J Antimicrob Chemother 2019; **74**: 1028–1034
doi:10.1093/jac/dky551 Advance Access publication 18 January 2019

Journal of Antimicrobial Chemotherapy

Progressive increases in fat mass occur in adults living with HIV on antiretroviral therapy, but patterns differ by sex and anatomic depot

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Received 12 August 2018; returned 25 October 2018; revised 21 November 2018; accepted 28 November 2018

Objectives: Although weight gain on ART is common, the long-term trajectory of and factors affecting increases in fat mass in people living with HIV are not well described.

Methods: Men and women living with HIV in the Modena HIV Metabolic Clinic underwent DXA scans every 6–12 months for up to 10 years (median 4.6 years). Regression modelling in both combined and sex-stratified models determined changes in and clinical factors significantly associated with trunk and leg fat mass over the study period.

Results: A total of 839 women and 1759 men contributed two or more DXA scans. The baseline median age was 44 years and BMI 22.9 kg/m^2; 76% were virologically suppressed on ART at baseline. For both sexes, trunk and leg fat consistently increased over the study period, with mean yearly trunk and leg fat gain of 3.6% and 7.5% in women and 6.3% and 10.8% in men, respectively. In multivariate analysis, factors associated with greater fat mass included female sex, per-year ART use (specifically tenofovir disoproxil fumarate and integrase strand transfer inhibitor therapy), per-unit BMI increase, no self-reported physical activity and CD4 nadir <200 cells/mm^3.

Conclusions: Among people living with HIV on ART, trunk and leg fat mass increased steadily over a median of 4.6 years of follow up, particularly among women. After controlling for traditional risk factors, HIV- and ART-specific risk factors emerged.

Introduction

As ART continues to increase life expectancy for people living with HIV (PLWH), optimization of comorbid conditions, such as cardiovascular disease (CVD) and diabetes mellitus (DM), has become a primary concern. Excess body weight is a known risk factor for CVD and DM in the general population, and a growing concern among PLWH.[1] Over the past 10–15 years BMI at the time of HIV seroconversion has increased, reflecting the increase in total body weight of the general population. Following initiation of ART, most individuals gain weight and many become overweight or obese.[2,3] Increases in BMI following ART initiation increase CVD risk,[4] and even modest weight gain is associated with greater risk of development of DM in PLWH compared with HIV-uninfected individuals.[3,4] Increases in central body fat are also associated with hepatic steatosis in PLWH.[5]

Several studies have evaluated changes in BMI and body composition after initiating ART.[6–12] However, point-prevalence and short-term longitudinal studies cannot be extrapolated to predict longer-term changes. Additionally, studies showing concomitant lean mass loss with fat mass gain on ART demonstrated that BMI alone insufficiently describes cardiometabolic risk in PLWH.[7,13] The aim of this study was to understand fat mass trajectory and factors associated with fat mass quantity in a large cohort of adult men and women with HIV on ART, and to determine sex-specific risk factors for any observed differences in trunk and leg fat quantity.

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. PLWH who attended the MHMC underwent DXA scans approximately every 6–12 months, beginning in 2004. We included

all participants who were on ART and who had at least two DXA scans during a period of up to 10 years.

Ethics

All study procedures were in accordance with the ethical standards of the Comitato Etico Provinciale di Modena and with the Helsinki Declaration of 1975, as revised in 2000. All participants provided written, informed consent.

