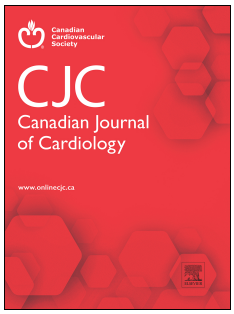

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Sarcopenic Obesity Phenotypes in Patients With HIV: Implications for Cardiovascular Prevention and Rehabilitation

Short title: Sarcopenic obesity in people living with HIV

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ABSTRACT

Background

To describe prevalence, incidence and risk factors for sarcopenic obesity (SO) phenotypes in people living with HIV (PWH) and their association with subclinical cardiovascular disease (CVD).

Methods

Observational, longitudinal study of PWH. A minimum of one criterion was necessary to diagnose sarcopenia: (i) weak hand grip (HG), (ii) low appendicular skeletal muscle index (ASMI), (iii) short physical performance battery (SPPB <11). Obesity was defined as (i) body mass index (BMI) ≥30 kg/m^2 or (ii) visceral adipose tissue (VAT) ≥160 cm^2. These variables combined generated five SO phenotypes: (i) severe SO: low HG+ low ASMI + low SPPB + high BMI; (ii) SO1: weak HG + high VAT; (iii) SO2: weak HG + high BMI; (iv) SO3: low ASMI + high VAT; (v) SO4: low ASMI + high BMI. Subclinical CVD was defined as carotid intima media thickness (IMT) ≥1 mm, presence of carotid plaque, or CAC score >10.

Results

Among 2379 PWH 72% men, median age was 52 years, median HIV vintage 21 years, and median BMI 24 kg/m^2. Two PWH had severe SO. The prevalence of SO1-SO4 was 19.7%, 3.6%, 20.8% and 0.8% respectively. Incidence of SO1-SO4 was 6.90, 1.2, 5.6 and 0.29 x 100 persons-year, respectively. SO1 was associated with risk of IMT ≥ 1, and SO3 with risk of CAC score >10.

Conclusions

There was a large variability in incidence and prevalence of SO phenotypes. The presence of SO may have important implications for cardiovascular prevention and cardiac rehabilitation of PWH who suffered an event.

Background

As the world population rapidly ages, it is predicted that by 2050 approximately 21% will be 60 years of age or older [1]. With the increasing number of older individuals in the population, their health has become a major focus of attention.

One condition that poses a significant threat to this demographic shift is sarcopenia, which involves a decline in skeletal muscle mass, muscle strength, and physical performance [2]. In 2018, the European Working Group on Sarcopenia in Older People (EWGSOP) revised the 2010 consensus definition of sarcopenia that aimed to foster advances in identifying and caring for people with sarcopenia. They also identified diagnostic tools to evaluate muscle mass and strength that contribute to its definition [3]. Sarcopenia is associated with a greater risk of experiencing negative health outcomes, such as falls [4], disability [5], hospitalization [6], and mortality [7]. Additionally, with aging comes an increase in fat mass, and obesity, which are major risk factors for cardiovascular and metabolic diseases [8,9].

Research has shown that sarcopenia is often accompanied by an increase in adipose tissue, leading to the emergence of a phenotype known as sarcopenic obesity (SO). This condition is considered more severe than either sarcopenia or obesity alone [10], heightening the risk of developing disabilities, cardiovascular and metabolic diseases, as well as mortality [11,12]. The prevalence of this condition in the general population is influenced by the diagnostic criteria applied to diagnose it, rendering the epidemiology of SO unclear.

This is even more relevant in people living with HIV (PWH) in whom SO prevalence, risk factors for its development and its association with clinically meaningful end-points are completely unknown. In this population at high risk of atherosclerotic cardiovascular events, both the virus and antiretroviral therapies (ART) have been associated with sarcopenia and obesity. The former has been described in the context of the so called “wasting syndrome” in the pre-ART era, or as the result of mitochondrial toxicity due to AZT and the D-drugs (DDI, D4T, DDC) in the early-ART era. The latter has been associated with central fat accumulation (lipo-hypertrophy), still present in the late-ART era [13], or as the result of weight gain associated with integrase strand transfer inhibitors (INSTI) and tenofovir alafenamide (TAF) used in contemporary ART regimens [13–17].

