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Disorders of Glucose Metabolism in HIV-Infected Women

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Abstract

Background—Abnormal glucose metabolism in HIV-infected patients has largely been attributed to protease inhibitor use. However most studies of glucose metabolism in HIV-infected patients have focused on men or have lacked appropriate controls.

Methods—We assessed factors associated with previously-diagnosed diabetes among 620 midlife women with- or at-risk for HIV infection. In a subset of 221 women without previously-diagnosed diabetes, we performed an oral glucose tolerance test (OGTT) with insulin levels, and assessed factors associated with abnormal glucose tolerance, insulin resistance, and insulin secretion.

Results—Thirteen percent had previously-diagnosed diabetes. Among women without previously diagnosed diabetes who underwent an OGTT, 6% had undiagnosed diabetes and 12% had impaired glucose tolerance (IGT). On multivariate analysis, factors associated with previously-diagnosed diabetes included current methadone treatment, body mass index, family history of diabetes, and physical inactivity. Factors independently associated with abnormal OGTT (IGT or diabetes) included age ≥50 y, family history of diabetes, physical inactivity, and pack-years of smoking. Factors independently associated with insulin resistance included waist circumference, Hispanic ethnicity, physical inactivity, and among HIV-infected women, use of non-PI HAART. Factors associated with lower insulin secretion included current opiate use (methadone or heroin) and older age.

Conclusions—Abnormal glucose metabolism is highly prevalent among midlife women with or at-risk for HIV infection, particularly those who use opiates. Women with classic diabetes risk factors, rather than solely those taking PIs, should be screened for diabetes in the primary care setting. Interventions targeting modifiable risk factors, including obesity and physical inactivity, are also warranted.

Keywords

human immunodeficiency virus (HIV); diabetes mellitus; antiretroviral therapy; women; drug use

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Introduction

Highly active antiretroviral therapy (HAART) has resulted in a dramatic decrease in the mortality of HIV-infected individuals [1]. As people with HIV live longer, they are likely to experience diseases of midlife, including type 2 diabetes. Several studies have reported an increased prevalence of impaired glucose tolerance (IGT) and diabetes among HIV-infected individuals [2,3]. These disorders have been largely attributed to protease inhibitor (PI) therapy [4,5], however other antiretroviral agents and classic risk factors for diabetes, including obesity, physical inactivity, and genetic background, may also play contributory roles. To date, most studies of glucose metabolism in HIV-infected patients have focused on men, or have lacked HIV-negative controls. One study that included women both with and without HIV found that PI use was associated with an increased risk of incident diabetes [6], but this study was limited by the fact that a screening blood test was not used to detect diabetes. The factors associated with undiagnosed diabetes and IGT among midlife HIV-infected women are not known.

The mechanism by which HIV-infected patients develop glucose intolerance is not completely understood. Insulin resistance among HIV-infected patients has been commonly described, and has alternately been attributed to a direct inhibitory effect on cellular glucose transport by PIs [7,8], or HAART-associated changes in fat distribution [9]. Impaired insulin secretion in HIV-infected patients has been less well-studied, although some data suggest an association between PI use and defects in B-cell function [3,10]. The relative contributions of PI use, fat distribution, and other factors to insulin resistance and impaired insulin secretion in HIV-infected patients have not been determined.

The objective of this study was to determine the associations of HIV, HAART and other factors with prevalent diabetes in a cohort of midlife women with or at-risk for HIV. In addition we performed an oral glucose tolerance test (OGTT) with insulin levels among a subset of women without a prior diagnosis of diabetes to identify factors associated with abnormal glucose tolerance, insulin resistance, and impaired insulin secretion.

