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Abdominal Fat Depots, Insulin Resistance, and Incident Diabetes Mellitus in Women With and Without HIV Infection

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Abstract

Objective—To determine the associations between visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (SAT) mass with homeostatic model assessment-insulin resistance (HOMA-IR) and incidence of diabetes mellitus in women with and without HIV infection.

Design—Cross-sectional design for associations between abdominal fat and HOMA-IR; longitudinal design for associations between abdominal fat and incident diabetes.

Methods—We assessed associations between dual X-ray absorptiometry scan-derived VAT and SAT with HOMA-IR in a subsample from the Women's Interagency HIV Study (n = 226 with and n = 100 without HIV) using linear regression. We evaluated associations of VAT, SAT, and HOMA-IR with incident diabetes mellitus using Cox proportional hazards models.

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Conflicts of Interest: No authors have commercial or other associations that might pose a conflict of interest.

Authors' Contributions: MJG, DBH, DRH, MTY, KA and AS conceived of and designed the study; KA, MC, AS, and PT contributed to data collection and funding; DRH and QS analyzed the data; MJG drafted the manuscript; all authors contributed to data interpretation, revision of the manuscript, and approved the final version of the manuscript.

Results—VAT mass was positively associated with log HOMA-IR in fully adjusted linear regression models stratified by HIV serostatus, including adjustment for SAT. During median follow-up of 10.6 years, incidence of diabetes was 1.63 [95% CI 1.15, 2.31] and 1.32 [95% CI 0.77, 2.28] cases per 100 person-years in women with and without HIV (P = 0.52). In a fully adjusted model, baseline VAT (hazard ratio [HR] 2.64 per kg; 95% CI [1.14, 6.12]; P=0.023) and SAT (HR 1.34 per kg; 95% CI [0.73, 2.45]; P=0.35) were associated with incident diabetes but the latter was not statistically significant.

Conclusions—VAT mass was independently associated with HOMA-IR in women with and without HIV and was independently associated with future development of diabetes.

Keywords

visceral adipose tissue; subcutaneous adipose tissue; insulin resistance; diabetes mellitus; HIV-1; women

Introduction

The risk of diabetes mellitus may be increased in people living with HIV infection relative to the general population [1–5], though data are conflicting [6, 7] and the pathogenesis is not completely understood. HIV-specific factors, such as use of older antiretroviral drugs with significant metabolic toxicities, may have contributed previously to greater risk of insulin resistance and diabetes but are largely of historical significance in the current HIV treatment era. These older drugs include indinavir, which inhibits the Glut-4 glucose transporter [8], and thymidine analogs, which likely reduce insulin sensitivity through mitochondrial toxicity [9] and associated subcutaneous adipose tissue (SAT) loss and alterations in adipokines and proinflammatory cytokines [10, 11]. Although loss of SAT is seldom a clinically significant issue with contemporary antiretroviral regimens, excess visceral adipose tissue (VAT) may continue to contribute to metabolic abnormalities such as insulin resistance since VAT tends to increase after initiation of antiretroviral therapy regardless of regimen type [12, 13].

Studies in the general population have shown that greater VAT mass is more strongly correlated with insulin resistance than is greater SAT mass [14–17] and that excess VAT is associated with incident pre-diabetes and diabetes mellitus [15, 18]. Several studies in the HIV population found associations between insulin resistance and abdominal adiposity assessed radiographically [19, 20], including measurement of VAT [21, 22]. While a recent cohort study found that gain in overall abdominal fat measured by sequential dual energy X-ray absorptiometry (DXA) scans in 58 men with HIV infection was associated with incident diabetes risk [23], no study to our knowledge has examined the specific relationship between VAT and incident diabetes mellitus in people living with HIV. Newer algorithms enable estimation of VAT from DXA scans [24], and DXA-derived VAT has been associated with impaired glucose tolerance and metabolic syndrome in the general population [25].

We hypothesized that VAT, compared with SAT, is more strongly associated with both insulin resistance and incidence of diabetes mellitus in women with and without HIV infection. Using data from the Women's Interagency HIV Study (WIHS), we evaluated

cross-sectional associations of DXA-derived VAT and SAT mass with insulin sensitivity, estimated by homeostatic model assessment-insulin resistance (HOMA-IR). We then examined associations of baseline VAT mass, SAT mass, and HOMA-IR with incident diabetes mellitus.