Subclinical CVD markers such as coronary artery calcification (CAC) and intima media thickness (IMT) may be meaningful end point associated with SO. They reflect the burden and severity of atherosclerosis in coronary and carotid arteries and are well-known markers of risk of adverse cardiovascular outcomes. The presence of SO and markers of CV risk poses a high level of complexity for cardiovascular prevention and rehabilitation of PWH.

The objective of the study was to describe the prevalence and incidence of and risk factors for different SO phenotypes and their association with subclinical CVD in consecutive PWH followed at a tertiary HIV center.

Methods

Study design and subjects

We conducted an observational, longitudinal and retrospective study in consecutive PWH followed at the Modena HIV Metabolic Clinic (MHMC) from January 2015 to September 2022. In this multidisciplinary tertiary care center, PWH are screened for chronic comorbidities and geriatric syndromes. Patients routinely undergo total body DEXA for body composition (Hologic, Inc., Technologic Srl, Italy), a hand grip (HG) assessment with a dynamometer and a functional evaluation with Short Physical Performance Test Battery (SPPB). Clinical activities were interrupted from February to October 2020 during the first wave of the COVID pandemic in Italy. PWH were eligible for this study if they had received ART for at least 12 months prior to inclusion and had been evaluated at least once for the presence of SO.

Lifestyle, medical, surgical history, current and past medications and HIV and ART history were obtained by interview and chart review. Body composition variables included: body mass index (BMI), total and truncal fat, visceral adipose tissue (VAT) measured by DEXA and computed tomography (CT), limb lean mass and appendicular skeletal muscular index (ASMI).

Physical function variables included HG test and SPPB. HG was assessed with a Jamar dynamometer, asking the patient to squeeze the dynamometer tightly with maximum force, then release it. Measurements were made three times in each hand, and the average of the 3 measurements was used

for analysis [18]. Cut-off points for low hand grip were derived from an equation that takes into consideration age, sex, height, and weight of a US reference population 18 to 85 years of age [19].

SPPB consists of a series of tests used to evaluate lower extremity functionality and mobility in older people. It combines scores of gait speed (score 0-4), balance test (score 0-4) and chair stand test (score 0-4). The score ranges from 0 (worst performance) to 12 (best performance). A scores <11 suggests the presence of possible sarcopenia.

Sarcopenia was defined as one or more of the following:

- weak hand grip, adjusted for sex and age;
- ASMI (l-ASMI) <7.26 /<5.45 kg/m^2 for men/women, assessed by DEXA;
- SPPB score <11.

Obesity was defined as one or both of the following:

- BMI ≥ 30 kg/m^2;
- VAT ≥ 160 cm^2.

The combination of these variables generated 5 different SO phenotypes:

1. Severe SO: weak HG+ low ASMI+ low SPPB + high BMI;
2. SO1: weak HG + high VAT;
3. SO2: weak HG + high BMI;
4. SO3: low ASMI + high VAT;
5. SO4: low ASMI + high BMI.

To calculate the prevalence of each SO phenotype, only the baseline data were considered. Baseline was defined as the first visit in which at least one SO phenotype was identified. In order to describe the population according to presence or absence of SO, PWH were divided into two groups: (i) PWH who never developed SO ("never") and (ii) PWH who had positive criteria for SO "at least once" over time.

