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Associations Between Subcutaneous Fat Density and Systemic Inflammation Differ by HIV Serostatus and Are Independent of Fat Quantity

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Abstract

Objectives: Adipose tissue (AT) density measurement may provide information about AT quality among people living with HIV. We assessed AT density and evaluated relationships between AT density and immuno-metabolic biomarker concentrations in men with HIV.

Design: Cross-sectional analysis of men enrolled in the Multicenter AIDS Cohort Study.

Methods: Abdominal visceral (VAT) and subcutaneous (SAT) AT density (Hounsfield Units, HU; less negative=more dense) were quantified from CT scans. Multivariate linear regression models described relationships between abdominal AT density and circulating biomarker concentrations.

Results: HIV+ men had denser SAT (−95 vs −98 HU HIV−, $p<0.001$), whereas VAT density was equivalent by HIV serostatus men (382 HIV−, 462 HIV+). Historical thymidine analog nucleoside reverse transcriptase inhibitor (tNRTI) use was associated with denser SAT but not VAT. In adjusted models, a 1 standard deviation (SD) greater SAT or VAT density was associated with higher levels of adiponectin, leptin, HOMA-IR and triglyceride:HDL cholesterol ratio and lower hs-CRP concentrations in HIV− men. Conversely, in HIV+ men, each SD greater SAT density was not associated with metabolic parameter improvements and was significantly ($p<0.05$) associated with higher systemic inflammation. Trends toward higher inflammatory biomarker concentrations per 1 SD greater VAT density were also observed among HIV+ men.

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Conclusions: Among men living with HIV, greater SAT density was associated with greater systemic inflammation independent of SAT area. AT density measurement provides additional insight into AT density beyond measurement of AT quantity alone, and may have implications for metabolic disease risk.

Background

In the general population, adipose tissue (AT) disturbances, such as lipodystrophy and obesity, are associated with increased risk for cardiovascular disease (CVD) and other age-related, chronic comorbid diseases.[1,2] Although the mechanisms are incompletely understood, AT dysfunction is both well documented in people living with HIV infection and an important complication of some antiretroviral therapy (ART) agents, notably stavudine, zidovudine and older protease inhibitors (PIs).[3,4] AT accumulation in the trunk and viscera (lipohypertrophy) is not limited to older ART regimens [5] and can occur with and without concurrent peripheral fat loss (lipoatrophy). [6] Visceral fat accumulation is particularly associated with chronic AT inflammation, insulin resistance, and CVD risk and mortality. [5,6]

Although most studies assessing relationships between AT and health outcomes focus on AT quantity and distribution,[7,8] AT quality may be associated with outcomes independent of quantity.[9–12] AT quality can be indirectly assessed by quantifying AT density (in Hounsfield units, HU) on computed tomography (CT).[10] With fat gain, AT depots can expand via hyperplasia (generation of new, similarly-sized adipocytes), in which density remains stable, or hypertrophy (existing adipocytes become lipid engorged), in which density declines.[10,13,14] In contrast, with wasting adipocytes become smaller and contain fewer lipids, reflected by increasing density. [15,16] AT inflammation and fibrosis also result in increased AT density,[10] and increasing AT density can be a marker of AT dysfunction. [16,17] In obesity, tissue inflammation and fibrosis are the sequelae of dysregulated AT remodeling, resulting in increased AT density and potentially increased cardiometabolic risk. [13,15] Conversely, lower visceral (VAT) and subcutaneous (SAT) AT density (reflective of adipocyte lipid engorgement, presumably without progression to significant fibrosis) have been associated with increased cardiometabolic risk, higher circulating leptin levels and lower adiponectin levels.[10,11]

Little is known about AT density and its relationship to chronic inflammation in treated HIV infection. With lipoatrophy, AT fibrosis and decreased adipocyte size may be reflected by higher AT density.[18] Additionally, abdominal SAT fibrosis was recently documented in people living with HIV on ART who were neither obese nor lipoatrophic, suggesting subclinical AT dysfunction.[19] This study aimed to better understand the independent role of AT density in people living with HIV on ART. The objectives of this study were to determine whether CT-quantified abdominal VAT and SAT density vary by HIV serostatus, and if relationships between CT-quantified VAT and SAT density and levels of circulating immuno-metabolic biomarkers vary by HIV serostatus, independent of AT quantity.