Methods

The WIHS is a prospective cohort study of primarily minority women with HIV and demographically similar women initially enrolled at six urban sites in the United States [26], [27] in 1994–95 (n=2,623) and subsequently in 2001–02 (n=1,143). Detailed demographic, clinical, and behavioral information is collected at each semi-annual study visit. Beginning in April 2001, 440 WIHS women enrolled in a Metabolic Substudy from three sites (Bronx, San Francisco and Chicago) underwent dual X-ray absorptiometry (DXA) scanning for bone density and regional fat mass at baseline and at follow up visits 2 and 5 years later [28]. Eligibility criteria for the substudy included weight < 119.7 kg, height < 1.85 m, and no recent use of corticosteroids, exogenous hormones, or drugs for osteoporosis [28]. The 226 women with HIV and 100 HIV seronegative women from this substudy with available data from DXA scans performed between 2003 and 2005 and no history of diabetes mellitus at the time of the DXA visit constituted the study sample for the present analyses.

Informed consent was obtained from all participants and human experimentation guidelines of the U.S. Department of Health and Human Services and those of the authors' institutions were followed in the conduct of this research.

Outcomes of Interest

Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated using the formula (insulin × glucose)/405 (with insulin measured in μIU/mL and glucose measured in mg/dL) [29] based on contemporaneous insulin and glucose measurements after a minimum 8 hour fast at the study visit closest in time to the DXA scan. Blood specimens were stored at −70°C until assayed at a central laboratory.

Diabetes mellitus at study entry and at subsequent visits was defined based on any of the following criteria: 1) report of diabetes medication; 2) fasting glucose >126 mg/dL or hemoglobin A1c ≥ 6.5% and confirmation by subsequent report of diabetes medication or laboratory parameter; and 3) self-reported diabetes with confirmation by subsequent report of diabetes medication, or evidence of at least two laboratory parameters indicative of diabetes (i.e. two fasting glucoses >126mg/dL or a fasting glucose >126mg/dL and hemoglobin A1c ≥ 6.5%) [30]. Time to incident diabetes mellitus (the date that diabetes was first identified) was calculated from the date of the DXA scan visit.

Exposures of Interest: DXA-Derived Adipose Tissue Depots

DXA scans for regional fat mass were performed using GE/Lunar Prodigy machines (Madison, WI, USA) [28] and read at a central location (Image Reading Center, Inc., New York, NY). The validated CoreScan™ algorithm estimated VAT and SAT mass based on detected width of SAT layer on the lateral abdomen and the anterior-posterior thickness of

the abdomen obtained by DXA [24, 31, 32]. These parameters were used to estimate android SAT, which was subtracted from total android fat mass to yield the estimate of VAT mass.

Covariates

Self-reported race and ethnicity were categorized as: White (including Hispanic and non-Hispanic), Black (including Hispanic and non-Hispanic) and Other (predominantly women who self-identified as Hispanic but not White or Black). Menopausal status was defined as self-reported amenorrhea at two consecutive semi-annual visits (i.e. 12 months or more) for women aged ≥ 45 years old. Alcohol intake was categorized based on the average number of drinks reported per week during the preceding 6 months: light use (1–3 drinks/ week), moderate use (4–7 drinks/week) and heavy use (>7 drinks/week).

Plasma HIV-1 RNA level (viral load) was assayed by isothermal nucleic acid sequence based amplification method (NASBA/Nuclisens, bioMerieaux, San Diego CA) with a detection limit of 80 copies/ml, and CD4 T-cell counts were measured by standard flow cytometry methods in both women with and without HIV. We decided *a priori* to include CD4 cell count as a covariate in exploratory linear regression models of both women with and without HIV based on data from the general population suggesting that CD4 count is associated with metabolic abnormalities [33, 34]. Hepatitis C virus (HCV) infection was assessed by testing for antibody to HCV by second or third-generation EIA (Ortho-Diagnostic Systems, Rochester, NY) with confirmation of reactive tests by HCV branched DNA (Quantiplex 2.0 branched chain DNA-enhanced label amplification assay; Chiron, Emeryville, CA) or by RT-PCR (COBAS Amplicor HCV Detection Kit; Roche Diagnostic Systems, Pleasanton, CA).

