-infected, taking PI-HAART. Among the 28 participants taking non-PI HAART, 20 (71%) were taking a non-nucleoside reverse transcriptase inhibitor and ≥2 nucleoside reverse transcriptase inhibitors (NRTIs), and 8 (29%) were taking ≥3 NRTIs only. Among the 70 participants taking PIs, 34 (49%) were taking lopinavir/ritonavir, 21 (30%) nelfinavir, 9 (13%) indinavir, 6 (9%) ritonavir, and 3 (4%) saquinavir. The median duration of PI use was 54.0 (IQR 24.0 – 82.5) months.

Anthropometrics and OGTT results

Anthropometrics and OGTT results are shown in Table 3. There was no significant difference in BMI, waist circumference, waist-hip ratio, insulin, or glucose levels by HIV serostatus, HAART, or PI use. Waist circumference, waist-hip ratio, and BMI were positively correlated

with insulin resistance (r=0.551, p<.0005; r=0.331, p<.0005; r=0.554, p<.0005) and 120-minute glucose levels (r=.186, p=.007; r=.118, p=.09; r=.199, p=.003), respectively.

Factors associated with insulin resistance

Insulin resistance (μU/mL·mmol) was greatest in participants with diabetes and lowest in those with normal glucose tolerance (mean ± SEM 11.07± 3.19 for diabetes, vs. 5.09 ± 0.70 for IGT, vs. 3.43 ± 0.20 for normal OGTT, p=.001). There was no difference in insulin resistance by HIV status, HAART or PI use (Table 3), even after excluding men with newly-diagnosed diabetes (mean ± SEM 3.89 ± 0.38 for HIV-uninfected, vs. 3.95 ± 0.63 for HIV-infected, antiretroviral-naïve, vs. 3.83 ± 0.68 for HIV-infected, on non-PI HAART, vs. 3.53 ± 0.28 for HIV-infected, on PI-HAART, p=0.96). The factors associated with insulin resistance on multivariate analysis are shown in Table 4. In a model controlling for HIV, HAART, and PI use, factors independently associated with insulin resistance included waist circumference (p<.0001), and a history of heroin use (p=.005); family history of diabetes was of borderline significance (p=.05). Substitution of BMI for waist circumference did not alter the results. Models excluding men with a history of steroid (n=2) or megestrol (n=2) use had similar results. There was no association between insulin resistance and age, race/ethnicity, physical activity, CD4+ count, methadone or cocaine use.

Prevalence of newly-diagnosed IGT and diabetes

Forty (18%) participants had an OGTT consistent with IGT, and an additional 15 (7%) with diabetes. Six (40%) men with diabetes had a fasting glucose level <126 mg/dL. Fifty-six (26%) men had impaired fasting glucose (IFG; fasting glucose ≥100 mg/dL and <126 mg/dL), of whom 15 (27%) had IGT and 5 (9%) had diabetes using 120-min glucose criteria only. There was no significant difference in IFG, IGT, or diabetes prevalence by HIV serostatus, HAART, or PI use (Table 3).

Factors associated with abnormal OGTT

The factors associated with an abnormal OGTT among Metabolic Substudy participants are shown in Table 5. In a logistic regression model controlling for waist circumference, family history of diabetes, physical activity, HIV, HAART, and PI use, factors independently associated with an abnormal OGTT included age ≥55 y (OR_{adj} 2.0, 95% CI 1.03, 3.9), and Hispanic ethnicity (reference: white, OR_{adj} 3.8, 95% CI 1.05, 14.0). These estimates were essentially unchanged when men with a history of using megestrol or prednisone were excluded. There was no association between glucose tolerance and CD4+ count, use of illicit drugs or methadone, positive CAGE test for alcoholism, or BMI, even if waist circumference was removed from the model.