Materials and Methods

Design and Sample

This was a cross-sectional analysis of men enrolled in the Cardiovascular Disease 2 (CVD2) sub-study of the Multicenter AIDS Cohort Study (MACS).

Participants

The MACS is an ongoing, multicenter (Pittsburgh, PA; Baltimore, MD/Washington, DC; Chicago, IL; and Los Angeles, CA), prospective, observational cohort study of men who have sex with men that began in 1984 to study the natural history of HIV infection. Participants are followed on a semi-annual basis for a standardized interview, clinical evaluations, laboratory tests and storage of specimens for the biorepository. The complete study design of the MACS has previously been described.[20]

A sub-cohort nested within the MACS, the MACS CVD2 study, was designed to assess metabolic, inflammatory, immunologic and HIV-specific factors leading to increased risk of cardiovascular disease. Complete methodological details of CVD2 have been previously described.[21,22] Briefly, men included in CVD2 were 40–70 years old, did not have a history of heart surgery or coronary angioplasty, weighed <300 pounds and were willing and able to provide informed consent.[21] Of note, men enrolled in CVD2 are generally similar to the larger MACS cohort. For this analysis, men with HIV were restricted to those with undetectable plasma HIV-1 RNA levels. In 2011 and 2012, CT-quantified VAT and SAT area measurements were obtained on CVD2 participants. Of the 1006 MACS CVD2 participants, 844 had available imaging and, for men with HIV, undetectable HIV-1 RNA, and were included in our analysis. The Institutional Review Boards of all participating sites approved the MACS and MACS CVD2 studies, and all participants provided written informed consent.

Variables

AT Density Assessment

Details of CVD2 CT scanning procedures previously have been described.[23,24] Briefly, non-contrast CT was performed to assess VAT and SAT at the level of L4-L5 using a single slice. All CT scans were read centrally by an experienced reader at the Los Angeles Biomedical Research Institute (Harbor-University of California, Los Angeles, Torrance, CA), who also assessed scan quality and consistency. For this analysis, all CT scans were re-interpreted for VAT and SAT area (in cm^2) and density (in HU) using OsiriX software (www.osirix-viewer.com) by the original team and under the direction of Dr. Matthew Budoff.

Biomarker Analysis

Adipokine levels were measured from blood samples drawn at the time of the CT at the University of Vermont Laboratory for Clinical Biochemistry Research (Burlington, Vermont, USA) under the direction of Dr. Russell Tracy, and stored at −70° Celsius. Fasting serum and plasma were analyzed for adiponectin, leptin, high-sensitivity C-reactive protein (hs-

CRP), interleukin (IL)-6, soluble tumor necrosis factor receptor I (sTNFRI) and soluble TNF receptor II (sTNFRII) concentrations. Total adiponectin, leptin and IL-6 were measured by enzyme-linked immunosorbent assays (R & D Systems, Minneapolis, MN, USA). The lower limit of detection for adiponectin was 390 ng/mL (interassay coefficient of variation [CV] 5.3–10.8%); for leptin, 1300 pg/mL (interassay CV range 5.9–6.8%); for IL-6, 0.5 pg/mL (interassay CV range 6.6–12.5%). hs-CRP was measured by nephelometry, with an interassay CV range of 4.5%-5.2%. sTNFRI and sTNFRII were measured via multiplexing using a Milliplex soluble cytokine receptor panel (Millipore, Billerica, MA). The interassay CV range was 4.6%-10.8% for sTNFRI, and 4.2%-7.9% for sTNFRII.