Statistical Analysis

Data were analyzed descriptively using plots, histograms, means, medians, standard deviations, skewness and kurtosis to identify erroneous values, outliers and optimal transformations. Due to right skewness, HOMA-IR was $\log_{10}$ transformed. Medians and first and third quartiles (Q1, Q3) summarize continuous variables. Differences between women with and without HIV infection were assessed by Wilcoxon rank-sum or chi-squared tests as appropriate.

Linear regression evaluated associations of VAT and SAT with $\log_{10}$ HOMA-IR in models stratified by HIV serostatus. Linear regression results are expressed as the beta-coefficient, which represents the linear change in outcome per unit change in covariate, with 95% confidence intervals. Cox proportional hazards models analyzed time to incident diabetes mellitus combining women with and without HIV infection in the primary analyses due to a small number of events. Exploratory analyses stratified the Cox models by HIV serostatus. Results are expressed as hazard ratios with 95% confidence intervals.

We assessed VAT and SAT in separate linear regression and Cox proportional hazards models and in models that included both VAT and SAT. For linear regression with log HOMA-IR as the outcome variable, we present unadjusted models (model 1) and models adjusted for age, race, and WIHS site (model 2); additionally adjusted for current smoking status, HCV infection status, and menopause status (model 3); and additionally adjusted for

body mass index (BMI) (model 4). We constructed the Cox proportional hazards models in a similar fashion but also adjusted for HIV serostatus starting in model 3, log HOMA-IR (but not BMI) starting in model 4, and then BMI in model 5. An additional series of models included the VAT/SAT ratio as the body fat parameter of interest. Supplementary models for both outcomes adjusted additionally for CD4 cell count.

Statistical analysis was performed using SAS version 9.4 software (SAS Institute Inc. Cary, NC, USA). Statistical significance was considered to be $P \leq 0.05$.

Results

Baseline Characteristics

Our study sample consisted of 226 women with HIV and 100 seronegative women with baseline DXA data initially collected between 2003 and 2005. The HOMA-IR assessment was performed a median of 29 days (Interquartile range [IQR]: 6, 83) after the DXA scan for women with HIV and 30 (IQR: 7, 110) days after for HIV-seronegative women. Table 1 summarizes baseline characteristics of the study sample. Compared to the HIV seronegative group, women living with HIV were older, more commonly post-menopausal and more likely to report prior injection drug use. The prevalences of HCV infection and hypertension were higher among the women with HIV. Among women with HIV, 61% were taking combination antiretroviral therapy (cART); median HIV-1 RNA level was 2.83 [1.90, 3.85] $\log_{10}$ copies/ml and 36.7% had HIV-1 RNA levels < 80 copies/ml. Their median current and nadir CD4 counts were 382 [252, 586] and 244 [146, 354] cells/mm^3, respectively. Women with HIV had lower median BMI and SAT mass but similar VAT mass compared to the HIV seronegative women. As a result, the VAT/SAT ratio was higher in the HIV-infected group.

Adjusted Associations of Abdominal Fat Measures with Log HOMA-IR

Table 2 summarizes serially adjusted linear regression models with log HOMA-IR as the outcome. Among women both with and without HIV, VAT when considered as the only body composition parameter was associated with HOMA-IR in all models, including after adjustment for BMI (model 4). In both groups of women, SAT when considered as the only body composition parameter was significantly associated with HOMA-IR in serially adjusted models until adjustment for BMI, which eliminated the statistical association. When combined in the same models, VAT but not SAT was statistically significantly associated with HOMA-IR in all models in both groups.

Associations of CD4 Cell Count with Log HOMA-IR

We performed analyses with further adjustment for CD4 cell count in addition to the covariates in the final models above (models 4). In separate models of women with and without HIV, CD4 cell count was independently associated with log HOMA-IR in models with either VAT, SAT, or both VAT and SAT as the body fat covariates regardless of HIV serostatus (supplementary tables 1 and 2). Adjustment for CD4 cell count did not substantially affect the beta coefficients of the VAT and SAT covariates in these models. In a model combining women with and without HIV, neither HIV serostatus nor the HIV*CD4 cell count interaction term was statistically associated with log HOMA-IR (data not shown).