Methods

Study participants

We performed a cross-sectional analysis of factors associated with previously-diagnosed diabetes among 620 women participating in the Menopause Study (Ms.), an ongoing longitudinal study of menopause and its sequelae in women with- or at-risk for HIV. Participant recruitment and study design have been described elsewhere [11]. Briefly, between September 2001 and January 2003, 332 HIV-infected and 288 uninfected women were enrolled from the community in the Bronx, NY. Enrollment was guided so that 50% of women were HIV-infected, and 50% uninfected; within each group, 50% reported illicit drug use in the last 5 years and 50% other high-risk behavior. Ms. 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 (high blood sugar) other than during pregnancy, age at diabetes diagnosis, and whether they had taken medication for diabetes. Participants were administered the CAGE questionnaire [12], with a positive response to ≥2 items indicating alcoholism [13]. Current illicit drug use was defined as use within the last six months. Physical activity was defined as moderate or strenuous exercise for

≥20 minutes on >1 day per week. Menopausal status was based on self-reported bleeding patterns, with perimenopause defined as having skipped 1-11 periods over the past year, and postmenopause as cessation of menses for ≥12 months [14].

Metabolic Substudy enrollment

Between June 2002 and December 2003, Ms. participants were screened for the Metabolic Substudy at research visits. To be enrolled, women 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, were pregnant, 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 [15] 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 for glucose and insulin determinations immediately before and 30 and 120 min after ingestion of dextrose. Waist and hip circumference were measured.

Assays

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 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 independent predictors of diabetes. Corresponding ORs and 95% CIs were computed.

For participants in the Metabolic Substudy, additional outcome measures were abnormal OGTT (IGT or diabetes), insulin resistance, and insulin secretion. 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]. Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR): (fasting insulin [μU/mL] × fasting glucose [mmol/L])/22.5 [17]. Insulin secretion was calculated using the 30-minute incremental ratio of insulin to glucose ($\Delta I_{30}/\Delta G_{30}$) [18].

Multivariate logistic regression analysis was performed to assess independent 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 $p \leq .2$. Comparisons of anthropometric parameters, glucose and insulin levels, insulin resistance, and insulin secretion for the enrollment groups and other factors of interest were performed using ANOVA or Kruskal-Wallis tests. For insulin resistance and insulin secretion, 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). These analyses were based on the ranks of the dependent variable, as these variables were not normally distributed. SPSS software version 10.0 was used for all other analyses. Statistical significance was determined using 2-tailed tests.

Results

Study participants (Table 1)

Of 620 participants, 332 (54%) were HIV-infected. Diabetes risk factors were common; 458 (74%) had a body mass index (BMI) ≥25 kg/m^2, 82 (13%) had delivered a baby weighing >9 pounds, and of 546 participants with available data, 242 (44%) had a first-degree relative with diabetes. HIV-uninfected participants had a higher prevalence of obesity (BMI ≥30 kg/m^2) (59% vs. 32%, p<.0005) and a higher mean waist circumference (mean ± SEM 98.4 ± 0.9 cm vs. 93.3 ± 0.8 cm, p<.0005) compared with infected women.

The majority (n=268, 81%) of HIV-infected participants were diagnosed with HIV ≥5 y ago, and most (n=287, 86%) were antiretroviral-experienced. Of 215 participants with a history of PI use, 146 (68%) had taken nelfinavir, 93 (43%) indinavir, 58 (27%) ritonavir, 57 (26%) lopinavir/ritonavir, 53 (25%) saquinavir, 12 (6%) amprenavir, and 1 (0.5%) atazanavir. The median duration of PI use was 32.0 (IQR 14.0-55.0) months.

Prevalence of previously-diagnosed diabetes

Of 620 participants, 79 (13%) reported being told by a healthcare provider that they had diabetes. The median age at diagnosis was 42 years (range 22-54). Sixty-eight percent (n=54) of women with diabetes were diagnosed within the last 5 years, and 85% (n=67) reported a history of taking anti-diabetic medication. There was no difference in diabetes prevalence by HIV status (12% for HIV-infected vs. 13% for uninfected, p=.75) or, among HIV-infected women, by PI use (15% for PI-experienced vs. 8% for PI-naive, p=.06).