Other Measurements

Age, race, ethnicity, smoking, alcohol and drug history, medication use and clinical diagnosis history were assessed by self-report unless otherwise defined. AIDS diagnosis, ART use and duration and concomitant medication use were confirmed via medical record review. Depression was defined as Center for Epidemiologic Studies Depression (CESD) Scale Score >16. Heavy alcohol use was defined as >13 alcoholic drinks per week. Height and weight were measured using standardized procedures and used to calculate body mass index (BMI) in kg/m^2. BMI was categorized as <18, 18-<25, 25-<30 or ≥30 kg/m^2. Waist circumference (cm) was measured using a standardized protocol.[25] Insulin resistance (IR) was calculated using the homeostatic model assessment (HOMA) equation (HOMA-IR=fasting insulin [mU/mL] X fasting glucose [mmol/L]/22.5). The ratio of triglyceride to HDL cholesterol was used a clinical predictor of insulin resistance.[26] Diabetes was defined as self-report or use of anti-diabetic medications. Hypertension was defined as resting blood pressure >130/90 mmHg, self-report of hypertension or use of anti-hypertensive medication. Metabolic syndrome was defined according to National Cholesterol Education Program III criteria.[27] Chronic hepatitis C virus (HCV) infection was defined as having a detectable plasma HCV RNA level. Chronic hepatitis B virus (HBV) infection was defined as positive HBV surface antigen or a documented diagnosis of chronic HBV infection. Among men with HIV, longitudinal data collected at study visits included HIV-1 RNA levels, $CD4^+$ T lymphocyte counts/mm^3 (CD4) and duration of ART use. CD4 nadir was defined as the lowest count prior to and including the CT scan date.

Statistical analysis

Continuous variables were presented as medians and interquartile ranges (IQR), and categorical variables as percentages. Comparisons of continuous variables between men with and without HIV were performed using the Wilcoxon rank-sum test, and for categorical variables using the x^2 test. Linear regression models assessed the associations between abdominal SAT and VAT density as independent variables (in separate models) and concentrations of circulating biomarkers of metabolic health and inflammation. Specifically, these models characterized the change in dependent variable (i.e., circulating biomarker concentration) associated with a one standard deviation (SD) change in AT density, which corresponded to 9 HU for SAT and 8 HU for VAT. Models adjusted for AT area, depression, heavy alcohol use, chronic HCV infection, current smoking, age and black race (variables significant in univariate analyses, data not shown). For men with HIV, we also assessed the relationship between abdominal AT density and prior exposure to thymidine analogue

nucleoside reverse transcriptase inhibitors (tNRTI), as well as interactions with HIV for each outcome. For all analyses, significance was defined using a nominal, two-sided α=0.05. Analyses were conducted in SAS 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

The characteristics of MACS men (n=844) who underwent non-contrast CT scans and had inflammatory biomarkers measured are shown in Table 1, stratified by HIV serostatus. The analysis included 382 men without HIV and 462 men with HIV. Men with HIV were younger, more likely to be black and/or of Hispanic ethnicity, had lower BMI and higher prevalence of metabolic syndrome and dyslipidemia. Men with HIV had a current median (interquartile range, IQR) CD4 count of 614 (443, 787) cells/μL and 14.8 (10.6, 21.1) years on ART. Among men with HIV, 88% had historical tNRTI use; 47% were currently on PIs; 54% on non-NRTIs (NNRTI); and 19% on integrase strand transfer inhibitor (INSTI)-based ART.

Men with HIV had less abdominal SAT quantity, but similar abdominal VAT quantity compared to men without HIV (Table 2). Circulating hs-CRP, sTNFRI, sTNFRII, sCD163 and sCD14 concentrations and HOMA-IR were significantly higher in men with HIV; adiponectin and leptin were significantly lower. Abdominal SAT density was greater among men with HIV, but abdominal VAT density was equivalent by HIV serostatus (Table 2). Historical tNRTI use was associated with greater abdominal SAT density [IQR] (−99 8 [−103.8, −95.0] in people living with HIV with no historical tNRTI vs −94.3 [−99.9, −88.1] with any tNRTI use, $p<0.001$) but not VAT density [IQR] (−90.5 [−95.9, −83.4] in people living with HIV with no historical tNRTI vs −92.3 [−97.4, −86.0] with any tNRTI use, $p<0.302$).