Definitions

Data were collected from the MHMC electronic database. The following baseline variables were collected from participants: age; smoking (number of cigarettes/day); physical activity [none, moderate (<4 h weekly), intensive (≥4 h weekly)]; hypogonadism (defined as post-menopausal in women and serum total testosterone <300 ng/dL in men);[14] metabolic syndrome (using NCEP-Adult Treatment Panel III criteria);[15] HCV seropositivity; duration of HIV infection; history of AIDS wasting; nadir CD4+ T lymphocyte (CD4) count; ART duration; and cumulative ART use by class and agent. 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. BMI was defined as weight in kilograms divided by height in metres squared. Lipodystrophy was defined using the Multicenter AIDS Cohort Study definition, with anthropometric categorizations of lipoatrophy, lipohypertrophy and mixed form.[16]

All participants underwent venous blood sampling at 8:00 AM after an overnight fast. HCV seropositivity was determined by antibody testing (anti-HCV; Abbott HCV EIA 3.0 enzyme immunoassay, Abbott Laboratories, Chicago, IL, USA). HIV-1 RNA was measured by Abbott RealTime™ HIV-1 assay (Abbott Laboratories; lower limit of detection 50 copies/mL), CD4 count by flow cytometry, 25-hydroxy (25-OH) vitamin D by chemiluminescence immunoassay (DiaSorin, Stillwater, MN, USA) and serum total testosterone by immunochemiluminescence (ADVIA Centaur; Siemens Medical Solutions, Tarrytown, NY, USA). Vitamin D insufficiency was defined as 25-OH vitamin D concentration <30 ng/mL. All participants were scanned using the same single densitometer (Hologic Discovery W, Inc., Waltham, MA, USA). The instrument was calibrated daily with a hydroxyapatite phantom.

Statistical analysis

Variables are expressed as median and IQR for continuous and percentage for categorical variables. To account for correlation within patients in outcome measures, mixed-effect regression models were created assuming compound symmetry variance–covariance structure for combined men and women to determine the sex-adjusted effect, and then in sex-stratified models to determine factors associated with fat mass by sex. A significant sex × year interaction in the combined model further supported the use of sex-stratified models. Mixed-effect regression models determined variables significantly ($P < 0.05$) associated with trunk and leg fat mass over the study period, after exclusion of variables not statistically or clinically significant in univariate analyses.

Mixed-effect models with random intercept and slope were adjusted for sex (for the combined model) and the following variables (time updated, where applicable): time in study; BMI; cumulative duration of tenofovir disoproxil fumarate use; cumulative duration of integrase strand transfer inhibitor use; age group by 5 year increments; self-reported physical activity level (none, moderate or intensive); hypogonadism; history of AIDS wasting; vitamin D insufficiency; and HCV seropositivity. Additional variables (including other ART classes/agents) were considered for inclusion, but excluded owing to either the extent of missing data or lack of significance in univariable models ($P > 0.10$). Stepwise forward model selection methods with backward elimination were used in building the final models. The covariates identified in the combined model were used in the sex-stratified models to examine their relationships with the outcomes in females and males separately. Annual change rates were calculated by applying simple regression to mean estimates derived from the mixed-effect models. A P value <0.05 was considered statistically significant. All analyses were conducted using SAS 9.4 (Cary, NC, USA).

Results

Study population

A total of 839 women and 1759 men contributed at least two DXA scans [median number of scans 5 (IQR 3–7)], with a median follow-up of 4.7 years (IQR 2.1–7.7). General characteristics at the initial assessment are shown in Table 1. All participants were Caucasian, and the median age was 44 years. The median time since HIV diagnosis was 14 years, and CD4 count 528 cells/mm^3; 76% had an HIV-1 RNA ≤50 copies/mL. Peripheral atrophy was

Table 1. Baseline demographic and clinical characteristics at time of first fat mass assessment