Factors associated with previously-diagnosed diabetes (Table 2)

After controlling for age, HIV, and HAART, factors independently associated with previously-diagnosed diabetes included current methadone treatment (OR_{adj} 1.8, 95% CI 1.01, 3.3), BMI (reference: <25.0 kg/m^2; for 25.0-29.9 kg/m^2, OR_{adj} 2.6, 95% CI 1.04, 6.7; for ≥30.0 kg/m^2, OR_{adj} 5.1, 95% CI 2.1, 12.1), family history of diabetes (OR_{adj} 2.7, 95% CI 1.6, 4.7), and physical activity (OR_{adj} 0.4, 95% CI 0.2, 0.96). History of PI use (reference: HIV uninfected; OR_{adj} 1.8, 95% CI 1.0, 3.2) and Black race (OR_{adj} 3.6, 95% CI 1.0, 12.9) were of borderline significance. Substitution of waist circumference for BMI did not significantly alter the results (OR_{adj} for waist circumference = 1.06 per cm, 95% CI 1.04, 1.08).

We further examined the relationship between methadone use and previously-diagnosed diabetes by calculating the odds of having diabetes for each quartile of current methadone dose. Compared to women taking 10-60 mg daily, the adjusted odds ratio (adjusted for BMI, HIV, and HAART use) was 3.4 (95% CI 0.6, 18.8) for 61-90 mg, 6.8 (95% CI 1.3, 35.5) for 91-120 mg, and 9.7 (95% CI 1.9, 49.6) for 121-200 mg.

Metabolic Substudy participants

Of 221 participants, 88 (40%) were HIV-uninfected; 31 (14%) were HIV-infected, antiretroviral-naïve; 34 (15%) were HIV-infected, taking non-PI HAART; and 68 (31%) were HIV-infected, taking PI-HAART. Among the 34 participants taking non-PI HAART, 21 (62%) were taking a non-nucleoside reverse transcriptase inhibitor and ≥2 nucleoside reverse transcriptase inhibitors (NRTIs), and 13 (38%) were taking ≥3 NRTIs only. Among the 68 participants taking PIs, 25 (37%) were taking nelfinavir, 18 (26%) lopinavir/ritonavir, 14 (21%) ritonavir, 13 (19%) indinavir, 8 (12%) saquinavir, 3 (4%) amprenavir, and 1 (1%) atazanavir. The median duration of PI use was 42.5 (IQR 28.5-66.0) months.

Anthropometrics and OGTT results (Table 3)

Compared with HIV-uninfected participants, women on non-PI HAART and PI-HAART had lower BMIs (mean ± SEM 31.1 ± 0.7 vs. 27.0 ± 0.8 kg/m^2, p=.015, and vs. 28.2 ± 0.6 kg/m^2, p=.045, respectively). There was no difference in waist-hip ratio, insulin, or glucose levels by HIV serostatus, HAART, or PI use. Waist circumference (r=0.498, p<.0005), waist-hip ratio (r=.351, p<.0005), and BMI (r=0.426, p<.0005) were significantly correlated with fasting insulin levels.

Prevalence of newly-diagnosed IGT and diabetes

Twenty-six (12%) participants had an OGTT consistent with IGT, and an additional 13 (6%) with diabetes. Three (23%) women with diabetes had a fasting glucose level <126 mg/dl. Compared with HIV-uninfected women, women on non-PI HAART were more likely to have IGT (26% vs. 9%, p=.02). Among HIV-infected women, there was no difference in IGT or diabetes prevalence by HAART or PI use.

Factors associated with abnormal OGTT (Table 4)

In a logistic regression model controlling for race/ethnicity, waist-hip ratio, HIV, HAART, and PI use, factors independently associated with abnormal OGTT included age ≥50 y (OR_{adj} 3.8, 95% CI 1.3, 11.2), family history of diabetes (OR_{adj} 2.7, 95% CI 1.2, 6.2), physical activity (OR_{adj} 0.2, 95% CI 0.1, 0.6), and smoking (OR_{adj} 1.5 per 10 pack-years, 95% CI 1.3, 1.8). These estimates were essentially unchanged when women with a history of using megestrol (n=1), prednisone (n=3), or estrogen and/or progesterone (n=12) were excluded. There was no association between glucose tolerance and CD4+ count, delivering a baby >9 pounds, use of illicit drugs or methadone, alcoholism, or BMI, even if waist-hip ratio was removed from the model.