Among men without HIV, a 1 SD (9 HU) greater SAT density was associated with physiologically-expected, lower concentrations of leptin, triglyceride-to-HDL cholesterol ratio and HOMA-IR and higher adiponectin concentrations, after adjusting for abdominal SAT area, depression, heavy alcohol use, chronic HCV infection, current smoking, age and black race. In contrast, among men with HIV, 1 SD greater SAT density was associated with statistically significantly higher levels of hs-CRP, IL-6, sTNFRI, sTNFRII and triglyceride-to-HDL cholesterol ratio. The differences in theses inflammatory biomarker concentrations were significant within group, and statistically different than the profiles observed in men without HIV (with the exception of IL-6, which did not reach between-group significance). Interestingly, 1 SD greater SAT density was associated with similarly more favorable HOMA-IR in men with and without HIV infection. (Table 3).

Relationships between abdominal VAT density and inflammatory biomarker concentrations varied less by HIV serostatus (Table 4): Among men without HIV, 1 SD (8 HU) greater VAT density was associated with statistically significant within-group lower concentrations of leptin, HOMA-IR, triglyceride-to-HDL cholesterol ratios and hs-CRP, and greater adiponectin concentrations. Results were similar for men with HIV, except that no statistically significant, within-group differences were observed in HOMA-IR or hs-CRP levels and this was significantly different than the variations observed among men without

HIV. Although the within-group differences in sTNFRI and sTNFRII did not reach statistical significance, concentration changes trended towards improvement in men without HIV and worsening in men with HIV, trends that were statistically different between groups (Table 4). Observed changes for both abdominal VAT and SAT density varied somewhat by BMI category, but generally followed similar trends (data not shown).

Discussion

To our knowledge, this is the first study to examine AT density and its relationship to circulating immuno-metabolic parameters in people living with HIV. Our findings demonstrate that men with HIV have denser abdominal SAT than men without HIV, but no difference in median abdominal VAT density. Among men without HIV, denser AT was also associated with more favorable concentrations of circulating biomarkers of metabolism and inflammation, consistent with findings in the general population. These trends are also physiologically expected; in the absence of pathological conditions, denser SAT is associated with more favorable AT function. In contrast, among men with HIV, denser abdominal SAT was associated with greater systemic inflammation. Specifically, among men living with HIV, greater abdominal SAT density was associated with higher circulating hs-CRP, IL-6, sTNFR I and sTNFRII levels, no changes in adiponectin or leptin, and mixed effects on measures of insulin resistance, with more favorable HOMA-IR but less favorable triglyceride:HDL cholesterol ratios.

Data from the Framingham Heart Study demonstrated that lower abdominal AT density was associated with adverse cardiometabolic risk that persisted even after adjustment for BMI and abdominal VAT or SAT quantity, with the most adverse risk profiles seen in persons with high abdominal VAT quantity and low density.[11] However, further analyses from the same group described an association between greater abdominal SAT density and cardiovascular disease burden only when in combination with a high VAT/SAT area ratio and after adjustment for SAT volume.[16] Such an association might be explained by reduced fat storage capacity of fibrosed SAT, or preferential new fat storage into visceral depots and other ectopic sites. [5,17,28] Another study showed lower abdominal VAT and SAT density to be associated with lower risk for subclinical atherosclerosis in the general population.[12] Fibrosed AT that is poorly vascularized and has higher excess collagen deposition can result in a less-negative HU value compared to non-fibrotic adipose tissue as a result of excess collagen and the radiographic properties of blood. Both tissue hypoxia and fibrosis result in adipocyte necrosis, leading systemic chronic inflammation and the development of atherosclerosis, potentially explaining the disparate findings.[29] Given the effect of tNRTIs on inhibition of lipolysis and adipocyte differentiation (resulting in subcutaneous lipoatrophy and truncal fat gain)[3], these findings from the general population may provide an analogy to aid interpretation.

There is growing evidence of HIV as an inflammatory process that is linked to accelerated atherosclerosis and cardiovascular disease. [30] Body fat composition changes following exposure to ART are frequently associated with known cardiovascular disease risk factors such as dyslipidemia and reduced insulin sensitivity. [31] Greater concentrations of several inflammatory biomarkers, including IL-6, sTNFRI and sTNFRII, are associated with greater