Discussion

In this study of predominantly older African American and Hispanic men with or at-risk for HIV, classic risk factors for diabetes were common: 58% had a BMI ≥25 kg/m^2, 39% had a first-degree relative with diabetes, and 70% were not physically active. Thus, not surprisingly, the 18% prevalence of previously-diagnosed diabetes in this cohort is higher than the age-adjusted rate of 6.6% found among men participating in the National Health and Nutrition Examination Survey 1999-2000 [17], or the rate of 8% found among the somewhat younger, predominantly white men with or at-risk for HIV participating in the Multicenter AIDS Cohort Study [8]. Despite this high prevalence, additional cases of diabetes and IGT were detected by an OGTT in a substantial number of participants. When we extrapolated the OGTT results from the Metabolic Substudy to the entire cohort, we estimated the prevalence of undiagnosed diabetes as 6%, and of IGT as 15%, meaning that approximately 39% of the cohort had

abnormal glucose tolerance. These findings demonstrate that abnormal glucose metabolism is a major health problem for older men with or at-risk for HIV.

A number of previous studies have reported an increased risk of incident hyperglycemia or diabetes with PI use [4,5,18]. In contrast, we did not observe a statistically significant association between PI use and insulin resistance or abnormal glucose tolerance. While the PI indinavir has been shown to have a direct effect on insulin resistance [19,20], most other PIs have not [21-24]; thus the fact that only 9 (13%) of the 70 PI-treated patients in our Metabolic Substudy were taking indinavir may explain this lack of an association. In addition, as demonstrated by Hadigan et al., in treatment-experienced patients such as ours, HAART-associated fat redistribution may be a more important determinant of insulin resistance than PI use [7]. While we did not assess peripheral lipoatrophy, in our cohort of mostly overweight and obese men, truncal adiposity, as measured by waist circumference [25], was strongly associated with previously-diagnosed diabetes and insulin resistance. Our finding that non-PI HAART was associated with previously-diagnosed diabetes should be interpreted cautiously, as the number of participants taking non-PI HAART was small, and this finding may be the result of multiple testing. Alternatively, this finding may reflect the observational nature of our study; aware of the putative association between PIs and diabetes, providers may have been less likely to prescribe PIs to persons with diabetes.

Most metabolic studies conducted in HIV-infected patients have not examined the relationship between substance abuse and disorders of glucose metabolism. A recent study of HIV-infected clinic patients with a high prevalence of drug abuse found that the metabolic syndrome was less common among patients with an injection drug use history than among patients in other HIV transmission groups [26]. In contrast, in our cohort of predominantly current and former drug users, we found that opiate use and a positive CAGE test for alcoholism were associated with abnormal glucose metabolism. Men receiving methadone were over six times more likely to have previously-diagnosed diabetes compared with men who were not receiving methadone. Furthermore a history of heroin use was associated with greater insulin resistance. The association between methadone use and diabetes is consistent with our prior findings in a demographically and behaviorally similar cohort of somewhat younger women with or at-risk for HIV [9]. While this association may reflect the fact that men receiving methadone were more likely to be in care, and thus more likely to have their diabetes diagnosed, it is also supported by observational studies in which opiate addicts were found to have greater insulin resistance [27] and impaired insulin secretion [28,29] compared with healthy controls. It is also possible that methadone and heroin use are markers of hepatitis C, a risk factor for diabetes which is prevalent among drug users [30,31]. Our finding that a positive CAGE test for alcoholism, present in almost half of our study sample, was associated with previously-diagnosed diabetes is consistent with prior epidemiologic studies that demonstrate an increased risk of diabetes associated with heavy alcohol use in men [32,33].

This study had several strengths, in particular the use of an HIV-uninfected comparison group with a similar demographic and behavioral profile. Inclusion of family history and physical activity data also allowed us to adjust for these important correlates of diabetes. The cross-sectional nature of our analysis does, however, limit our ability to assess causal relationships of antiretroviral treatment and other factors with abnormal glucose metabolism. In addition we did not assess the effect of hepatitis C on glucose metabolism. Prospective studies are necessary to investigate these important issues. Finally, the findings in our cohort of predominantly older African American and Hispanic men may not apply to other HIV-infected populations with different sociodemographic characteristics. However given that both HIV infection and diabetes are more prevalent among African Americans and Hispanic Americans than non-Hispanic whites [17,34], understanding the epidemiology of abnormal glucose metabolism in this population is of great importance.