Characteristic	Women ($N = 839$)	Men ($N = 1759$)
Age, years, *n* (%)		
>55	37 (4)	166 (9)
51–55	71 (9)	197 (11)
46–50	183 (22)	450 (26)
41–45	303 (36)	536 (31)
35–40	182 (22)	265 (15)
<35	63 (8)	145 (8)
BMI, kg/m^2 (IQR)	21.6 (20.0–24.1)	23.5 (21.6–25.5)
Smoker, *n* (%)	349 (41.6)	740 (42.1)
Smoking, pack years (IQR)	10.0 (1.1–20.0)	12.5 (0–25.0)
Physical activity, *n* (%)		
none	577 (69)	1020 (58)
moderate	184 (22)	438 (25)
intensive	44 (5)	224 (13)
Hypogonadism[a] (%)	124 (15)	124 (7)
Metabolic syndrome, *n* (%)	84 (10)	144 (8)
HCV seropositivity, *n* (%)	250 (30)	468 (27)
Vitamin D insufficiency, *n* (%)	414 (49)	831 (47)
History of AIDS wasting, *n* (%)	113 (13)	81 (5)
CD4 nadir <200 cells/mm^3, *n* (%)	448 (53)	856 (49)
HIV-1 viral load ≤50 copies/mL, *n* (%)	646 (77)	1319 (75)
Lipodystrophy, *n* (%)		
no lipodystrophy	118 (14)	346 (20)
lipoatrophy	209 (25)	682 (39)
central fat accumulation	97 (12)	153 (9)
mixed form	365 (44)	514 (29)
ART duration, years (IQR)	9.6 (5.6–13.1)	8.3 (3.4–12.0)
TDF use, *n* (%)	538 (64)	1144 (65)
INSTI use, *n* (%)	70 (8)	129 (7)
Trunk fat mass, kg (IQR)	7.0 (5.2–9.2)	5.8 (4.1–8.1)
Leg fat mass, kg (IQR)	3.0 (1.9–4.8)	2.0 (1.2–3.7)

TDF, tenofovir disoproxil fumarate; INSTI, integrase strand transfer inhibitor.
[a]Defined as post-menopausal female or male hypogonadism.

diagnosed in 32% of persons, and was more frequent among men (35% versus 30%). Lipodystrophy status did not change over the follow-up period. At baseline, 7% of men were hypogonadal and 15% of women were post-menopausal, with 24% categorized as post-menopausal at any point after baseline. Median BMI was in the normal range for both sexes. Median (IQR) baseline trunk fat mass was 7.0 kg (5.2–9.2 kg) for women and 5.8 kg (4.1–8.1 kg) for men. Median (IQR) baseline leg fat mass was 3.0 kg (1.9–4.8 kg) for women and 2.0 kg (1.2–3.7 kg) for men.

Factors associated with trunk fat mass

For both sexes, trunk fat mass steadily increased over the study period (Figure 1), with a mean yearly trunk fat gain of 3.6% (246 g; SD 1118 g) for women and 6.3% (438 g; SD 1026 g) for men. In combined mixed-effect models, greater trunk fat mass over the study period was associated with female sex, older age, no self-reported physical activity, CD4 nadir <200 cells/mm^3, per-unit BMI increase, per-year any ART use, and per-year integrase strand transfer inhibitor and tenofovir disoproxil fumarate use (Table 2). Hypogonadism, vitamin D insufficiency, HCV seropositivity, history of AIDS wasting and HIV-1 RNA >50 copies/mL were associated with less trunk fat over the study period.

Sex-stratified models (Table 3) yielded similar results with a few exceptions: among women, post-menopausal status was associated with greater trunk fat, as was per-year use of any ART, but not per-year use of tenofovir disoproxil fumarate or integrase strand transfer inhibitor. Women with AIDS wasting had less trunk fat.