Factors associated with insulin resistance

Compared with other enrollment groups, insulin resistance was greatest among women on non-PI HAART (Table 3). Insulin resistance (μU/mL·mmol) was greater among Hispanics compared with Blacks and whites (mean ± SEM 4.95 ± 0.52 vs. 3.36 ± 0.27 vs. 3.40 ± 0.59, p=.009), and among those who were not physically active compared to those who were (4.04 ± 0.26 vs. 3.94 ± 0.60, p=.07). Waist circumference (r=0.487, p<.0005), waist-hip ratio (r=0.355, p<.0005), and BMI (r=0.426, p<.0005) were positively correlated with insulin resistance. There was no association between insulin resistance and age, family history of diabetes, or illicit drug use. In a model controlling for HIV, HAART, and PI use, factors independently associated with insulin resistance were waist circumference (p<.0001), Hispanic ethnicity (p=.01), and physical activity (p=.03). In a model including HIV-infected women only, after controlling for race/ethnicity, physical activity and CD4+ count, waist circumference (p<.0001) and non-PI HAART (p=.03) were independently associated with insulin resistance. In both models, substitution of BMI for waist circumference did not alter

the results. Models excluding women with a history of steroid or hormone use had similar results.

Factors associated with insulin secretion

Insulin secretion ($\mu U/mL \cdot mg/dL^{-1}$) was lowest in participants with diabetes and highest in those with normal glucose tolerance (mean ± SEM 0.74 ± 0.25 for diabetes, vs. 1.68 ± 0.41 for IGT, vs. 2.11 ± 0.17 for normal OGTT, p = .002). Insulin secretion was lower among HIV-uninfected women compared with HIV-infected women (1.65 ± 0.17 vs. 2.22 ± 0.23, p = .04), however there was no difference in insulin secretion by HAART or PI use (Table 3). Insulin secretion was lower among current users of methadone (1.39 ± 0.31 vs. 2.10 ± 0.17, p = .02), heroin (1.26 ± 0.23 vs. 2.10 ± 0.17, p = .04), and cocaine (1.56 ± 0.26 vs. 2.14 ± 0.18, p=.04). Methadone, heroin, and cocaine use were correlated, therefore two separate multivariate models were constructed: one containing current opiate (heroin or methadone) use, and one current cocaine use. In a model controlling for enrollment group, factors associated with lower insulin secretion included current opiate use (p=.02) and older age (p=.03). The model containing current cocaine use had similar results for current cocaine use (p=.02).

Discussion

In this cohort of predominantly Black and Hispanic midlife women with or at-risk for HIV, risk factors for diabetes were common: 74% had a BMI ≥25 kg/m^2, 79% were physically inactive, 44% had a first-degree relative with diabetes, and 13% had delivered a baby >9 pounds. Thus, not surprisingly, the 13% prevalence of previously-diagnosed diabetes in this cohort is higher than the rate of 1% found in women aged 40-55 years participating in Study of Women's Health Across the Nation (SWAN), a multiethnic, multicenter study of the menopausal transition [19]. Despite this high prevalence, additional cases of diabetes and IGT were detected by 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 5%, and of IGT as 10%. These findings suggest that abnormal glucose metabolism is a major health problem for midlife women with or at-risk for HIV.

