Intermuscular and subcutaneous adipose tissue distributions differ in HIV+ versus HIV-men and women

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Abstract

Background—Loss of subcutaneous (SAT) with sparing of visceral (VAT) adipose tissue (AT) has been documented in HIV + men and women. Intermuscular AT (IMAT) rivals VAT in independent associations with cardiovascular risk.

Objective—To determine whether the size and distribution of IMAT differs in HIV+ vs. HIV-men and/or women.

Design—We used whole-body MRI to measure VAT, IMAT and four SAT compartments and compared them by HIV status using whole-body skeletal muscle (SM) or total AT (TAT) as co-variates in multi-ethnic groups of healthy HIV- (*n*=86) and stable HIV+ (*n*=76) men and women.

Results—The sizes of AT depots (adjusting for SM) did not differ by HIV status, except for smaller gluteal SAT (lower trunk, between L_4-L_5 to greater trochanter) in both sexes (P<0.05). The AT distribution (adjusting for TAT) was significantly different, with larger VAT (P<0.05) and smaller gluteal and limb SAT (P<0.05) in both HIV+ sexes; IMAT increased more with TAT in HIV+ vs. HIV- men (P<0.05 for slope interaction) but there were no significant differences in women. There were significant race by HIV interactions in AT distribution with more pronounced VAT differences in non-Hispanic white men and larger trunk SAT in African Americans HIV+ vs. HIV-.

Conclusion—The AT distribution differed markedly in HIV+ vs. HIV- with limb and lower body SAT representing a smaller proportion of TAT in HIV+ in both sexes and IMAT representing a larger proportion of TAT in HIV+ vs. HIV- men.

Keywords

fat distribution; muscle adipose tissue infiltration; HIV; magnetic resonance imaging

Introduction

Since the advent of highly active anti-retroviral treatment (HAART), the percentage of individuals living with HIV above the age of 50 increased from 17% to 23% between 2001

and 2004 and is predicted to approach 50% by 2015 [1-3]. Individuals with HIV experiencing longer survival will also be affected by metabolic complications known to occur in these circumstances [4]. Such adverse effects include type 2 diabetes mellitus (DM), cardiovascular disease (CVD), osteoporosis, as well as deleterious adipose tissue (AT) distribution [5-6].

Prior cross-sectional reports have characterized changes in fat distribution in HIV+ as a loss of AT from the limbs and face (peripheral) with an increase in central adiposity (the HIV lipodystrophy syndrome) [7-14]. The deleterious effect of increased visceral AT (VAT) and the protective effect of gluteal-femoral AT with regard to metabolic abnormalities and CVD have been established in HIV- populations [15-16]. However the distribution of AT in the lower body is complex with lipid being stored in various compartments: superficial subcutaneous AT, over the muscle fascias (SAT), inter-muscular AT visible by CT or MR imaging between the muscle fibers and underneath the muscle fascia (IMAT) [17] and lipid stored inside the muscle, invisible in a regular MR image but detectable by NMR spectroscopy (extramyocellular lipid or EMCL and intramyocellular lipid or IMCL) [18]. Increased IMCL was correlated strongly with insulin resistance in HIV+ men and with decreased lower body fat by DXA in HIV+ women [18-20]. However much less is known about the distribution of the other AT depots in the lower body, SAT vs. IMAT, in HIV+ men and women. Recently, a larger IMAT was shown to rival VAT in independent associations with cardiovascular risk in HIV- [21-23]. IMAT also represented a larger proportion of whole-body AT (TAT) with increasing age and was proposed as a risk factor for physical limitation and decreased strength in older HIV- adults [24-25]. While we have reported that a relatively larger IMAT and smaller SAT in the lower body correlated with insulin resistance in obese women, independent of HIV status [26], whether IMAT represents a higher proportion of TAT in HIV+ vs. HIV- women or men is not known.

Therefore, the aim of the present study was to determine whether differences in IMAT measured by whole-body MRI exist in a larger cohort of multi-ethnic HIV+ vs. HIV- men and women. We hypothesized that SAT will represent a smaller and IMAT will represent a larger proportion of TAT in HIV+ vs. HIV- individuals. Since HIV/AIDS is diagnosed disproportionately in males versus females in any given year (74% vs. 26% respectively) and since AT distribution is significantly different in men vs. women independent of ethnicity [17,24] we also examined interactions between HIV status and sex. When examining differences in the regional AT depots we controlled for TAT but also, separately, for the whole-body skeletal muscle (SM), as these two variables may be differentially affected by HIV status and HAART in the current treatment era [14].