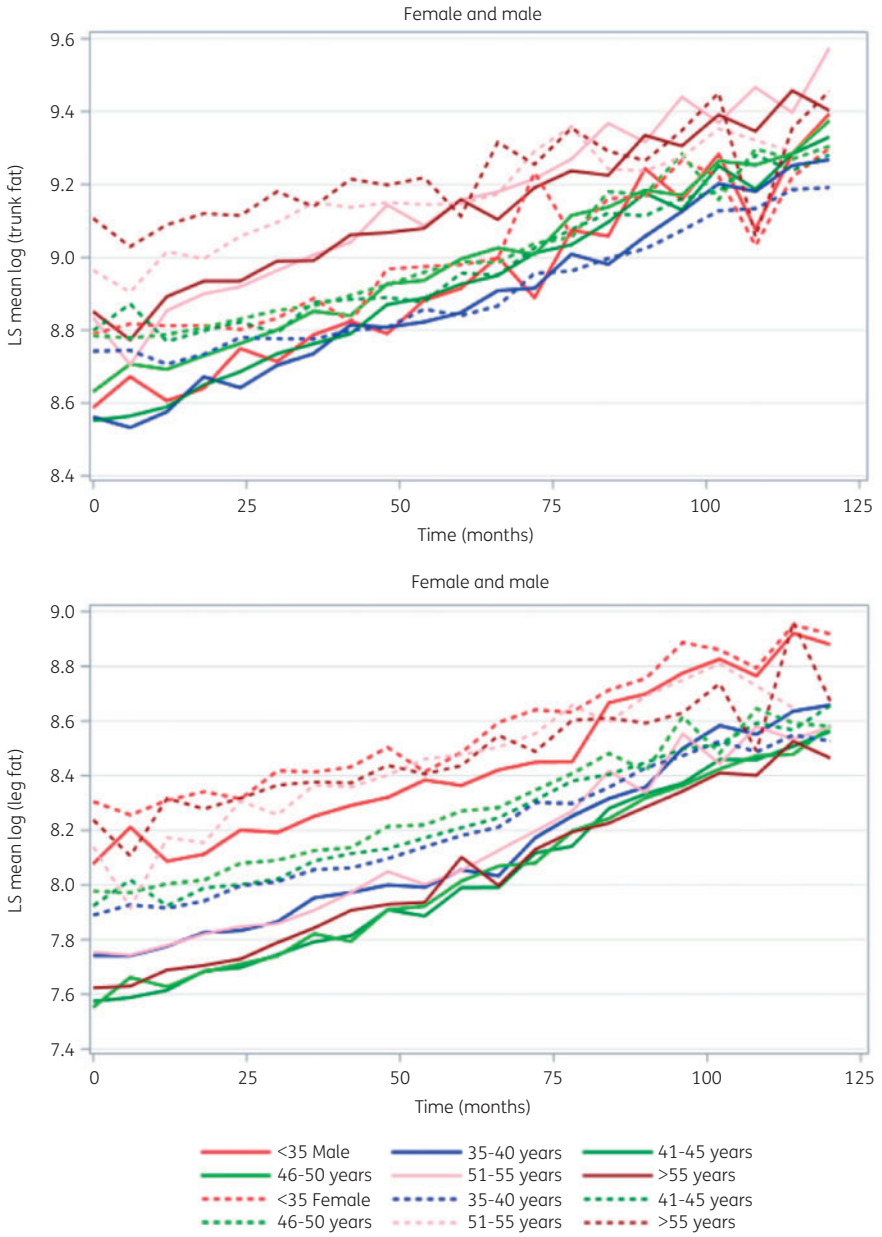

Figure 1. Trunk and leg fat over study period. LS, log transformed.

Table 2. Combined sex model for trunk fat

Variable	Model estimate (SE)	Effect size	*P* value
Female sex	0.488 (0.017)	+63%	<0.0001
BMI (kg/m^2)[a]	0.104 (0.001)	+11%	<0.0001
Age, years[b]			
>55	0.112 (0.032)	+12%	0.0004
51–55	0.162 (0.030)	+18%	<0.0001
46–50	0.075 (0.026)	+8%	0.0004
No regular physical activity[c]	0.062 (0.009)	+6%	<0.0001
Moderate physical activity[c]	0.049 (0.008)	+5%	<0.0001
CD4 nadir <200 cells/mm^3	0.047 (0.012)	+5%	<0.0001
Per-year ART use	0.004 (0.001)	+0.4%	0.0004
Per-year INSTI use	0.00005 (0.00002)	+<0.1%	0.002
Per-year TDF use	0.004 (0.001)	+0.4%	0.001
Hypogonadism	−0.024 (0.010)	−2%	0.02
Vitamin D insufficiency	−0.016 (0.007)	−2%	0.03
HCV seropositivity	−0.046 (0.013)	−4%	0.0005
History of AIDS wasting	−0.060 (0.010)	−6%	<0.0001
HIV-1 RNA >50 copies/mL[d]	−0.013 (0.006)	−1%	0.02