Incidence of Diabetes Mellitus

The median duration of follow-up for the combined group of women with and without HIV was 10.6 [6.6, 11.8] years (with 2944 person-years in total; 1961 for women with HIV and 983 for women without HIV). During this time, there were 45 incident cases of diabetes: 32 cases in women with HIV and 13 among women without HIV. The incidence of diabetes was 1.63 [1.15, 2.31] per 100 person-years in women with and 1.32 [0.77, 2.28] in women without HIV (P = 0.52).

Associations of Abdominal Fat Measures with Incident Diabetes Mellitus

We constructed serially adjusted Cox proportional hazards models of the association with time to incident diabetes mellitus. All women were included in these models due to a small number of events; HIV serostatus was not associated with diabetes risk in any model. We first evaluated SAT and VAT separately with respect to diabetes incidence. When considered as the only body composition parameter in a model adjusted for age, race, WIHS site, menopausal status, smoking status, HIV status, HCV status, and log HOMA-IR, SAT was the only factor statistically associated with incident diabetes (HR 1.40 per kg; 95% CI [1.00, 1.94]; P = 0.047) (Table 3, model 4). This association between SAT and incident diabetes was no longer statistically significant (HR 1.40; 95% CI [0.76, 2.60]; P = 0.28) after further adjustment for BMI (model 5), although BMI was also not statistically significant in this model. In contrast, in models with VAT as the only abdominal fat parameter, VAT remained the only factor statistically associated with incident diabetes (HR 2.69 per kg; 95% CI [1.17, 6.20]; P = 0.020) after full adjustment, including for BMI (model 5). When included in the same fully adjusted model (model 5), VAT but not SAT was statistically significantly associated with incident diabetes (HR 2.64 per kg VAT; 95% CI [1.14, 6.12]; P = 0.023; HR 1.34 per kg SAT; 95% CI [0.73, 2.45]; P = 0.35). The VAT/SAT ratio was not associated with diabetes risk in adjusted models. The series of models summarized in Table 3 yielded similar results with inclusion of CD4 cell count as a covariate; CD4 cell count was not associated with incident diabetes in these models (data not shown).

Exploratory models stratified on HIV serostatus yielded qualitatively similar results to those combining women with and without HIV, albeit the associations with VAT were not all statistically significant (data not shown).

To explore the relationships between insulin sensitivity, VAT, and incident diabetes, we constructed a series of Cox proportional hazards models including women with and without HIV. Both baseline log HOMA-IR (HR 1.64; 95% CI [1.03, 2.63]; P = 0.039) and VAT (HR 2.34 per kg [1.42, 3.89]; P = 0.0009) were associated with incident diabetes in separate, unadjusted models. VAT remained statistically associated with incident diabetes with modest attenuation of the hazard ratio (HR 2.14 per kg; 95% CI [1.22, 3.77]; P = 0.008) after adjustment for log HOMA-IR, which was no longer statistically significant (HR 1.22 per unit; 95% CI [0.69, 2.16]; P = 0.50).

Discussion

We used DXA-derived estimates of VAT and SAT to characterize associations with HOMA-IR and incident diabetes in a cohort of women with and without HIV infection. In cross-sectional analyses, VAT was positively associated with HOMA-IR in both women with and without HIV, before and after adjusting for BMI and demographic and behavioral covariates. In contrast, SAT was initially associated with HOMA-IR in both groups of women in multivariable models, but was not significantly associated with HOMA-IR after further adjustment for BMI or VAT. In longitudinal analyses, baseline VAT remained associated with incident diabetes mellitus after adjustment for HOMA-IR. The association of VAT with incident diabetes was independent of both SAT and BMI and was, in fact, the only factor statistically associated with incident diabetes in fully adjusted models combining women with and without HIV. Taken together, our data suggest that greater VAT mass is associated with future development of diabetes in both women with HIV infection and demographically similar HIV seronegative women.

Other investigators have used more traditional DXA parameters, including the fat mass ratio (the ratio of percent trunk mass to percent lower limb fat mass), to show associations between truncal adiposity and HOMA-IR in people living with HIV [19, 20]. Our data extend these findings by demonstrating a specific association between VAT, rather than SAT, and HOMA-IR. Our findings are consistent with data from Grunfeld and colleagues who demonstrated an independent association between VAT measured using MRI and HOMA-IR in people with and without HIV infection in the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study [22], and also demonstrated an association between upper trunk fat, a parameter that we were not able to measure, with HOMA-IR.