Methods

The study involved a retrospective analysis of archived data from HIV+ and HIV- men and women who had been recruited for multiple different studies of body composition that occurred from 1999-2004. All individuals had undergone analysis of body fat depots via whole body MRI while at weight stability, for cross-sectional analyses or as baseline studies prior to interventions. The 162 participants included 35 HIV+ and 26 HIV- men as well as 41 HIV+ and 60 HIV- women.

The HIV+ subjects were stable with or without HAART which was typical of previously used antiretroviral regimens at the time when the studies were conducted (1999-2004). Overall 25% of subjects were HAART-naïve, 75% were taking nucleoside reverse transcriptase inhibitors (NRTI), 43% were taking protease inhibitors (PI) and 37% were taking non-nucleoside reverse transcriptase inhibitors (NNRTI). Twenty-three percent (23%) of men were HAART-naive, 3% were on NRTI-s alone, 37% were on NRT-s plus PI-s, 31%

were on NRTI-s plus NNRTI-s and 3% were on a three drug combination. The respective frequencies in women were 15%, 5%, 32%, 24% and 15% and did not differ significantly from the frequencies in men. The ethnicity breakdown in the HIV+ group was 60% African Americans, 13% Non-Hispanic whites, 22 % Hispanics and 5% others.

The HIV- subjects were healthy adults and none were on investigational agents. The ethnicity breakdown was 43% African Americans, 46% Non-Hispanic whites, 8% Hispanics and 3% others.

All studies as well as the current analysis were approved by the Institutional Review Board of St. Luke's Roosevelt Hospital Center.

Magnetic resonance imaging

AT and SM volumes were measured by whole-body MRI as previously reported [26]. Briefly, subjects were placed in a 1.5 T scanner ($\times$ 6 Horizon; General Electric, Milwaukee, WI, USA) with their arms extended above their heads. The entire body was visualized on a scout coronal image (6$\times$ Horizon) and the axial level of L_4-L_5 was identified. The scans used to calculate the various depot compartments were acquired by contiguous axial slices of 10-mm thickness at 40-mm intervals below L_4-L_5 to the toes and above this level to the fingertips. The images were then subsequently analyzed on SLICEOMATIC image analysis software (version 4.2; Tomovision, Montreal, QC, Canada). [25] AT volumes were calculated by measuring the relevant tissue area in each slice with the use of threshold methods and manual delineation to draw boundaries among different tissues. The volume between slices was extrapolated from area measurements. The following fat depots were calculated: total visceral (VAT), IMAT, and 4 SAT compartments – Leg (below greater trochanter), Lower Trunk (greater trochanter to L_4-L_5), Upper Trunk (above L_4-L_5 to the shoulders) and Arms (above the shoulders) SAT. IMAT was defined as the AT visible between the muscle groups and beneath the muscle fascia. [26] The gray level intensity (threshold value) of the AT in the SAT region was first determined and used as reference and this value was reduced by 20% to identify the IMAT threshold.

The MRI scans were read at the New York Obesity Research Center Image Reading Center at St. Luke's Roosevelt Hospital Center. The CV on repeated readings of the same 2 scans by observers analyzing the images was 3.8 % for TAT, 3.4% for SAT, 9.7% for VAT, 2.2 % for SM, and 7.3 % for IMAT.

Statistical analysis

Group data are presented as means ± standard error. Differences in age, weight, height, BMI, SM, and TAT by HIV or by sex were analyzed separately by student's t-test. A general linear model (GLM) was used to compare AT depots by sex and HIV status after adjusting for age, height, and either skeletal muscle (SM) or total adipose tissue (TAT). SM was used to determine differences between groups in absolute AT volume, while TAT was used to evaluate differences in relative AT distribution. When interactions between sex and HIV status were significant results were presented separately in the four groups. When interactions were not significant differences were reported by HIV status in men and women combined. Because we have previously shown that AT distribution is influenced by race in HIV- cohorts [17] we conducted additional analyses to assess whether there were any interactions between HIV sex and race in a subset of subjects with races (African American, non-Hispanic white or Hispanic) represented in all the four groups (HIV+ and HIV-, men and women). A *P*-value <0.05 was considered statistically significant. All analyses were performed with Statistica version 6 for Windows.