SE, standard error; TDF, tenofovir disoproxil fumarate; INSTI, integrase strand transfer inhibitor.
[a]Per-unit increase.
[b]Reference group: <35 years of age.
[c]Reference: intense regular physical activity.
[d]Reference: >50 copies/mL.

In men, greater trunk fat was associated with per-year use of tenofovir disoproxil fumarate and integrase strand transfer inhibitor. Less trunk fat was associated with HCV seropositivity and hypogonadism, regardless of testosterone use (data not shown). Vitamin D deficiency was not significant in the sex-stratified models.

Factors associated with leg fat mass

For both sexes, leg fat also steadily increased over the study period (Figure 1), with a mean (SD) yearly leg fat gain of 7.5% (187 g) for women and 10.8% (232 g) for men. In combined-sex mixed-effect models (Table 4), leg fat mass was greater for women compared with men over the study period. Individuals with higher BMI, per-year tenofovir disoproxil fumarate and integrase strand transfer inhibitor use, and no self-reported physical activity also had greater leg fat, whereas hypogonadism/post-menopausal state was associated with less leg fat.

In contrast to the combined-sex model, in sex-stratified models (Table 5), women who were postmenopausal had greater leg fat mass, whereas men with hypogonadism had less leg fat mass. Per-year tenofovir disoproxil fumarate use was associated with greater leg fat in both men and women. Among women only, less leg fat was associated with age 36–50 years compared with age <35. In men, lower physical activity and a diagnosis of metabolic syndrome were associated with greater leg fat. As with trunk fat mass, per-year integrase strand transfer inhibitor use was associated with greater leg fat mass in men.

Table 3. Sex-stratified model for trunk fat

	Women			Men		
Variable	model estimate (SE)	effect size	*P* value	model estimate (SE)	effect size	*P* value
BMI (kg/m^2)[a]	0.094 (0.002)	+10%	<0.0001	0.110 (0.002)	+12%	<0.0001
Age, years[b]						
>55	0.102 (0.052)	+11%	0.05	0.112 (0.038)	+12%	0.003
51–55	0.158 (0.043)	+17%	0.0003	0.161 (0.037)	+18%	<0.0001
46–50	0.086 (0.036)	+9%	0.02	0.075 (0.032)	+8%	0.02
No regular physical activity[c]	0.041 (0.015)	+4%	0.006	0.066 (0.010)	+7%	<0.0001
Moderate physical activity[c]	0.030 (0.015)	+3%	0.04	0.048 (0.009)	+5%	<0.0001
CD4 nadir <200 cells/mm^3	0.035 (0.017)	+4%	0.04	0.052 (0.016)	+5%	0.0009
Per-year ART use	0.007 (0.002)	+0.7%	<0.0001	NS	NS	NS
Per-year INSTI use	NS	NS	NS	0.00004 (0.00002)	+<0.1%	0.03
Per-year TDF use	NS	NS	NS	0.006 (0.002)	+0.6%	0.0003
Hypogonadism	0.039 (0.012)	+4%	0.001	−0.043 (0.015)	−4%	0.003
History of AIDS wasting	−0.095 (0.015)	−10%	<0.0001	NS	NS	NS
HIV-1 RNA >50 copies/mL[d]	0.019 (0.009)	+2%	0.03	−0.032 (0.007)	−3%	<0.0001
Vitamin D insufficiency	NS	NS	NS	NS	NS	NS
HCV seropositivity	NS	NS	NS	−0.043 (0.017)	−4%	0.01

SE, standard error; NS, not significant; TDF, tenofovir disoproxil fumarate; INSTI, integrase strand transfer inhibitor.
[a]Per-unit increase.
[b]Reference group: <35 years of age.
[c]Reference: intense regular physical activity.
[d]Reference: >50 copies/mL.