We have demonstrated that diabetes and IGT affect a major proportion of older men with or at-risk for HIV, particularly those who abuse opiates or alcohol. Given the lifestyle characteristics and genetic predisposition of this population, it is likely that the burden of disease will increase as these men age. Based on our findings, we recommend that clinicians screen for diabetes in all HIV-infected patients with diabetes risk factors, regardless of whether or not they require HAART. In addition, interventions targeting modifiable risk factors, including overweight and physical inactivity, should be implemented in HIV primary care settings. The potential impact of opiate and alcohol abuse on glucose metabolism should be recognized in clinical care, and addressed in future research studies of HIV-infected persons.

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Abbreviations

HAART
highly active antiretroviral therapy

IGT
impaired glucose tolerance

PI
protease inhibitor

HIV
human immunodeficiency virus

OGTT
oral glucose tolerance test

OR
odds ratio

CI
confidence interval

CV
coefficient of variance

CHAMPS
Cohort of HIV at-risk Aging Men's Prospective Study

BMI
body mass index

IFG
impaired fasting glucose

SEM
standard error of the mean

ANOVA
analysis of variance

Table 1

Participant Characteristics[a,b]

	Entire Cohort (N=643)		Metabolic Substudy (N=216)	
	HIV-Uninfected (N = 279)	**HIV-Infected (N = 364)**	**HIV-Uninfected (N = 90)**	**HIV-Infected (N = 126)**
Median age, y (range)	54 (50-81)	54 (49-75)	54 (50–73)	54 (49-75)
Race/ethnicity, N (%)[b]				
African American	134 (48)	221 (61)	50 (56)	85 (68)
White	56 (20)	44 (12)	16 (18)	12 (10)
Hispanic	80 (29)	86 (24)	20 (22)	24 (19)
Other	9 (3)	13 (4)	4 (4)	5 (4)
Unemployed, N (%)[c, d]	214 (77)	321 (88)	67 (74)	116 (92)
Graduated high school, N (%)	194 (70)	261 (72)	65 (72)	96 (76)
Body mass index, N (%)[c]				
< 18.5 kg/m^2 (underweight)	3 (1)	7 (2)	2 (2)	2 (2)
18.5 –24.9 kg/m^2 (normal)	86 (31)	172 (47)	39 (43)	60 (48)
25 – 29.9 kg/m^2 (overweight)	114 (41)	137 (38)	32 (36)	51 (40)
≥ 30 kg/m^2 (obese)	76 (27)	48 (13)	17 (19)	13 (10)
Waist circumference >102 cm, N (%)[c,d]	75 (27)	46 (13)	16 (18)	13 (10)
Family history of diabetes, N (%)[d]	109 (39)	135 (37)	36 (40)	40 (32)
Physical activity, N (%)[d]	80 (29)	109 (30)	27 (30)	47 (37)
Smoking, N (%)[b]				
Never	26 (9)	35 (10)	5 (6)	13 (10)
Former	49 (18)	100 (28)	13 (14)	33 (26)
Current	204 (73)	229 (63)	72 (80)	80 (64)
Ever injected drugs, N (%)	179 (64)	226 (62)	54 (60)	81 (64)
Ever used heroin, N (%)[c]	220 (79)	236 (65)	65 (72)	83 (66)
Ever used cocaine, N (%)[b]	254 (91)	310 (85)	79 (88)	107 (85)
Heroin use in last 6 months, N (%)[b, d]	61 (22)	53 (14)	20 (22)	17 (14)
Cocaine use in last 6 months, N (%)[d]	80 (29)	101 (28)	27 (30)	39 (31)
Current methadone treatment, N (%)[c]	76 (27)	46 (13)	9 (10)	17 (14)
Positive CAGE test for alcoholism, N (%)	125 (45)	176 (48)	41 (46)	59 (47)
Medication use, N (%)				
Megestrol	0 (0)	3 (1)	0 (0)	2 (2)
Prednisone	1 (0.4)	6 (1.6)	0 (0)	2 (2)
CD4+ count, N (%)[d]				
≤200 cells/mm^3		75 (21)		25 (20)
201-500 cells/mm^3		154 (42)		60 (48)
>500 cells/mm^3		96 (26)		32 (25)
Antiretroviral use (N, %)				
Never		38 (10)		28 (22)
Yes, but PI-naive		57 (16)		28 (22)
Yes, including a PI		269 (74)		70 (56)