Our study is the first, to our knowledge, to demonstrate an association between baseline VAT and incident diabetes mellitus in a study population largely consisting of people living with HIV. Other studies of HIV-infected populations have used anthropometric measurements or clinical assessment of lipoatrophy and lipohypertrophy as potential predictors of future diabetes mellitus; these evaluations are limited by the requirement to have trained clinicians who can perform anthropometry and the subjectivity of clinical assessment. For example, in a French cohort, Capeau and colleagues found that clinically ascertained lipoatrophy but not lipohypertrophy was associated with diabetes risk [35]. In contrast, an analysis from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) found that clinically observed fat gain rather than loss was associated with incident diabetes mellitus [36]. Consistent with these findings, a recent Thai cohort study found that time-updated elevated waist circumference was associated with incident diabetes[37].

Of note, while we found that both baseline HOMA-IR and VAT were associated with incident diabetes in unadjusted models, adjustment for each other attenuated the association between VAT and incident diabetes and HOMA-IR was no longer statistically significant. This suggests that HOMA-IR mediates the relationship between VAT and diabetes risk. Others have shown associations between HOMA-IR and incident diabetes in HIV-infected populations [20, 35], but our data importantly show that baseline VAT may be associated with diabetes risk through its effects on insulin sensitivity, as assessed by HOMA-IR, at least

among women. Therefore VAT could represent a potential target for reducing risk of diabetes mellitus in women living with HIV infection.

We found positive correlations between CD4 cell count and log HOMA-IR in both women with and without HIV infection. This observation is broadly consistent with emerging data from the general population on positive associations of lymphocyte count or subsets with insulin resistance, components of the metabolic syndrome, or diabetes mellitus. For example, in the Insulin Resistance Atherosclerosis Study, total lymphocyte count was positively correlated with HOMA-IR and associated with incident diabetes mellitus[38]. Similarly, in a study of 60 individuals with HCV infection in Taiwan, CD4 cell counts were higher in those with versus those without metabolic syndrome [33]. Tanigawa and colleagues demonstrated associations between the number of components of the metabolic syndrome and both overall number of circulating CD4 cells and specifically the number of memory CD4+ T-cells in a study of middle-aged Japanese men [34]. Lastly, in a cross-sectional analysis from the Multi-Ethnic Study of Atherosclerosis, CD4+ memory T-cell number was positively associated with prevalent diabetes mellitus whereas CD4+ naïve T-cell number was inversely associated after adjustment for age, sex, race/ethnicity, and BMI [39].

Our study has several key strengths, including its focus on a well-characterized, racially and ethnically diverse group of women who are representative of the population of women with HIV in the United States. Our median follow-up of over 10 years, standardized DXA scan protocol with central reading, and established definition of diabetes mellitus [2] are additional strengths.

Study limitations include the single baseline measurements of body composition and HOMA-IR used in the longitudinal analyses of incident diabetes mellitus. In this regard, however, data from the Multicenter AIDS Cohort Study has demonstrated remarkably stable HOMA-IR measurements over a 10-year follow-up period in men with HIV infection [40], and this may apply to women as well. Due to sample size constraints, our primary longitudinal models included both women with and without HIV infection, though exploratory analyses were qualitatively similar after stratification on HIV serostatus. Due to prevalent use of antiretroviral therapy at entry into the cohort among some participants, we were not able to quantify cumulative exposure to specific antiretrovirals and therefore did not include this potential confounding factor in our models of women with HIV. We also note that the relatively low baseline rate of virologic suppression among women with HIV, which is likely due in part to frequent deferral of cART initiation during the initial time period of this study, may limit the generalizability of our findings to current clinical practice. Similarly, the evolution of HIV management and antiretroviral regimens over the past 15 years affects our ability to generalize to women who are diagnosed with HIV in the current treatment era. Lastly, the algorithm used to derive VAT from DXA scans has not been validated specifically in people living with HIV, and validation studies in the general population have either not specified the race/ethnicity of participants [31][Xia] or have not included African-Americans [24], which comprised the majority of women in this study. The relationship between VAT mass and risk of impaired glucose tolerance and diabetes mellitus may differ by race [25].