Table 4. Combined-sex model for leg fat

Variable	Model estimate (SE)	Effect size	*P* value
Female sex	0.741 (0.028)	+210%	<0.0001
BMI (kg/m^2)[a]	0.084 (0.002)	+9%	<0.0001
Age, years[b]			
>55	−0.278 (0.054)	−27%	<0.0001
51–55	−0.173 (0.051)	−17%	0.0007
46–50	−0.248 (0.045)	−25%	<0.0001
41–45	−0.300 (0.043)	−30%	<0.0001
35–40	−0.257 (0.046)	−26%	<0.0001
No regular physical activity[c]	0.049 (0.009)	+5%	<0.0001
Moderate physical activity[c]	0.043 (0.008)	+4%	<0.0001
Metabolic syndrome	0.021(0.009)	+2%	0.03
CD4 nadir <200 cells/mm^3	0.171 (0.021)	+18%	<0.0001
Per-year ART use	−0.016 (0.002)	−2%	<0.0001
Per-year INSTI use	0.00009 (0.00001)	+<0.1%	<0.0001
Per-year TDF use	0.007 (0.002)	+<0.1%	<0.0001
Hypogonadism	−0.048 (0.011)	−5%	<0.0001
Vitamin D insufficiency	−0.023 (0.008)	−2%	0.003
History of AIDS wasting	NS	NS	NS
HIV-1 RNA >50 copies/mL[d]	NS	NS	NS

SE, standard error; NS, not significant; TDF, tenofovir disoproxil fumarate; INSTI, integrase strand transfer inhibitor.
[a]Per-unit increase.
[b]Reference group: <35 years of age.
[c]Reference: intense regular physical activity.
[d]Reference: >50 copies/mL.

Discussion

In this large cohort of women and men living with HIV on ART and with up to 10 years of follow-up, trunk and leg fat mass both increased steadily throughout the observation period, and HIV- and ART-related factors influenced fat mass. Importantly, many patients referred to the MHMC are treatment-experienced, and most were virologically suppressed on ART at cohort enrolment (76%). Thus, these increases in fat mass were above and beyond those associated with ART initiation, and occurred in all age groups, across ART classes and in both sexes. Not unexpectedly, women had greater trunk and leg fat mass over the study period, but the rate of fat mass increase was greater among men. Hypogonadal/post-menopausal state was associated with greater fat mass in women only, and irrespective of testosterone use (for men). Traditional factors associated with weight gain in the general population, such as reduced physical activity, were also observed in this cohort.

In this cohort of PLWH, we observed that trunk and leg fat mass increased at all age intervals for both men and women. This is in contrast to the general population, where several epidemiological studies have associated older age with stabilization of fat mass.[17,18] In a sample of healthy Italian individuals, limb fat mass percentage increased in women up to 70 years of age, then remained stable.[18] US epidemiological data on total and percentage body fat from the third National Health and Nutrition Examination Survey (NHANES) showed a decrease in total body fat and fat-free mass after age 55 in both men and women.[19] When compared with the US population, the rates of trunk fat mass gain among PLWH in our cohort were greater than expected for age.[20–23] Longitudinal data from the NHANES showed increases in trunk fat by DXA of only 0.8 kg/decade in men and 0.5 kg/decade in women.[23] In a subset of participants with DXA data from the ACTG ART initiation trial A5224s, Women's Interagency HIV Study (WIHS) and Boston Area Community Health/Bone (BACH/Bone) Survey studies, compared with HIV-uninfected individuals, PLWH had greater adjusted total, trunk and limb fat gain than expected for age both during the post-ART initiation period (weeks 0–96) and over a median of 7 years of follow-up.[7] Although the mechanism of greater than expected weight gain for age in PLWH on ART has not been well defined, the steady increase in fat mass seen in our cohort during a period of up to 10 years of follow-up is consistent with previous studies looking at BMI trends,[4,8,12] and worrisome in a patient population already at increased cardiometabolic risk.