[a] HIV, human immunodeficiency virus; PI, protease inhibitor

[b] $P < .05$ for chi-square test comparing HIV-infected and uninfected participants in entire cohort

[c] $P < .0005$ for chi-square test comparing HIV-infected and uninfected participants in entire cohort

[d] Missing data for unemployed (n=10), waist circumference (n=15), family history of diabetes (n=19), physical activity (n=4), heroin use (n=4), cocaine use (n=4), CD4+ count (n=39)

Table 2

Factors Associated with Previously-Diagnosed Diabetes among CHAMPS Participants on Multivariate Logistic Regression Analysis[a]

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
HIV-infected, antiretroviral-naive[b]	0.3 (0.1, 1.2)	0.4 (0.1, 1.3)
HIV-infected, antiretroviral-experienced, PI-naive[b]	0.9 (0.6, 1.4)	1.8 (1.03, 3.0)
HIV-infected, PI-experienced[b]	0.6 (0.3, 1.4)	1.4 (0.6, 3.6)
Current methadone treatment	4.5 (2.9, 7.1)	6.7 (3.8, 11.9)
Positive CAGE test for alcoholism	1.5 (1.0, 2.2)	1.7 (1.1, 2.7)
Body mass index		
25 – 29.9 kg/m^2 (overweight) [c]	1.6 (1.0, 2.5)	1.4 (0.8, 2.5)
≥ 30 kg/m^2 (obese) [c]	3.1 (1.8, 5.3)	3.3 (1.8, 6.2)
Waist circumference >102 cm	2.5 (1.6, 4.0)	---
Family history of diabetes	3.1 (2.0, 4.7)	3.5 (2.2, 5.6)
Physical activity	0.8 (0.5, 1.2)	0.9 (0.5, 1.5)
Race/ethnicity		
African American[d]	1.0 (0.5, 1.7)	1.0 (0.5, 2.0)
Hispanic[d]	1.1 (0.6, 2.1)	0.7 (0.3, 1.4)
Other[d]	1.0 (0.3, 3.4)	1.4 (0.4, 5.4)
Age ≥55 years	1.1 (0.7, 1.6)	1.4 (0.9, 2.2)

[a] OR, odds ratio; CI, confidence interval, HIV, human immunodeficiency virus; PI, protease inhibitor

[b] Reference: HIV-uninfected

[c] Reference: <25 kg/m^2 (underweight/normal)

[d] Reference: White

Table 3

Anthropometric and Metabolic Parameters in Metabolic Substudy Participants by HIV Status and Use of HAART[a,b]