Study outcomes

Subclinical cardiovascular disease was assessed with at least one of the following imaging techniques, performed within six months from the SO evaluations. Carotid intima-media thickness (cIMT) was

measured with high-resolution B-mode ultrasound imaging by trained sonographers. The presence of subclinical carotid atherosclerosis was identified as cIMT ≥1 mm, presence of plaque, or both. Coronary artery calcification (CAC) was investigated with multi-slice computed tomography. Total calcium scores were calculated by an experienced radiologist based on the well-established Agatston methodology [20]. Presence of subclinical atherosclerosis was defined as a CAC score >10 [21]. The choice to perform cIMT or CAC depended exclusively on the availability of the radiology services during the ambulatory clinic visit. The project received approval from the Research Ethics Board of the Area Vasta Nord Regione Emilia-Romagna.

Statistical analysis

Continuous data are presented as mean and standard deviation for normally distributed or median and inter-quartile range (IQR) for non-normally distributed variables, while categorical data are presented as numbers and percentages . The prevalence of each SO phenotype was calculated based on the first visit in which both sarcopenia and obesity were found, according to the definitions provided above. The cumulative incidence of each SO phenotype was calculated as the new occurrence of SO over time during the study period. As of January 2015, HG assessment was introduced as a routine measurement for all patients attending the MHMC. The incidence of SO during the observational period was calculated in PWH with at least two available evaluations without missing data.

The impact of each sarcopenia and obesity phenotype alone and in combination (considering the SO1-SO4 phenotypes) on subclinical CVD was evaluated with Poisson regression models. The severe sarcopenia phenotype (first SO phenotype) was not used in the Poisson models because only 2 patients were affected by it. An interaction term between sarcopenia and obesity was calculated to better assess their impact on the outcome of interest.

The association between outcomes of interest (IMT and CAC) and SO was evaluated considering the rate of each outcome, computed as the number of events over the total number of evaluations per patient, and the percentage of SO positive evaluations over the follow-up period. Event rate was assessed with a generalized linear model with Poisson distribution using the total number of

evaluations as offset. Results are reported as estimates (incidence rate ratio, IRR) and corresponding 95% confidence interval (95% CI). In this study, an event was defined as any instance in which an abnormal measurement of subclinical CVD was reported during a clinic visit.

All tests were two-sided, and the statistical significance was set at 5%. The statistical software R (version 4.2.2) was used to analyze the data.

Results

A total of 2379 PWH were evaluated at least once for SO. Median age was 52 (IQR=10) years, 72% were men. The median time since HIV diagnosis was 21 (IQR=14.6) years, median current CD4 was 712 (IQR=366)/µL, and median CD4/CD8 ratio = 0.88 (IQR=0.55). Sarcopenia and obesity median variables in the whole population were as follows: BMI=24 (IQR=4.5), VAT=147 (IQR=114) cm^2, ASMI in men=7.50 (1.15) kg/m^2, ASMI in women = 5.71 (1.09) kg/m^2. Low hand grip was measured in 538, and SPPB <11 in 177 PWH. Supplemental Table S1 shows the demographic and clinical characteristics of the entire population.

Severe sarcopenia, defined according to the EWGSOP guidelines, in this large cohort was identified in only 2 patients, both meeting the obesity definition. Therefore, we considered the combination of less restrictive criteria for sarcopenia and identified 4 different SO phenotypes at baseline: SO1 (weak HG + high VAT) was present in 243 out of 1236 PWH in whom variables were evaluated at least once (prevalence: 19.7%; incidence 6.90 x 100 persons-year). SO2 (weak HG + high BMI) was present in 79 out of 2183 PWH in whom defining variables were measured at least once (prevalence: 3.6%; incidence 1.2 x 100 persons-year). SO3 (low ASMI + high VAT) was present in 170 out of 817 PWH in whom defining variables were assessed at least once (prevalence 20.8%; incidence 5.6 x 100 persons-year). Finally, SO4 (low ASMI + high BMI) was present in 17 out of 2224 PWH in whom defining variables were assessed at least once (prevalence: 0.76%; incidence 0.29 x 100 persons-year). Figure 1 shows the cumulative incidence plot for all SO phenotypes over time.