Although the per-year effect sizes are small, the associations of integrase strand transfer inhibitor and tenofovir disoproxil fumarate use with greater trunk and leg fat mass in both the combined-sex model and among men in sex-stratified models are novel and clinically important. Since ART is a lifelong commitment, small per-year effects may have large cumulative effects, again creating concern for exacerbation of cardiometabolic risk. Of note, we did not explore the potential effects of all individual ART agents and/or combinations, and previously published data on weight or body composition changes with specific ART agents vary. For example, a study of ART-naive individuals starting a raltegravir- or efavirenz-based regimen showed greater weight gain in the efavirenz arm after 96 weeks.[24] However, ACTG A5260s, a randomized trial comparing tenofovir disoproxil fumarate plus emtricitabine plus either raltegravir or a boosted PI, showed no difference by ART regimen in regional fat quantity by DXA scan at 96 weeks.[25] A recent observational study showed a significant increase in weight in virologically suppressed individuals switched from an efavirenz-containing regimen to a dolutegravir-based regimen (versus continued efavirenz).[26] Although our analysis focused on classes of ART (because of the wide variety of combinations of exposure over the study period), future analyses are needed to understand the role of individual drug exposure on weight trajectory.

A CD4 nadir <200 cells/mm^3 was associated with greater trunk fat mass in both the combined and sex-stratified models. In a longitudinal analysis of BMI changes in the Swiss HIV Cohort Study, lower CD4 nadir had the strongest association with BMI increase during the follow-up period, which persisted into 1–4 years of ART.[8] Other reports demonstrating an effect of CD4 nadir on BMI following ART initiation have also been reported.[7,27] Lipodystrophy status was reassessed throughout the study period, but did not change significantly over time within individuals in spite of continuous extremity fat gain that could indicate partial reversibility of lipoatrophy. However, the lipodystrophy assessment was clinician based and not an objective measurement of fat quantity. Interestingly, in this cohort hypogonadism in men was associated with less fat mass, even after adjustment for testosterone use. Although use of testosterone in PLWH has been associated with a decrease in total body fat, it did not have an effect on visceral fat.[28] Hypogonadism has also not been significantly associated with increases in BMI.[29]

Table 5. Sex-stratified model for leg fat

	Women			Men		
Variable	model estimate (SE)	effect size	*P* value	model estimate (SE)	effect size	*P* value
BMI (kg/m^2)[a]	0.080 (0.002)	+8%	<0.0001	0.087 (0.002)	+9%	<0.0001
Age, years[b]						
>55	NS	NS	NS	−0.333 (0.064)	−33%	<0.0001
51–55	NS	NS	NS	−0.233 (0.062)	−23%	0.0002
46–50	−0.171 (0.078)	−17%	0.028	−0.292 (0.055)	−29%	<0.0001
41–45	−0.269 (0.074)	−27%	0.0003	−0.319 (0.054)	−31%	<0.0001
35–40	−0.263 (0.077)	−26%	0.0005	−0.239 (0.057)	−24%	<0.0001
No regular physical activity[c]	NS	NS	NS	0.056 (0.011)	+6%	<0.0001
Moderate physical activity[c]	NS	NS	NS	0.047 (0.010)	+5%	<0.0001
Metabolic syndrome	NS	NS	NS	0.28 (0.011)	+3%	0.018
CD4 nadir <200 cells/mm[c]	0.035 (0.017)	+4%	0.04	0.052 (0.016)	+5%	0.0009
Per-year ART use	−0.012 (0.004)	−1%	0.006	−0.016 (0.002)	−2%	<0.0001
Per-year INSTI use	NS	NS	NS	0.00001 (0.00002)	+<0.1%	<0.0001
Per-year TDF use	0.007 (0.002)	+0.7%	0.005	0.006 (0.002)	+0.6%	0.0003
Hypogonadism	0.031 (0.013)	+3%	0.02	−0.072 (0.018)	−7%	<0.0001
Vitamin D insufficiency	NS	NS	NS	NS	NS	NS
HCV seropositivity	NS	NS	NS	NS	NS	NS
History of AIDS wasting	NS	NS	NS	NS	NS	NS
HIV-1 RNA >50 copies/mL[d]	NS	NS	NS	NS	NS	NS

