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Changes in Central Adipose Tissue after Switching to Integrase Inhibitors

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Abstract

Background: Treatment with integrase strand transfer inhibitors (INSTIs) has been associated with excess weight gain, however the long-term effect of INSTI-based regimens on adipose tissue (AT) compartments remains unknown.

Objectives—To evaluate the effect of switching to an INSTI on visceral (VAT) and subcutaneous (SAT) AT in virologically-suppressed adults with HIV.

Methods: We performed a retrospective observational cohort study of ART experienced adults referred to the metabolic Clinic of the University of Modena and Reggio Emilia who had ≥2 assessments of body composition by abdominal computed tomography. An interrupted time series model with mixed-effect model incorporated was used to calculate VAT and SAT change rate, adjusting for smoking status, use of alcohol, and physical activity.

Results: A total of 698 patients were included: 156 who switched to an INSTI-based regimen and 542 who did not. After switch to INSTI, mean SAT area increased approximately 3-fold (before 0.27 vs after 0.73 cm^2/month; p=0.011), and VAT area 7-fold (0.18 vs 1.30 cm^2/month; p<0.001).

Conclusions: Among PLWH on ART, both SAT and VAT gain accelerated after switching to an INSTI-based regimen. The associations between INSTIs and central adiposity require further investigation.

Keywords

INSTI; central adiposity; weight; fat

Introduction

Growing evidence suggests that different adipose tissue (AT) compartments contribute differing effects on cardiovascular risk. (1–3) Visceral AT (VAT) quantity has been

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demonstrated to correlate with traditional cardiovascular risk factors as well as development of atherosclerosis. (4,5) Cardiovascular disease (CVD) is an important cause of morbidity and mortality in people living with HIV (PLWH). VAT accumulation is correlated with multiple metabolic risk factors that can heighten CVD risk in this population.(3,6) Increased VAT has also been found to be associated with increased insulin resistance and cardiovascular events in PLWH. (7–9)

Although weight gain following antiretroviral therapy (ART) initiation is common with most modern ART regimens, recent studies suggest that integrase strand transfer inhibitors (INSTI)-based ART use can be associated with excess weight gain in some persons. (10–12) In a recent analysis among AIDS Clinical Trials Group (ACTG) participants who were virologically suppressed, switch to INSTI-based ART resulted in significant increases in annualized, within-person weight gain. (12) ART initiation is associated with weight gain, with data suggesting greater weight gain rates with INSTIs, rilpivirine, and tenofovir alafenamide (TAF). (13–15) The long-term effect of INSTI-based regimens on specific AT compartments remains unknown. We hypothesized that the switch to an INSTI-based regimen in virologically-suppressed PLWH would be associated with greater VAT and SAT changes over time compared to individuals who remained on non-INSTI ART.

Methods

Study population

This is a secondary analysis of existing longitudinal data from the multidisciplinary Modena HIV Metabolic Clinic (MHMC), at the University of Modena and Reggio Emilia, Italy from 2016–2019 PLWH on ART who had at least 2 abdominal computed tomography (CT) scans were included. All study procedures were in accordance with the ethical standards of the “Comitato Etico Regionale area vasta Nord”. All participants provided written informed consent prior to initiation of study procedures.

Assessments

Data were collected from the MHMC electronic database. The following baseline variables were collected from participants: age; smoking (none, moderate [≤10 cigarettes/day], intensive [>10 cigarettes/day]); physical activity (none, moderate [<4hours weekly], intensive [≥4 hours weekly]); alcohol use (none, moderate [≤20 g/day], heavy [>20 g/day]), duration of HIV (months); and cumulative ART use by class. Body weight was measured using a digital scale to the nearest 0.1 kg, with participants wearing light clothes without shoes. Height was measured using a wall-mounted stadiometer to the nearest 0.1 cm. Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. CT scans and measurements of VAT and SAT were performed with a 64-multislice CT and associated workstation (LightSpeed VTC; GE, Milwaukee, WI). VAT and SAT were measured on a single abdominal CT section at the level of fourth lumbar vertebrae by a blinded reader.