prevalence of coronary artery stenosis in people living with HIV independent of traditional and HIV-related risk factors.[32] Persistently elevated circulating IL-6, hs-CRP, and d-dimer levels after ART initiation have been associated with increased all-cause mortality, including non-AIDS related deaths.[33] In our study, greater abdominal SAT density was associated with higher circulating hs-CRP, IL-6, sTNFRI and sTNFRII levels only in men living with HIV, suggesting an AT pathology contributing to these systemic levels of inflammation. Lipoatrophic SAT is characterized by decreased adipocyte size with increased fibrosis and chronic low-level inflammation, reflected by high levels of expression of these inflammatory biomarkers.[18,34] Additionally, in patients with ART-associated lipodystrophy syndrome, TNF-α and IL-6 expression correlate positively with SAT apoptosis and fibrosis, [35] which is reflected by increased AT density. Although no significant changes were seen in HOMA-IR with greater abdominal SAT density, there was an association with higher triglyceride-to-HDL cholesterol ratios in men with HIV. Higher triglyceride-to-HDL ratios are associated with insulin resistance and compensatory hyperinsulinemia as well as increased risk of CVD. [26,36]

In an analysis from the MACS CVD2 sub-study, adiponectin, an adipokine and major mediator between AT and cardiovascular disease, was lower in men living with HIV independent of AT area.[21] In our study, an increase in SAT density was not associated with a significant increase in adiponectin, as it was in men without HIV, further suggesting AT dysfunction in men living with HIV and denser SAT. Untreated HIV infection can lead to decreased adipocyte differentiation and impairment of proteins related to adipocyte metabolism, including adiponectin, which may initiate alterations of AT function that are further amplified by ART (18,36) and/or central lipohypertrophy and result in worsening cardiometabolic risk.[38] These findings highlight the importance of early HIV diagnosis and prevention of obesity throughout the lifespan, independent of ART use, as well as the need for better understanding of AT health and its potential clinical implications in people living with HIV.

In this cohort of men with long-term HIV infection, historic exposure to either zidovudine (AZT) or stavudine (d4T) was 88%, and 41.5% had concomitant exposure. This history of tNRTI exposure was associated with higher SAT density and lower VAT density, consistent with AT redistribution from the subcutaneous to visceral space (preferential distribution to ectopic sites). NRTI exposure causes peripheral fat wasting through mitochondrial toxicity in SAT adipocytes. [39] Higher SAT density in tNRTI-exposed persons may represent lipoatrophic AT with decreased adipocyte size and increased fibrosis, macrophage infiltration and inflammation.(18, 38) Although switching from a tNRTI-based ART regimen to abacavir- or tenofovir-containing regimens has led to some improvement in limb fat quantity as measured by dual X-ray absorptiometry(39–41), higher SAT density after controlling for SAT quantity suggests that the detrimental AT effects of tNRTI exposure are incompletely reversible. Although observational studies have found that d4T is associated with a greater risk of SAT loss than AZT,[44] given the high rate of mixed tNRTI exposure in our cohort we did not evaluate the effects of these agents on SAT quality individually.

There are several limitations of our study: While AT density from CT scans has been shown to reflect adipocyte size (and thus quality) in people living with HIV[45], no AT biopsy

specimens were available, preventing assessment of the underlying biological causes of differences in fat density (such as inflammation or fibrosis). Additionally, the MACS cohort includes only adult men, which may limit the generalizability of our findings to women or children. Similarly, there was a high proportion of men living with HIV who had history of exposure to tNRTI, and relationships between AT density and inflammation in persons exposed to tNRTIs may not be representative of people living with HIV started on newer ART regimens; however, many patients with tNRTI exposure are still alive and may suffer from health concerns related to the long legacy effects of these drugs. The strengths of this study include the use of the large, well-characterized MACS cohort, which provides high-quality, detailed biochemical and clinical data in men-who-have-sex-with-men with and without HIV.

In conclusion, the data presented here provide a first analysis of the relationship between AT density and immuno-metabolic parameters in men living with HIV in comparison to otherwise similar HIV-uninfected control men. We demonstrated relationships between greater CT-quantified AT density (as a surrogate measure of AT quality) and greater levels of systemic inflammation associated with increased cardiometabolic risk among men living with HIV that were not apparent among men without HIV. Future measurement of AT density may provide additional insight into AT function beyond measurement of AT quantity alone and may have implications for assessment of long-term cardiovascular risk.