In summary, DXA-derived VAT mass was positively associated with HOMA-IR in women with and without HIV both before and after adjusting for BMI and other covariates, whereas the association between SAT mass and HOMA-IR was not independent of BMI. Furthermore, we found that baseline VAT mass was strongly and independently associated with incident diabetes mellitus. Since VAT mass appears to increase after initiation of antiretroviral therapy even with contemporary drug regimens [12, 13], future longitudinal studies should characterize the effects of changes in VAT and insulin sensitivity on risk of diabetes mellitus in people with HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline Characteristics of Study Participants

	HIV-infected (n = 226)	HIV-uninfected (n = 100)	P-value
Age (years)	42.6 (37.8, 48.5)	36.5 (30.4, 44.3)	<0.0001
Race/ethnicity			
White	37 (16.4%)	23 (23.0%)	0.36
Black	148 (65.5%)	61 (61.0%)	
Other	41 (18.1%)	16 (16.0%)	
Education < high school	89 (39.4%)	33 (33.0%)	0.27
Smoking			
Current	136 (60.2%)	63 (63.0%)	0.36
Former	46 (20.4%)	14 (14.0%)	
Never	44 (19.5%)	23 (23.0%)	
Injection drug use (ever)	82 (36.3%)	21 (21.0%)	0.006
Alcohol use			
None	113 (50.0%)	35 (35.0%)	0.08
Low (1–3 drinks/wk)	91 (40.3%)	50 (50.0%)	
Moderate (4–7 drinks/wk)	11 (4.9%)	7 (7.0%)	
High (≥7 drinks/wk)	11 (4.9%)	8 (8.0%)	
Post-menopausal	61 (27.0%)	3 (3.0%)	<0.0001
Current opioid use	45 (19.9%)	21 (21.0%)	0.82
Hypertension	64 (28.3%)	18 (18.0%)	0.048
Use of anti-hypertensive medication	43 (19.0%)	8 (8.0%)	0.011
HCV-infected	77 (34.1%)	15 (15.0%)	0.0004
Current CD4 count (cells/mm^3)	382 (252, 586)	1095 (836, 1251)	<0.0001
Nadir CD4 count (cells/mm^3)	244 (146, 354)	N/A	
Log_{10} HIV-1 RNA (copies/ml)	2.83 (1.90, 3.85)	N/A	
HIV-1 RNA < 80 copies/ml	83 (36.7%)	N/A	
On cART	138 (61.1%)	N/A	
Body mass index (kg/m^2)	27.0 (23.3, 31.0)	29.9 (25.0, 36.0)	0.0003
SAT mass (kg)	1.28 (0.86, 1.83)	1.85 (1.10, 2.79)	<0.0001
VAT mass (kg)	0.55 (0.20, 0.87)	0.56 (0.21, 1.07)	0.34

	HIV-infected (n = 226)	HIV-uninfected (n = 100)	P-value
VAT/SAT ratio	0.35 (0.21, 0.55)	0.29 (0.20, 0.44)	0.007
Total cholesterol (mg/dL)	166 (145, 195)	171 (155, 208)	0.058
HDL-cholesterol (mg/dL)	44 (35, 57)	53 (46, 61)	<0.0001
eGFR (ml/min per 1.73 m^2)	94.6 (80.0, 109.5)	98.8 (83.9, 113.4)	0.21
HOMA-IR	2.02 (1.33, 3.79)	1.86 (1.32, 3.23)	0.47
Fasting glucose (mg/dL)	83 (77, 92)	85 (78, 90)	0.33
Fasting insulin (μIU/mL)	10.0 (7.0, 17.0)	9.0 (6.5, 15.0)	0.26
Hemoglobin A1c (%)	5.3 (5.0, 5.5)	5.3 (5.0, 5.6)	0.28

Data are expressed as median (Q1, Q3), or n (%). P-values are by Wilcoxon rank-sum test or Chi-squared test as appropriate.