Statistical analysis

All the statistical analyses were conducted with SAS® 9.4 (Cary, NC, SAS Institute Inc.). All data points were screened to remove errors that were confirmed by clinicians, and outliers were identified through distribution checking but kept in subsequent analyses for robustness. Participants with only one CT scan were excluded from the study population. Baseline characteristics were summarized based on the first participant record as median and interquartile range for continuous variables, and as percentage for categorical variables, respectively. All CT scans collected after ART switch were aligned in time before subsequent analyses. All statistical tests were two-sided at a 5% significance level. An interrupted time series analysis combined with a mixed-effects model was applied to calculate the VAT and SAT change with the issues of self-control, self-correlation and irregular observations addressed simultaneously. Factors such as age, sex, HIV experience time, nadir $CD4^+$ T cell <200 cells/mm^3, physical activity, alcohol use and smoking history were considered when developing the full models to estimate the changes in VAT and SAT over time.

Results

Study population

Baseline characteristics of the 698 PLWH are shown in Table 1; 156 switched to an INSTI-based regimen. All participants were Caucasian, and 68% were men. Median baseline BMI was in the normal range. Each participant had approximately 3 CT scans done over a median of 36.6 months (approximately one every 18 months). The median time from switch to first CT scan was 10.7 (range 6.2–24.8) months; median time from switch to last CT scan was 20.6 (range 10.8–85.4) months. Most (99.1%) had been on tenofovir alafenamide (TAF). One third of the participants were women, with a median age (standard deviation) of 45 (6.7) years in the non-switch cohort and 46.1(6.7) in the switch group; at baseline 32 (16.5%) were menopausal in the non-switch group vs 13 (32.5%) in the switch group. People who had been switched to INSTIs had significantly longer time on ART, less prevalence of $CD4^+$ T cell count nadir <200 cells/mm^3, and higher baseline VAT area (Table 1).

Changes in VAT and SAT

Baseline SAT and VAT area are shown in Table 1. In simple models, the average SAT area gain after switch to INSTI increased from 0.27 cm^2/month to 0.73 cm^2/month (p=0.011), and the average VAT area gain increased from 0.18 cm^2/month to 1.30 cm^2/month (p<0.001) (Figure 1). BMI change rate was similar following switch to INSTI (beta estimate 0.0005, p=0.9). In mixed-effects models (Table 2), greater SAT area over the study period was associated with a switch to INSTI and moderate alcohol use, whereas male sex, longer HIV duration, any use of tobacco, and vigorous physical activity were associated with less SAT. Greater VAT area was associated with a switch to INSTI, male sex, increasing age, and moderate alcohol us. Use of tobacco was associated with less VAT area.

In sex-stratified models, differences emerged. In men, the average SAT area gain rate after switch to INSTI increased from 0.21 cm^2/month to 0.78 cm^2/month (p=0.012); the average

VAT area from 0.24 cm^2/month to 1.56 cm^2/month (p<0.001). In women, switch to INSTI was not significantly associated with changes in SAT (0.4 cm^2/month to 0.53 cm^2/month, p=0.61) or VAT area change rate (0.10 cm^2/month to 0.29 cm^2/month, p=0.46).

Discussion

In this longitudinal study of PLWH on ART, switch to INSTI-based ART was associated with significant increases in central adiposity compared to measurements in adults who did not switch, with greater increases seen in VAT area. Traditional factors associated with weight gain, such as alcohol use and sedentary lifestyle, were also observed, yet INSTI use maintained an independent effect after controlling for these factors. Central obesity, in particular excess VAT accumulation, has negative metabolic effects and has been associated with increased mortality, cardiovascular disease, neurocognitive impairment, and fatty liver disease among PLWH. (8,16,17) To our knowledge, this is the first data describing increases in SAT and VAT after switch to an INSTI in PWH on long-term ART.

VAT may be a unique pathogenic fat depot and is its accumulation is associated with increased likelihood of having metabolic syndrome, low high density lipoprotein (HDL)-c, increased triglycerides, and increased fasting glucose levels. (1,5) Matushita et al. found that a ≥50 cm^2 increase in VAT over 3 years was associated with increased odds of hyperglycemia, hypertriglyceridemia and low HDL-c.(18) Additionally, increases in VAT have been associated with the prevalence of hypertension independent of BMI and weight circumference. (1) In PWH, greater VAT has been associated with prevalent CVD. (8,9) In ACTG A5260s, increases in VAT were more pronounced with raltegravir-based regimen relative to Darunavir/ritonavir, with greater gains seen in women and black participants.(19) The etiology of weight gain and its distribution in persons with undetectable plasma HIV-1 RNA who switch to an INSTI-based regimen is unclear, and may differ by ART regimen.