Results

Subject characteristics and unadjusted values for the whole-body SM and AT and regional AT volumes are shown in Table 1 while comparisons of absolute AT volumes after adjusting for age, height and SM are shown in Table 2 and after adjusting for age, height and TAT are shown in Table 3.

In our cohort men were older and had lower BMI than women (Table 1). Expected differences in body composition and body fat distribution between men and women were found in both HIV+ and HIV-groups (Table 1-3) with higher SM, lower TAT and relatively more VAT and less Leg SAT in men than in women. The rise in IMAT with SM was steeper in women compared to men ($P<0.05$), for both the HIV+ and the HIV- groups.

Age did not differ by HIV status (Table 1). HIV+ and HIV- women had similar BMI, SM, TAT and all AT compartments except for Lower Trunk SAT (includes gluteal regional), which was smaller in HIV+ women ($P=0.02$). HIV+ men had lower BMI, weight and SM than HIV- men (Table 1); SM was not different in HIV+ vs. HIV- men after adjusting for weight and height ($P=$NS). With regard to the AT, HIV+ men had lower TAT and peripheral SAT (Arms, Lower Trunk and Legs) than HIV- men, but similar VAT and IMAT (Table 1). After adjusting for age, height and SM, the only significant difference by HIV status was observed for Lower Trunk SAT (includes gluteal region) which was smaller in HIV+ vs. HIV-men and women (Table 2). In terms of the relative AT distribution, after adjusting for age, height and TAT, HIV+ men and women had more VAT and less SAT, specifically Arm and Lower Trunk SAT than HIV-counterparts (Table 3). For IMAT, there was a significant sex by HIV interaction ($P=0.028$). For men, the relationship between IMAT and SM and the mean values for IMAT were similar between HIV+ vs. HIV – ($P=0.093$) but there was a greater rise in IMAT with TAT for HIV+ than for HIV- (Figure 1, $P<0.05$). The slope of rise with either SM or TAT and the mean values for IMAT did not differ significantly in HIV+ vs. HIV- women (Tables 2 and 3, Figure 1).

We performed additional analyses to determine whether HAART or race influenced our results. Excluding the HIV+ HAART naïve from the database or using HAART category type as factor (naïve, NRTI, PI or NNRTI) instead of the HIV+ status in similar analyses as presented above did not modify the results. Addition of race to the above presented analyses in a subset of subjects (African Americans, non-Hispanic whites and Hispanics) showed no significant 3-way interactions (race by HIV by sex), but resulted in some changes. In Table 2: a) There were significant race by HIV ($P=0.009$) and sex by race ($P=0.006$) interactions for VAT; in post-hoc analyses VAT was significantly higher only in HIV+ vs. HIV- non-Hispanic white men ($P<0.00001$); b) The sex by HIV interactions for IMAT were not significant; the P value for the main HIV effect on IMAT was 0.05; c) The P value for differences in Lower Trunk SAT changed from 0.025 to 0.082 (NS). In Table 3: a) There was a significant race by HIV ($P=0.007$) interaction for VAT; in post-hoc analyses VAT was significantly higher only in HIV+ vs. HIV- non-Hispanic whites ($P<0.0001$); b) The sex by HIV interaction for IMAT was not significant; the P value for the main HIV effect on IMAT was 0.014; c) The P values for differences in Arm SAT changed from 0.024 to 0.052 and for differences in Leg SAT changed from 0.25 to 0.014; d) There was a significant race by HIV ($P=0.038$) interaction for Upper Trunk SAT; in post-hoc analyses Upper Trunk SAT was significantly higher only in HIV+ vs. HIV- African Americans ($P<0.0001$).

Discussion

This study investigated differences in AT sizes and distribution between HIV+ and HIV-men and women; in addition to previous reports [11-14,26-28] it emphasized the newly

described depot IMAT. This study is unique in that by using the whole body MRI technique we separated IMAT, the visible AT between the muscle fibers and underneath the muscle fascia, from SAT, the AT between the muscle fascia and the skin. We found no significant differences in IMAT or VAT by HIV status when adjusting for SM alone; in contrast, VAT represented a higher proportion of TAT in HIV+ than in HIV- and the rise in IMAT with TAT was steeper in HIV+ men than in HIV- men or both HIV+ and HIV- women. We also found, as previously described, smaller limb and lower trunk SAT in HIV+ vs. HIV-, by comparing subdivisions of SAT without interference from IMAT or organ and muscle fat, such as when these regional measurements were determined by dual-energy X-ray absorptiometry (DXA) [13-14,17,24].