Table 2

Associations Between Body Fat Measurements and Log_{10} Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) in Serially Adjusted Linear Regression Models

Body Fat Predictor Variable(s):	VAT only (per kg)		SAT only (per kg)		VAT and SAT Together			
					VAT (per kg)		SAT (per kg)	
	Beta [95% CI]	P value	Beta [95% CI]	P value	Beta [95% CI]	P value	Beta [95% CI]	P value
Among HIV seropositive Women Only (n = 226)								
Model 1	**0.45 [0.31, 0.58]**	**<0.0001**	**0.14 [0.066, 0.22]**	**0.0004**	**0.43 [0.26, 0.59]**	**<0.0001**	0.018 [−0.072, 0.11]	0.69
Model 2	**0.45 [0.31, 0.60]**	**<0.0001**	**0.15 [0.071, 0.23]**	**0.0003**	**0.44 [0.27, 0.62]**	**<0.0001**	0.011 [−0.083, 0.11]	0.81
Model 3	**0.46 [0.32, 0.61]**	**<0.0001**	**0.14 [0.063,0.23]**	**0.0005**	**0.46 [0.28, 0.64]**	**<0.0001**	0.005 [−0.088, 0.099]	0.90
Model 4	**0.37 [0.19,0.56]**	**<0.0001**	−0.097 [−0.25, 0.052]	0.20	**0.39 [0.20, 0.57]**	**<0.0001**	−0.12 [−0.27, 0.023]	0.10
Among HIV Seronegative Women Only (n = 100)								
Model 1	**0.48 [0.32,0.63]**	**<0.0001**	**0.20 [0.13, 0.27]**	**<0.0001**	**0.32 [0.098, 0.54]**	**0.005**	0.093 [−0.008, 0.19]	0.071
Model 2	**0.44 [0.29, 0.60]**	**<0.0001**	**0.19 [0.12, 0.26]**	**<0.0001**	**0.29 [0.038,0.53]**	**0.024**	0.090 [−0.019, 0.20]	0.10
Model 3	**0.49 [0.33, 0.65]**	**<0.0001**	**0.21 [0.13, 0.28]**	**<0.0001**	**0.31 [0.061, 0.56]**	**0.015**	0.10 [−0.006, 0.21]	0.065
Model 4	**0.28 [0.030, 0.54]**	**0.029**	0.080 [−0.085, 0.24]	0.34	**0.27 [0.007, 0.53]**	**0.044**	0.040 [−0.13, 0.21]	0.64

Model 1 is unadjusted. Model 2 is adjusted for age, race, and WIHS site. Model 3 is additionally adjusted for current smoking status, HCV infection status, and menopause status. Model 4 is additionally adjusted for body mass index.

Table 3

Serially Adjusted Cox Proportional Hazards Models of Time to Incident Diabetes Mellitus in Women with and Without HIV Infection

Body Fat Predictor Variable(s):	VAT only (per kg)		SAT only (per kg)		VAT and SAT Together					
					VAT (per kg)		SAT (per kg)		VAT/SAT	
	Hazard ratio [95% CI]	P value	Hazard ratio [95% CI]	P value	Hazard ratio [95% CI]	P value	Hazard ratio [95% CI]	P value	Hazard ratio [95% CI]	P value
Model 1	**2.34 [1.42, 3.89]**	**0.0009**	1.23 [0.94. 1.60]	0.13	**2.50 [1.37, 4.57]**	**0.0028**	0.94 [0.67, 1.31]	0.70	**2.06 [1.05. 4.02]**	**0.036**
Model 2	**2.51 [1.43, 4.38]**	**0.0013**	**1.41 [1.04, 1.90]**	**0.026**	**2.33 [1.15, 4.72]**	**0.019**	1.07 [0.72, 1.58]	0.73	1.78 [0.83, 3.82]	0.14
Model 3	**2.83 [1.60, 4.99]**	**0.0003**	**1.50 [1.09, 2.05]**	**0.012**	**2.52 [1.24, 5.16]**	**0.011**	1.12 [0.74, 1.67]	0.60	1.89 [0.88, 4.03]	0.10
Model 4	**2.57 [1.36, 4.85]**	**0.0036**	**1.40 [1.00, 1.94]**	**0.047**	**2.31 [1.07, 4.96]**	**0.032**	1.11 [0.74, 1.66]	0.50	1.49 [0.63, 3.56]	0.36
Model 5	**2.69 [1.17, 6.20]**	**0.020**	1.40 [0.76, 2.60]	0.28	**2.64 [1.14, 6.12]**	**0.023**	1.34 [0.73, 2.45]	0.35	1.74 [0.70, 4.31]	0.23

Model 1 is unadjusted. Model 2 is adjusted for age, race, and WIHS site. Model 3 is additionally adjusted for current smoking status, HCV infection status, and menopause status. Model 4 is additionally adjusted for log HOMA-IR. Model 5 is additionally adjusted for body mass index.