Parameter	HIV-Uninfected (N=90)	HIV-Infected, Antiretroviral -naïve (N=28)	HIV-Infected, on non-PI HAART (N=28)	HIV-Infected, on PI-HAART (N=70)
Anthropometric measurements				
Body mass index, kg/m^2	25.9 ± 0.5	25.7 ± 0.8	25.8 ± 0.7	24.8 ± 0.5
Waist circumference, cm [c]	91.9 ± 1.3	90.2 ± 1.9	88.0 ± 1.8	88.8 ± 1.2
Hip circumference, cm [c]	98.4 ± 1.0	96.1 ± 1.8	96.8 ± 1.5	94.6 ± 1.0
Waist-hip ratio[c]	0.93 ± 0.01	0.93 ± 0.01	0.91 ± 0.01	0.94 ± 0.01
Oral glucose tolerance test				
Fasting insulin level, μU/mL[c]	18.7 ± 2.1	16.4 ± 2.2	17.7 ± 3.2	15.7 ± 1.2
Fasting glucose level, mg/dL	96.5 ± 1.8	97.0 ± 2.2	98.1 ± 2.5	92.8 ± 1.6
Glucose level at 120 min, mg/dL	118.5 ± 4.4	130.8 ± 7.7	123.4 ± 9.4	116.2 ± 4.8
HOMA-IR, μU/mL·mmol/L[c]	4.76 ± 0.65	4.04 ± 0.59	4.52 ± 0.96	3.67 ± 0.29
Impaired Fasting Glucose, N (%)	24 (27)	11 (39)	9 (32)	12 (17)
Impaired Glucose Tolerance, N (%)	16 (18)	8 (29)	2 (7)	14 (20)
Diabetes, N (%)	7 (8)	3 (11)	2 (7)	3 (4)

[a] HAART, highly active antiretroviral therapy;

[b] Data are mean ± standard error unless otherwise indicated

[c] Data missing for fasting insulin (n=5), waist circumference (n=4), hip circumference (n=6)

Table 4

Factors Associated with Insulin Resistance in Metabolic Substudy Participants by Non-Parametric Analysis of Covariance

Variable	Unadjusted Mean (S.E.)	P (multivariate analysis)[a]
Ever used heroin		.005
No	3.66 (0.60)	
Yes	4.57 (0.38)	
Waist circumference[b]	0.551[b]	<.0001
Family history of diabetes		.05
No	3.65 (0.24)	
Yes	5.48 (0.80)	
Enrollment group		0.70
HIV-uninfected	4.76 (0.65)	
HIV-infected, antiretroviral naïve	4.04 (0.59)	
HIV-infected, on non-PI HAART	4.52 (0.96)	
HIV-infected, on PI-HAART	3.67 (0.29)	

[a] Non-parametric analysis of covariance was performed to adjust the effect of possible confounding on the observed mean differences. This analysis was based on the ranks of insulin resistance.

[b] Waist circumference was entered into the model as a continuous variable. The result of the univariate analysis for this parameter is shown by the Spearman correlation coefficient (*r*).

Table 5

Factors Associated with an Abnormal Glucose Tolerance Test (Impaired Glucose Tolerance or Diabetes) in Men on Multivariate Logistic Regression Analysis[a]

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age >=55 y	2.2 (1.2, 4.0)	2.0 (1.03, 3.9)
Race/ethnicity		
African American[b]	2.0 (0.6, 6.2)	2.2 (0.7, 7.0)
Hispanic[b]	3.4 (1.0, 11.6)	3.8 (1.05, 14.0)
Waist circumference >102 cm	2.0 (0.9, 4.5)	1.7 (0.7, 4.4)
Body mass index		
25 – 29.9 kg/m^2 (overweight) [c]	1.1 (0.6, 2.2)	------[d]
≥ 30 kg/m^2 (obese) [c]	1.6 (0.7, 4.0)	------[d]
HIV-infected, antiretroviral-naïve[e]	2.5 (1.0, 6.3)	2.5 (0.9, 6.8)
HIV-infected, on non-PI HAART[e]	0.9 (0.4, 1.9)	0.9 (0.4, 2.1)
HIV-infected, on PI-HAART[e]	0.4 (0.1, 1.4)	0.6 (0.2, 2.0)
Family history of diabetes	1.0 (0.5, 1.8)	0.9 (0.5, 1.9)
Physical activity	0.6 (0.3, 1.1)	0.6 (0.3, 1.4)

[a] OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy

[b] Reference: White

[c] Reference: <25 kg/m^2 (underweight/normal).

[d] Variable not included in the final model

[e] Reference: HIV-uninfected