SE, standard error; NS, not significant; TDF, tenofovir disoproxil fumarate; INSTI, integrase strand transfer inhibitor.
[a]Per-unit increase.
[b]Reference group: <35 years of age.
[c]Reference: intense regular physical activity.
[d]Reference: >50 copies/mL.

There are several limitations to our study. First, a comparable HIV-uninfected control population was not available for comparison, and we cannot determine whether these changes are greater than in the general Italian population or consistent with normal ageing. Comparison with the US population does not fully overcome this limitation. Second, this Italian HIV cohort comprises only Caucasian participants, and fat mass quantities and changes may differ among African American and Hispanic persons.[22] We also did not include detailed, person-level dietary information; however, steady increases in fat mass in the entire cohort over the study period of 10 years suggest changes at the population level. Finally, we did not have control over the type of ART used, as medications were prescribed by the participant's primary HIV care provider. Despite these limitations, strengths of our study include fat mass measurements at several timepoints and intervals of only 6–12 months, with a median of five scans over 4.6 years, allowing us to closely trend fat mass over time. In fact, with up to 10 years' worth of serial DXA data on participants and a high number of DXA scans per participant, our data may represent the most closely documented (greatest number of observations within the follow-up period) changes reported to date. Measurement of body composition analysis by DXA adds significantly to the understanding of observed weight changes that can be missed when only BMI is used, particularly in a population at risk of losing lean mass and with higher visceral fat-to-BMI ratios.[7,30–32] Finally, our analysis included a large proportion of women living with HIV, allowing exploration of factors associated with fat mass controlling both for sex and by sex.

Conclusions

In this large, well-characterized cohort of PLWH on long-term ART, we report continued increases in trunk and leg fat mass in both men and women well beyond ART initiation. We also describe important associations between fat gain and both traditional and HIV-/ART-specific risk factors that vary by sex. Clinicians should be aware that fat gain will continue beyond ART initiation/the 'return to health' phase and may occur at greater rates than expected for age. Early targeted interventions are needed to prevent potential cardiometabolic complications associated with increased fat mass, particularly among those at risk of greater weight gain, including post-menopausal women and persons with prolonged ART use and/or older age. The relationship between the cumulative use of tenofovir disoproxil fumarate and integrase strand transfer inhibitors and greater fat mass requires further study.

Acknowledgements

The authors would like to thank the participants and staff of the Modena HIV Metabolic Clinic for their participation and hard work. Specifically, we would like to thank Andrea Malagoli, Stefano Zona, Marianna Menozzi, Valentina Masi, Maria Mancini, Agnese Caselgrandi and Maria Giulia Corni for their time and dedication to the Cohort's daily operations and data management.

Funding

This study was supported by the National Institute on Ageing of the National Institute of Health (K23AG050260; R01AG054366 to K. M. E.) and the National Institute of Allergy and Infectious Diseases (K24 AI120834 to T. T. B. and K23 AI110532 to J. E. L.).

Transparency declarations

T. T. B. has served as a consultant to Gilead Sciences, Merck, BMS, Theratechnologies and EMD-Serono. J. E. L. has served as a consultant to Merck and Gilead Sciences, and receives research funding from Gilead Sciences. G. G. has served as a consultant to Gilead Sciences, Merck, and ViiV. K. M. E. has received research funding (paid to the University of Colorado) from Gilead Sciences. J. F. has served as a consultant for Theratechnologies and EMD-Serono. All other authors: none to declare.

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