To our knowledge, this is the first report of a difference in IMAT by HIV in men with a wide range of body weight. Whole-body MRI has been used before by us and others [11,13-14,26-27,28] to compare AT depots in HIV+ vs. HIV-; however, IMAT was not separated from SAT in the majority of these previous reports. Our findings suggest that if the loss of fat in HIV+ individuals occurs in the protective AT depots of the lower body, then IMAT, just as VAT, is relatively spared. This relative sparing of IMAT may remain significant in terms of metabolic consequences. Not all AT depots carry equivalent metabolic risk [27]. Enlarged VAT and IMAT have both been associated with an unfavorable metabolic profile and enlarged IMAT was associated with chronic disease incidence and functional decline in old age, independent of the total amount of body fat [23-26]. In addition, short-term inactivity substantially increased IMAT (15-20%), without changing SAT, in healthy young men and women [24-25,29-31]. Close to 50% of the HIV population is expected to be over the age of 50 by 2015 [2-3]. At present, there is limited knowledge about longitudinal body composition changes with aging in the HIV+ population. Decreased muscle strength, independent of muscle wasting, has been linked to increased cytokines, specifically TNF-α, [32], which in turn correlates with the immune function in HIV+ individuals. [33] Given our findings, studies considering the relationship between cytokines, IMAT accumulation and muscle strength in HIV individuals would be relevant.

We confirmed previous findings that, in the era of antiretroviral therapy, the HIV infection is associated with lipoatrophy i.e. smaller SAT in limbs and lower trunk without loss of VAT and, as we show here first, without loss of IMAT [11,13-14,26-28]. Without adjusting for race, whether correcting for SM or TAT, we found that gluteal SAT was the SAT sub compartment most affected by HIV, in both men and women while the leg SAT (below the greater trochanter) was not smaller in HIV+ vs. HIV- women, not unlike some [26] but not all of our previous reports [28]. However when race was added to the analyses adjusted leg SAT means were significantly smaller in both HIV+ vs. HIV- men (10.3±0.5 vs 11.8±0.7 l) and, albeit less so, in HIV+ vs. HIV- women (12.1±0.5 vs. 12.9±0.5 l). Other significant race by HIV interactions were found for VAT and upper trunk SAT, with differences being most pronounced in non-Hispanic white men and African Americans, respectively. Although consistent with known differences in HIV- populations, because of the small number of subjects in our individual data cells when broken down by race, these findings must be confirmed in larger cohorts.

The strength of our study includes the use of whole body MRI with the novel addition of measuring IMAT and SAT sub-compartments in a cohort of HIV+ and HIV- men and women with a wide weight range. The limitations include the use of a convenience sample of HIV+ and HIV- men and women, lack of information with regard to viral load and CD4 counts, lifestyle activity patterns and a heterogeneous HAART regimen which did not allow us to report in detail on the role of the different anti-retrovirals on AT size and distribution. We have previously reported that a regimen of diet and exercise in obese HIV+ women

promoted weight loss but that the VAT and IMAT decreases were less than expected from a similar intervention in HIV- obese women [34]. Therefore we hypothesize that differences in physical activity patterns in HIV+ vs. HIV- would have been unlikely to explain the differences in IMAT we have observed. Also, in this study we were unable to attribute the AT findings to a specific HAART regimen. Previous reports have established that AT changes in HIV are mainly associated with the separate or combined use of two major classes of drugs, NRT-s and PI-s [35]. The inclusion or exclusion of HIV+ who were HAART naïve in our study did not modify the results however since they represented a small percentage of the subjects a definitive conclusion on whether the HIV itself was associated with AT depots changes cannot be made. Further studies examining these aspects could provide additional knowledge into the effect of the HIV/HAART on AT distribution.

In conclusion, IMAT and SAT distributions differ in HIV+ vs. HIV-. Our findings strongly suggest that IMAT and SAT should be separated when studying differences in AT distribution in HIV+ vs. HIV-. *In-vitro* studies investigating the possibility that these AT depots may be differentially affected by HIV/HAART should be conducted.