Prior cohort studies in which screening tests for diabetes were not performed found an independent association between PI use and incident hyperglycemia or diabetes [5,6]. Using an OGTT, we found that non-PI HAART, and not PI-HAART, was associated with IGT and insulin resistance. These contradictory findings may reflect differential screening practices; given clinicians' awareness of the association between PIs and diabetes, they may be more likely to screen for, and therefore diagnose, diabetes in PI-treated patients. Alternatively, these findings may suggest that HAART in general, rather than solely PI use, is associated with glucose intolerance in HIV-infected persons. While indinavir has been associated with early direct effects on insulin sensitivity [10,20], recent studies have demonstrated that other PIs differ in their ability to induce insulin resistance [21-23]. Further, in a study of treatment-experienced patients, Hadigan et al. found that fat redistribution, and not PI use, was associated with IGT and diabetes [9]. While we did not assess peripheral lipoatrophy, in our cohort of mostly overweight and obese women, truncal adiposity, as measured by waist circumference [24], was strongly associated with insulin resistance.

Both opiate use and cigarette smoking were associated with abnormal glucose metabolism. Women receiving methadone were nearly twice as likely to have previously-diagnosed diabetes compared with women who were not receiving methadone. Furthermore current opiate use was associated with lower insulin secretion. The dose-response relationship between methadone and odds of previously-diagnosed diabetes suggests a direct association between opiate use and glucose metabolism. Also supporting this association are experimental studies that found opiate use impaired insulin secretion and glucose tolerance [25-27]. Alternatively,

opiate use may be a marker of hepatitis C, a risk factor for diabetes [28,29] which was not assessed in this study. Our finding that pack-years of smoking was associated with abnormal glucose tolerance is consistent with studies in HIV-uninfected individuals that demonstrate an association between insulin resistance and smoking [30,31].

We have demonstrated that diabetes and IGT affect a major proportion of midlife women with or at-risk for HIV, particularly those who use opiates. Given the high prevalence of obesity, physical inactivity, and family history of diabetes in this population, it is likely that the burden of disease will increase as these women age. Currently, the International AIDS Society-USA guidelines for diabetes screening in HIV-infected individuals target PI-treated patients [32]. Based on our findings, we recommend expansion of screening for diabetes by HIV providers to include patients with classic diabetes risk factors, including being overweight, having a family history of diabetes, and having delivered a baby >9 pounds [16]. In addition, interventions aimed at ameliorating modifiable risk factors, including obesity and physical inactivity, should be implemented in HIV primary care settings.

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Table 1

Participant Characteristics[a,b]

	Entire Cohort (N=620)		Metabolic Substudy (N=221)	
	HIV-Uninfected (N = 288)	**HIV-Infected (N = 332)**	**HIV-Uninfected (N = 88)**	**HIV-Infected (N = 133)**
Median age, y (range)	45 (35-71)	44 (35-66)	44 (37-70)	45 (35-66)
Race/ethnicity, N (%)[c]				
Black	119 (41)	191 (58)	36 (41)	76 (57)
White	38 (13)	20 (6)	11 (12)	10 (8)
Hispanic	122 (42)	118 (36)	39 (44)	45 (34)
Other	9 (3)	3 (1)	2 (2)	2 (2)
Unemployed, N (%)[c]	209 (73)	284 (86)	66 (75)	112 (84)
Menopause status, N (%)				
Pre-menopausal	145 (50)	160 (48)	48 (54)	73 (55)
Peri-menopausal	101 (35)	112 (34)	26 (30)	40 (30)
Post-menopausal	42 (15)	60 (18)	14 (16)	20 (15)
Body mass index, N (%)[c]				
< 25 kg/m^2 (lean/normal)	48 (17)	113 (34)	13 (15)	44 (33)
25 – 29.9 kg/m^2 (overweight)	68 (24)	114 (34)	26 (30)	47 (35)
≥ 30 kg/m^2 (obese)	171 (59)	105 (32)	49 (56)	42 (32)
Mean waist circumference, cm (SD) [d]	98.4 (15.2)	93.3 (14.6)	95.1 (13.1)	91.9 (13.1)
Delivered baby > 9 pounds, N (%)	39 (14)	43 (13)	11 (12)	19 (14)
Family history of diabetes, N (%)	118 (41)	124 (37)	37 (42)	50 (38)
Physical activity, N (%)	65 (23)	67 (20)	32 (36)	28 (21)
Smoking, N (%)[e]				
Never	23 (8)	33 (10)	8 (9)	14 (10)
Former	54 (19)	90 (27)	13 (15)	34 (26)
Current	211 (73)	209 (63)	67 (76)	85 (64)
Ever used heroin or cocaine, N (%)[e]	268 (93)	293 (88)	83 (94)	116 (87)
Ever injected drugs, N (%)	129 (45)	147 (44)	36 (41)	53 (40)
Current heroin use, N (%)[e]	40 (14)	27 (8)	12 (14)	9 (7)
Current cocaine use, N (%)	58 (20)	66 (20)	15 (17)	30 (23)
Current methadone treatment, N (%)[c]	102 (35)	69 (21)	16 (18)	14 (10)
Positive CAGE test for alcoholism, N (%)	110 (38)	127 (38)	32 (36)	60 (45)
Medication use, N (%)				
Megestrol	0 (0)	6 (2)	0 (0)	1 (1)
Prednisone[e]	9 (3)	3 (1)	1 (1)	2 (2)
Estrogen and/or progesterone	9 (3)	17 (5)	4 (4)	8 (6)
CD4+ count, N (%)				
≤200 cells/mm^3		42 (13)		13 (10)
201-500 cells/mm^3		130 (39)		53 (40)
>500 cells/mm^3		127 (38)		57 (43)
Antiretroviral use (N, %)				
Never		45 (14)		31 (23)
Yes, but PI-naive		72 (22)		34 (26)
Yes, including a PI		215 (65)		68 (51)