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Table 1.

Baseline Demographics and Clinical Characteristics of Participants.

	HIV− (N= 382)	HIV+ (N= 462)
Age in years, (IQR)	55 [50, 62]	53 (48, 58)
African American race, n (%)	91 (23.8)	137 (29.7)
Smoking, n (%)	79 (21.0)	120 (26.1)
Heavy alcohol use[a], n (%)	36 (10.3)	20 (4.7)
Illicit drug use, n (%)	187 (52.7)	270 (60.8)
Body mass index, kg/m^2 (IQR)	26.6 (24.1, 30.0)	25.7 (23.3, 28.4)
Waist circumference, cm (IQR)	96.7 [89.2, 106.5]	94.35 (87.5, 101.7)
Total cholesterol, mg/dL (IQR)	190 (166, 214)	188 (163, 214)
HDL cholesterol, mg/dL (IQR)	51 (42, 6)	46 (38.3, 54.3)
Triglycerides, mg/dL (IQR)	102 (75, 151)	141 (97.5, 204.5)
LDL cholesterol, mg/dL (IQR)	112 (91, 135)	107 (83, 131)
Fasting glucose, mg/dL (IQR)	96 (89, 105)	98 (91, 107)
Hemoglobin A1C, % (IQR)	5.6 (5.4, 5.8)	5.5 (5.3, 5.8)
HOMA-IR (IQR)	2.8 (2.0, 4.2)	3.24 (2.4, 4.9)
C-reactive protein, ug/mL	0.96 (0.53, 1.9)	1.22 (0.67, 2.7)
Fibrinogen, ml/dL	332.5 (293, 375)	324 (273, 373)
IL-6, pg/mL	1.31 (0.9, 2.1)	1.44 (0.9, 2.3)
Adiponectin, ng/mL	7056 (4936, 10275)	5912 (3672, 9659)
Leptin, pg/mL	6318 (3180, 11791)	5496 (2504, 10790)
Soluble TNF R1, pg/mL	1160 (958, 1376)	1184 (991, 1486)
Soluble TNF R2, pg/mL	5868 (4973, 6879)	6347 (5312, 7942)
Soluble CD163, ng/mL	549 (432, 697)	656 (490, 827)
Soluble CD14, ng/mL	1280 (1115, 1458)	1625 (1400, 1853)
Current CD4$^+$ T cell count, cells/μL (IQR)	-	614 (443, 787)
CD4$^+$ T cell nadir, cells/μL (IQR)	-	281.5 (172, 391)
HIV-1 RNA <50 copies/mL (IQR)	-	0 (0)
History of AIDS diagnosis, n (%)	-	72 (15.6)
Years since ART initiation, (IQR)	-	14.84 (10.6, 21.1)
History of AZT use, n (%)	-	322 (72.7)
History of d4T use, n (%)	-	252 (56.9)
History of AZT or d4T use, n (%)	-	390 (88)
History of concomitant use of AZT and d4T, n (%)	-	184 (41.5)
Cumulative use of AZT, years (IQR)	-	3.2 (0–7.2)
Cumulative use of d4T, years (IQR)	-	0.7 (0–3.9)
On ART since last visit, n (%)		
PI	-	208 (47)
NRTI	-	417 (94.1)
NNRTI	-	240 (54.2)
INSTI	-	84 (19)

IQR=interquartile range, HDL=high density lipoprotein, LDL=low density lipoprotein, HOMA-IR= homeostasis model assessment-insulin resistance, AT=adipose tissue, HCV=hepatitis C virus, HBV=hepatitis B virus, AIDS=Acquired Immunodeficiency Syndrome, ART=antiretroviral therapy, PI=protease inhibitor, NRTI=nucleoside reverse transcriptase inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor, INSTI=integrase strand transfer inhibitor.

[a] defined as >13 alcoholic drinks per week

[b] defined as Center for Epidemiology Studies Depression Scale Score >16

[c] defined as HCV RNA positivity

[d] Defined as positive HBV surface antigen or diagnosis of chronic HBV infection

[e] Measured from abdominal CT scan

Table 2.