Many previous studies that have reported associations between INSTI use and weight gain and have suggested sex differences have investigated ART-naïve participants. In the NAMSAL study, weight gain ≥10% was greater in women started on an INSTI; however, no difference in overweight or obesity incidence was seen between men and women on dolutegravir. (20) In a recent study evaluating risk factors for ≥5% body weight gain in virologically-suppressed participants who were switched to an INSTI-based regimen, no sex differences emerged. (21) Risk factors associated with weight gain among women include minority race and age ≥50 years, which may account for the discrepancy in our findings. (12,22) In a previous analysis of this cohort, greater trunk and leg fat mass increases were associated with per-year INSTI use. However, in sex-stratified models, this association was only significant for men. (23)

Limitations of our study include overlapping and small sample size regarding specific INSTI agents to make comparisons among regimens and the confounding effects of different NRTI backbones that are difficult to control for. While other studies have evaluated differences by INSTI agent, our findings suggest SAT and VAT changes may be a class effect. Our analysis did not evaluate other potential contributors to weight gain such as diet, concomitant medications, or psychiatric comorbidities. Most participants were middle age Caucasian

men, and our results may not reflect changes in the general population; however, the VAT gain rate might be higher in blacks and older PWH given they are at higher risk for weight gain once on an INSTI-based regimen. (12) Lastly, VAT and SAT area were determined from a single slice CT scan at each assessment, which could affect reliability of the longitudinal changes, though CTs were consistently performed at the sample anatomic level, on the same scanner and read by a central reader.

In summary, we report the first data describing changes in anatomical AT compartments in PLWH on ART after switching to an INSTI-based regimen while on ART. These data suggest that INSTI use is associated with increased rate of gain of both abdominal VAT and SAT that may lead to increased odds of developing components of the metabolic syndrome and its associated risk of cardiovascular disease. Further work is needed to understand the longitudinal changes in central adiposity associated with INSTI and the consequences on cardiometabolic risk, particularly among at-risk populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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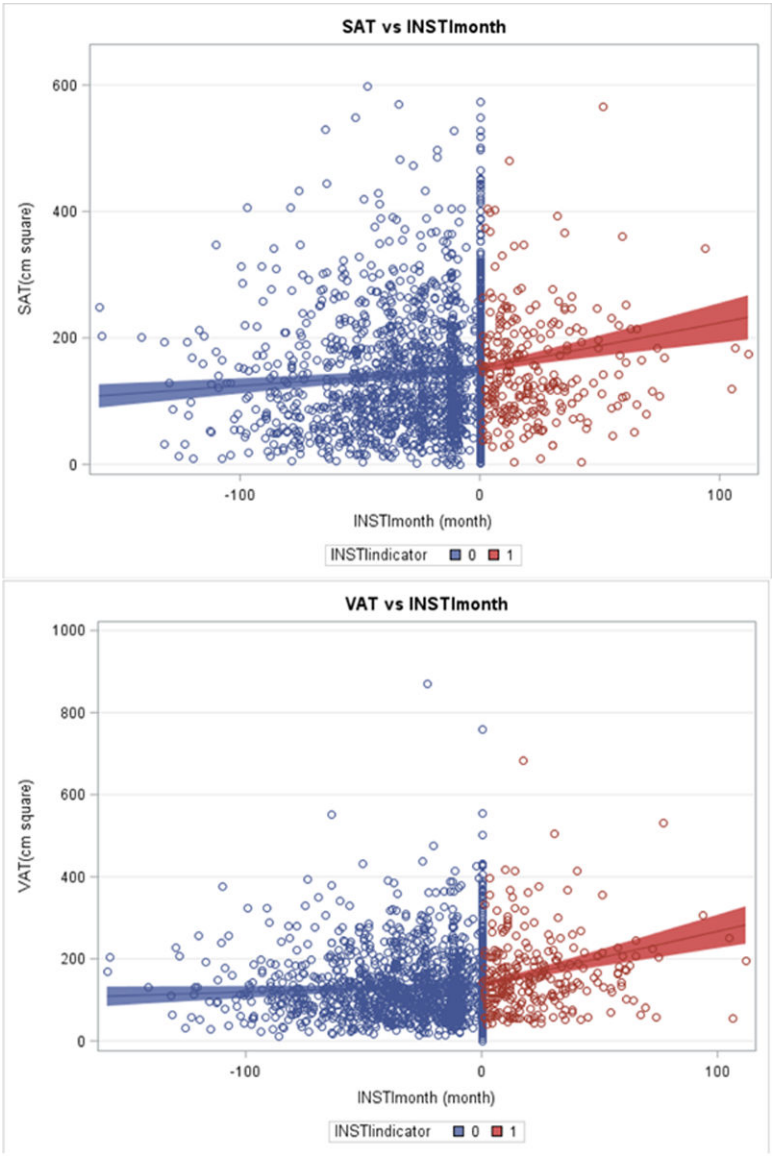