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

[b] Missing data for unemployed (n=2); family history of diabetes (n=74), body mass index (n=1); waist circumference (n=9); heroin use (n=3); cocaine use (n=3); methadone treatment (n=1); CD4+ count (n=33)

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

[d] $P < .0005$ for Student's t-test comparing HIV-infected and uninfected participants in entire cohort

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

Table 2

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

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
HIV-infected, antiretroviral-naive[b]	0.5 (0.1, 1.6)	0.5 (0.1, 1.9)
HIV-infected, antiretroviral-experienced, PI-naive[b]	0.6 (0.2, 1.5)	0.8 (0.3, 2.2)
HIV-infected, PI-experienced[b]	1.2 (0.7, 1.9)	1.8 (1.0, 3.2)
Current methadone treatment	1.8 (1.1, 3.0)	1.8 (1.01, 3.3)
Body mass index		
25 – 29.9 kg/m^2 (overweight) [c]	1.8 (0.8, 4.2)	2.6 (1.04, 6.7)
≥ 30 kg/m^2 (obese) [c]	3.9 (1.9, 8.2)	5.1 (2.1, 12.1)
Waist circumference (per cm)	1.06 (1.04, 1.08)	----
Family history of diabetes	3.0 (1.8, 5.1)	2.7 (1.6, 4.7)
Physical activity	0.6 (0.3, 1.1)	0.4 (0.2, 0.96)
Race/ethnicity		
Black[d]	2.0 (0.7, 6.0)	3.6 (1.0, 12.9)
Hispanic[d]	2.1 (0.7, 6.1)	2.6 (0.7, 9.4)
Other[d]	2.7 (0.4, 16.8)	4.8 (0.6, 37.4)
Age ≥50 years	1.8 (1.0, 3.2)	1.6 (0.8, 3.0)
Delivered a baby >9 pounds	2.0 (1.1, 3.6)	------[e]
Peri-menopausal[f]	1.1 (0.7, 2.0)	------[e]
Post-menopausal[f]	2.0 (1.1, 3.7)	------[e]