Acknowledgments

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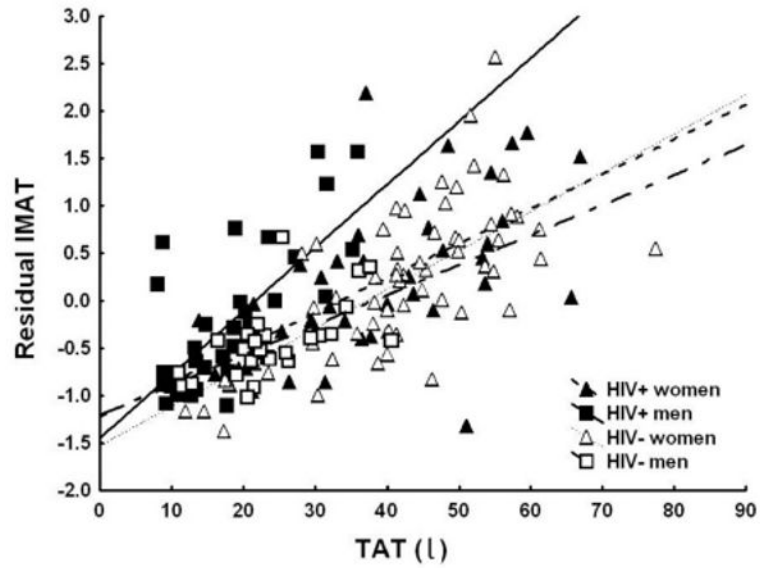
Figure 1.
Relationship between residual IMAT and TAT. Filled squares: HIV+ men. Open squares: HIV- men. Filled triangles: HIV+ women. Open triangles: HIV- women. Residual IMAT (intermuscular adipose tissue) is the difference between the observed and the expected values of IMAT, calculated through multiple regressions as a function of age and height. IMAT and TAT (whole-body adipose tissue) were measured by whole-body MRI. For the difference in slopes, $P<0.05$ men and $P=NS$ for women.

Table 1

Subject characteristics and magnetic resonance imaging (MRI) measurements in HIV-positive and HIV-negative men and women.

Subject characteristic	Men		Women		P-Value* by Sex		P-Value* by HIV status	
	HIV+ n=35	HIV- n=26	HIV+ n=41	HIV- n=60	HIV+	HIV-	Men	Women
Age (years)	44.9 ± 1.3	45.8 ± 1.5	41.5 ± 1.2	40.7 ± 1.0	0.08	0.005	0.68	0.59
Race (%) **	17/48/26/9	69/23/8/0	10/71/8/0	37/52/8/3	0.37	0.01	0.001	0.003
HAART (%) #	23/3/37/31/3	-------	15/5/32/24/15	--------	NS	-------	------	------
Weight (kg)	74.5 ± 2.5	85.4 ± 2.9	81.8 ± 2.3	86.6 ± 1.9	0.02	0.76	0.0005	0.16
BMI (kg/m^2)	24.2 ± 0.8	26.7 ± 0.9	31.4 ± 0.7	32.5 ± 0.6	<0.00001	<0.00001	0.0001	0.32
SM (l)	27.8±0.7	32.3±0.8	21.5±0.6	22.7±0.5	<0.00001	<0.00001	0.00001	0.15
TAT (l)	18.4±2.0	24.3±2.3	38.5±1.8	41.9±1.5	<0.00001	<0.00001	0.006	0.21
VAT (l)	3.3±0.3	2.9±0.3	2.8±0.3	2.5±0.2	0.27	0.18	0.50	0.24
IMAT (l)	1.2±0.1	0.9±0.1	1.7±0.1	1.7±0.1	0.002	<0.00001	0.10	0.99
Total Sat (l)	14±1.8	20.5±2	34±1.6	37.7±1.3	<0.00001	<0.00001	0.0001	0.14
Arm Sat (l)[1]	2.3±0.2	3.1±0.2	3.8±0.2	4.3±0.2	<0.00001	0.0002	0.0007	0.09
Upper Trunk Sat (l)[2]	4.3±0.6	5.5±0.7	10±0.6	10.8±0.5	<0.00001	<0.00001	0.06	0.38
Lower Trunk Sat (l)[3]	1.8±0.4	3.5±0.5	5.9±0.4	7.3±0.3	<0.00001	<0.00001	0.00008	0.02
Leg Sat (l)[4]	5.6±0.8	8.5±0.9	14.3±0.7	15.4±0.6	<0.00001	<0.00001	0.00003	0.30

All values are mean ± standard error. BMI, body mass index, SM, skeletal muscle, TAT, total adipose tissue, VAT, visceral adipose tissue; IMAT, inter-muscular adipose tissue; SAT, subcutaneous adipose tissue; HAART: highly-active anti-retroviral therapy;

[1] includes all SAT of the arms above the shoulders;

[2] includes all SAT above L4-L5 up to the shoulders;

[3] includes all SAT between greater trochanter and L4-L5;

[4] includes all SAT below the greater trochanter;

* P-values derived by t-test analysis, significant if <0.05

** Number of Non-Hispanic whites/African Americans/Hispanics/others as % of total sample in each group, P value shown for the difference between % non-Hispanic whites;

Number of HIV men or women who were treatment-naïve, on NRTI alone, on NRTI-s plus PI, on NRTI-s plus NNRTI, or on 3 drug combination, as % of total sample in each group.