Figure 1.

Changes in SAT and VAT before and after INSTI initiation

SAT=Subcutaneous adipose tissue; VAT=visceral adipose tissue; INSTI=Integrase strand transfer inhibitor.

Table 1.

Baseline Demographic & Clinical Characteristics at Time of First Assessment

Characteristics	Never switched to INSTI (N=542)	Switch to INSTI (N=156)
Male sex (%)	370 (68)	106 (68)
Age (years, IQR)	46 (42–51)	48 (44–53)
Body mass index (kg/m^2, IQR)	22.9 (20.9–25.0)	23.7 (21.2–25.7)
Smoker (%)		
Moderate	98 (18)	22 (14)
Intensive	143 (27)	38 (25)
Physical activity [n (%)]		
None	331 (62)	81 (53)
Moderate	150 (28)	57 (37)
Intensive	52 (10)	16 (10)
Alcohol use (%)		
Moderate	219 (41)	59 (38)
Intensive	2 (0.4)	3 (2)
CD4 Nadir <200 cells/ mm^3 (%)	259 (48)	58 (38)
HIV-1 VL ≤50 (%)	433 (86.4)	124 (84.9)
HIV duration (months, IQR)	189 (135–249)	219 (164–272.5)
Prior PI use (%)	N/A	134 (86)
SAT area (cm^2, IQR)	115 (66–178)	129 (105–244)
VAT area (cm^2, IQR)	110 (72–157)	126.5 (87–185)

IQR= interquartile range, INSTI=integrase strand transfer inhibitor, PI=protease inhibitor, SAT= subcutaneous adipose tissue, VAT=visceral adipose tissue.

Table 2.

Combined Sex Model for SAT and VAT area

	SAT area		VAT area	
Characteristic	**Model Estimate (SE)**	**P value**	**Model Estimate (SE)**	**P value**
Time on INSTI	0.33 (0.07)	<0.0001	0.0078	0.9278
Time on INSTI*Switch to INSTI	0.52 (0.18)	0.0042	1.04	<.0001
Sex[1]	−57.0 (7.30)	<0.0001	2.99	<.0001
HIV duration, months	−0.10 (0.04)	0.0218	38.1	<.0001
Moderate alcohol use[2]	15.3 (5.04)	0.0025	18.6	0.0006
Intensive alcohol use[2]	7.09 (20.70)	0.73	19.7	0.463
Moderate tobacco use[3]	−26.7 (6.32)	<0.0001	−22.0	0.0017
Intensive tobacco use[3]	−25.03 (6.29)	<0.0001	−20.4	0.9278
Moderate physical activity[4]	5.37 (4.69)	0.0004		
Intense physical activity[4]	−19.3 (8.00)	0.002		

[1]Reference group women

[2]Reference group no alcohol use

[3]Reference group no tobacco use

[4]Reference no physical activity, SAT= subcutaneous adipose tissue, VAT=visceral adipose tissue, SE= standard error, INSTI=integrase strand transfer inhibitor.