Adipose Tissue Area and Density by HIV serostatus

	HIV− (N=382)	HIV+ (N=462)	P value
Subcutaneous AT area[c], mm^2(IQR)	233 (170, 319)	184 (115, 274)	<0.001
Visceral AT area, mm^2 (IQR)	140 (89, 212)	156 (99, 223)	0.037
Total AT area, mm^2(IQR)	380 (274, 520)	348 (251, 468)	0.004
Subcutaneous AT density, HU (IQR)	−98 (−103, −93)	−95 (−100, −89)	<0.001
Visceral AT density, HU (IQR)	−92 (−96, −86)	−92 (−97, −86)	0.313

AT=adipose tissue, IQR=interquartile range, HU=Hounsfield unit.

Table 3.

Effects of 1 Standard Deviation Difference on SAT Density on Immuno-metabolic Markers*

	HIV−	HIV+	P value
Adiponectin	19.4% (9.8%, 29.8%)[b]	4.7% (−2.2%, 12.2%)	0.010
Leptin	−18.1% (−25.9%, −9.5%)[a]	2.9% (−5.4%, 11.9%)	<0.001
HOMA-IR	−10.0% (−16.2%, −3.2%)[a]	−11.0% (−16.1%, −5.7%)	0.780
Triglyceride:HDL	−8.4% (−15.5%, −0.6%)[a]	7.9% (0.8%, 15.6%)[b]	0.001
hs-CRP	−8.9% (−20.4%, 4.3%)	11.7% (0.0%, 24.8%)[b]	0.013
IL-6	4.0% (−5.1%, 14.0%)	10.9% (2.9%, 19.5%)[b]	0.250
Soluble TNF R1	−0.2% (−4.7%, 4.5%)	7.0% (3.0%, 11.1%)[b]	0.012
Soluble TNF R2	−2.4% (−6.3%, 1.7%)	4.9% (1.5%, 8.5%)[b]	0.003

SD=standard deviation, SAT=subcutaneous adipose tissue, HOMA-IR=homeostasis model assessment-insulin resistance, HDL=high density lipoprotein, hs-CRP=high sensitivity C-reactive protein, IL=interleukin, TNF=tumor necrosis factor

*Adjusted for SAT area, CESD>16, >13 alcoholic drinks per week, chronic HCV infection, current smoker, age at visit and black race

[a]Associated with statistically significant within-group lower concentrations of Immuno-metabolic marker.

[b]Associated with statistically significant within-group higher concentrations of Immuno-metabolic marker.

Table 4.

Effects of 1 Standard Deviation Difference on VAT Density on Immuno-metabolic Markers*

	HIV−	HIV+	P value
Adiponectin	21.2% (11.4%, 31.9%)[b]	28.5% (19.7%, 38.1%)[b]	0.203
Leptin	−24.4% (−31.6%, −16.5%)[a]	−18.8% (−25.4%, −11.6%)[a]	0.189
HOMA-IR	−13.6% (−20.2%, −6.5%)[a]	−5.4% (−11.6%, 1.3%)	0.039
Triglyceride:HDL	−21.7% (−29.0%, −13.8%)[a]	−18.2% (−24.7%, −11.1%)[a]	0.409
hs-CRP	−16.4% (−27.5%, −3.5%)[a]	5.0% (−7.1%, 18.6%)	0.004
IL-6	1.7% (−7.9%, 12.4%)	5.8% (−2.7%, 15.0%)	0.471
Soluble TNF R1	−2.7% (−7.4%, 2.3%)	2.8% (−1.4%, 7.3%)	0.043
Soluble TNF R2	−4.0% (−8.1%, 0.3%)	3.1% (−0.7%, 7.0%)	0.003

SD=standard deviation, VAT=visceral adipose tissue, HOMA-IR=homeostasis model assessment-insulin resistance, HDL=high density lipoprotein, hs-CRP=high sensitivity C-reactive protein, IL=interleukin, TNF=tumor necrosis factor

*Adjusted for SAT area, CESD>16, >13 alcoholic drinks per week, chronic HCV infection, current smoker, age at visit and black race

[a]Associated with statistically significant within-group lower concentrations of Immuno-metabolic marker.

[b]Associated with statistically significant within-group higher concentrations of Immuno-metabolic marker.