Table 2

Comparisons of regional AT volumes by whole-body MRI, adjusting for age, height and SM.

Regional AT volume	Men		Women		P-Value[*] By HIV
	HIV+	HIV-	HIV+	HIV-	
VAT (l)	3.2 ± 0.3	2.6 ± 0.4	2.9 ± 0.3	2.6 ± 0.2	0.097
IMAT (l)	1.2 ± 0.1	0.9 ± 0.1	1.8 ± 0.1	1.7 ± 0.1	-------
Total SAT (l)	10.8 ± 1.8	12.2 ± 2.5	38.0 ± 1.7	40.5 ± 1.4	0.23
Arm SAT (l)[1]	2.0 ± 0.2	2.3 ± 0.3	4.1 ± 0.2	4.5 ± 0.2	0.084
Upper Trunk SAT (l)[2]	3.3 ± 0.6	2.8 ± 0.8	11.3 ± 0.6	11.6 ± 0.5	0.85
Lower Trunk SAT (l)[3]	1.1 ± 0.4	1.7 ± 0.6	6.8 ± 0.4	7.9 ± 0.3	0.025
Leg SAT (l)[4]	4.3 ± 0.8	5.5 ± 1.0	15.8 ± 0.7	16.4 ± 0.6	0.21

All values are mean ± standard error. SM, whole-body skeletal muscle; VAT, visceral adipose tissue; IMAT, inter-muscular adipose tissue; SAT, subcutaneous adipose tissue;

[1] Arm SAT: includes all SAT of the arms above the shoulders;

[2] Upper Trunk SAT: SAT above L4-L5 up to the shoulders;

[3] Lower Trunk SAT: SAT between greater trochanter and L4-L5;

[4] Leg SAT: SAT below the greater trochanter.

[*] P-value calculated by GLM, significant if <0.05 (adjusted for age, height and SM);

-- HIV by Sex interactions for IMAT (M<F for both HIV+ and HIV- groups, P<0.0006, HIV differences in men P=0.093, in women P=0.475.)

Table 3

Comparison of regional AT distribution by whole-body MRI, adjusting for age, height and TAT.

Regional AT volume	Men		Women		P-Value* By HIV
	HIV+	HIV-	HIV+	HIV-	
VAT (l)	4.6 ± 0.3	3.9 ± 0.3	2.2 ± 0.2	1.7 ± 0.2	0.007
IMAT (l))	-------	-------	1.8 ± 0.1	1.7 ± 0.1	-------
Total SAT (l)	27.0 ± 0.3	28.2 ± 0.4	29.4 ± 0.3	30.0 ± 0.2	0.00001
Arm SAT (l)[1]	3.6 ± 0.2	3.9 ± 0.2	3.3 ± 0.1	3.5 ± 0.1	0.024
Upper Trunk SAT (l)[2]	8.5 ± 0.3	8.1 ± 0.4	8.5 ± 0.3	8.3 ± 0.2	0.235
Lower Trunk SAT (l)[3]	4.5 ± 0.2	5.1 ± 0.2	5.0 ± 0.2	5.7 ± 0.2	0.00001
Leg SAT (l)[4]	10.4 ± 0.5	11.3 ± 0.5	12.6 ± 0.4	12.6 ± 0.3	0.25

All values are mean ± standard error. TAT, whole-body, total adipose tissue; VAT, visceral adipose tissue; IMAT, inter-muscular adipose tissue; SAT, subcutaneous adipose tissue;

[1] Arm SAT: includes all SAT of the arms above the shoulders;

[2] Upper Trunk SAT: SAT above L4-L5 up to the shoulders;

[3] Lower Trunk SAT: SAT between greater trochanter and L4-L5;

[4] Leg SAT: SAT below the greater trochanter.

* P-Value calculated by GLM, significant if <0.05 (adjusted for age, height, and TAT);

---HIV by Sex interactions for IMAT (HIV+>HIV- in men P<0.00001, in women P=0.284.