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

[b] Reference: HIV-uninfected

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

[d] Reference: White

[e] Variable did not remain in the final multivariate model

[f] Reference: pre-menopausal

Table 3

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

Parameter	HIV-Uninfected (N=88)	HIV-Infected, Antiretroviral-naïve (N=31)	HIV-Infected, on non-PI HAART (N=34)	HIV-Infected, on PI-HAART (N=68)
Anthropometric measurements				
Body mass index, kg/m^2	31.1±0.7	29.7±1.4	27.0±0.8[c]	28.2±0.6[c]
Waist circumference, cm [d]	95.1±1.4	93.4±2.9	88.8±1.9	92.6±1.5
Hip circumference, cm [d]	108.4±1.2	103.3±3.1	101.4±1.9	104.0±1.5
Waist-hip ratio[d]	0.88±0.01	0.91±0.01	0.88±0.01	0.90±0.01
Fasting plasma measurements				
Glucose level, mg/dL	98.4±3.6	92.4±2.4	96.2±4.0	90.3±1.9
Insulin level, μU/mL	15.8±1.2	15.3±1.9	17.6±2.3	16.3±1.5
HOMA-IR, μU/mL·mmol/L	4.10±0.44	3.62±0.50	4.50±0.74	3.85±0.41
Oral glucose tolerance test				
Glucose level at 30 min, mg/dL [d]	150.0±4.8	132.1±5.2	144.1±5.2	139.0±3.6
Insulin level at 30 min, μU/mL [d]	84.0±6.8	88.9±13.5	114.3±14.8	104.0±10.9
Glucose level at 120 min, mg/dL	117.1±6.2	105.5±8.4	111.2±5.3	109.1±3.4
$\Delta I_{30}/\Delta G_{30}$ (μU/mL·mg/dL $^{-1}$) [d]	1.65±0.17	2.28±0.45	2.45±0.47	2.09±0.33
Impaired Glucose Tolerance, N (%)	8 (9)	1 (3)	9 (26)[e]	8 (12)
Diabetes, N (%)	7 (8)	2 (6)	1 (3)	3 (4)

[a] HAART, highly active antiretroviral therapy; HOMA-IR, homeostasis model assessment insulin resistance; $\Delta I_{30}/\Delta G_{30}$, incremental ratio of insulin to glucose at 30 min

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

[c] P< .05 compared to HIV-uninfected women; ANOVA

[d] Data missing for waist circumference (n=2), hip circumference (n=2), waist-hip ratio (n=3), 30 min insulin level (n=2), 30 min glucose level (n=1), $\Delta I_{30}/\Delta G_{30}$ (n=10)

[e] P< .05 compared to HIV-uninfected women; Fisher's exact test

Table 4

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

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age >=50 y	4.1 (1.7, 9.7)	3.8 (1.3, 11.2)
Family history of diabetes	1.5 (0.8, 3.1)	2.7 (1.2, 6.2)
Physical activity	0.4 (0.2, 1.1)	0.2 (0.1, 0.6)
Smoking (per 10 pack-years)	1.4 (1.1, 1.8)	1.5 (1.3, 1.8)
Waist-hip ratio > 0.8	2.3 (0.7, 8.1)	2.7 (0.7, 10.6)
Body mass index		
25 – 29.9 kg/m^2 (overweight) [b]	1.1 (0.4, 2.7)	------[c]
≥ 30 kg/m^2 (obese) [b]	0.9 (0.4, 2.2)	------[c]
Race/ethnicity		
Black[d]	1.8 (0.5, 6.5)	2.7 (0.6, 11.7)
Hispanic[d]	1.5 (0.4, 5.6)	1.4 (0.3, 6.4)
HIV-infected, antiretroviral-naïve[e]	0.5 (0.1, 1.9)	0.5 (0.1, 2.2)
HIV-infected, on non-PI HAART[e]	2.0 (0.8, 5.1)	2.6 (0.8, 7.9)
HIV-infected, on PI-HAART[e]	0.9 (0.4, 2.2)	1.4 (0.5, 3.9)

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

[b] Reference: <25 kg/m^2 (lean/normal)

[c] Variable did not remain in the final multivariate model

[d] Reference: White

[e] Reference: HIV-uninfected