Demographic, anthropometric, lifestyles and clinical characteristics are summarized for each SO phenotype in Tables 1-4. The comparison between PWH with and without each SO phenotype considers all available observations and not only the baseline data. The column labeled “At least once” refers to PWH in whom SO was identified at any time point from baseline to follow up. The column “Never” refers to PWH who never had any SO criteria at any time point.

Risk factors for each SO phenotype including demographics, lifestyle and clinical characteristics were assessed with logistic regression analyses and are presented in Table 5. In detail, age at baseline (IRR = 1.04, 95% CI: 1.03, 1.05, p<0.001), male sex (IRR = 5.05, 95% CI: 3.45, 7.74, p<0.001), and low physical activity (IRR = 1.89, 95% CI: 1.46, 2.45, p<0.001) were associated with higher risk of SO1 (Table 5). Age at baseline, male sex, time since HIV infection and low physical activity were associated with SO2, SO3 and SO4 (Table 5).

Clinical endpoint were markers of subclinical CVD. Specifically, IMT≥1 mm was identified in 240 of 1159 PWH with available assessments, that accounted for a prevalence of 17.2%, and an incidence of 2.35 x 100 persons-year. CAC>10 was identified in 691 of 1122 PWH with available assessments, that accounted for a prevalence of 38.1%, and an incidence of 5.6 x 100 persons-year.

The impact of each sarcopenia and obesity alone and in combination (considering the SO1-SO4 phenotypes) on IMT ≥ 1mm (Table 6) and CAC score >10 (Table 7) was evaluated with Poisson regression models. In detail, SO1 phenotype (IRR = 1.05, 95% CI: 1.01, 1.09, p = 0.024) was associated with risk of IMT ≥ 1mm, while weak grip, high VAT and the interaction between weak grip and VAT were not (Table 3, panel A). Obesity, defined as BMI ≥ 30 kg/m^2 (IRR = 1.13, 95% CI: 1.03, 1.22, p = 0.003) was associated with IMT ≥ 1mm, while SO2, weak grip and the interaction between weak grip and BMI were not (Table 6). In the Poisson regression for CAC score >10, none of the variables in the models were associated with the outcome (Table 7).

Discussion

To the best of our knowledge, this is the first study exploring SO in PWH, a special population at particularly high risk of atherosclerotic cardiovascular events. While weight gain and obesity are well characterized in these patients, mainly due to the effects of contemporary ART drugs, sarcopenia has been overlooked. In a previous report from the same cohort, utilizing sequential DXA scans in 839 women and 1,759 men, we described a steady decline in appendicular lean mass during a follow-up of 10 years [23].

In this study we initially described "severe sarcopenia" according to the 2018 revised consensus definition of the European Working Group on Sarcopenia in Older People (EWGSOP) [3]. This restrictive definition comprises anthropometric (ASMI) and functional (HG and SPPB) variables to best identify people at higher risk of adverse health outcomes. Contrary to our expectations, in this large cohort only 2 PWH met the EWGSOP criteria, and both were obese. Hence, these criteria may not be helpful to identify SO in PWH and specifically in patients attending the MHMC. We may speculate that since the "severe sarcopenia" construct was developed for older geriatric patients, these individuals are poorly represented in HIV cohorts. Additionally, we cannot exclude a population selection bias at the MHMC, in consideration of the mobility issues affecting PWH with sarcopenia that may limit referral to our clinic.

We further described the recurrence of the 4 SO phenotypes in PWH attending the MHMC on a yearly basis. All SO occurrences accumulated during follow-up, with an incidence rate decreasing in the following order: SO1, SO3, SO2 and SO4. This observation suggests that SO will increase in the future, in particular the SO1 and SO2 phenotypes, in parallel with the aging of PWH.

A few issues regarding the SO definition criteria deserve discussion. ASMI is a variable derived from appendicular lean mass assessed with DEXA. This technology cannot discriminate the presence of fat infiltration in the muscles, and fat is therefore included in the mass computation. Additionally, hand grip cut-offs are less well standardized in a relatively young population. A BMI ≥ 30 kg/m^2, that was chosen to define obesity, is much less common in PWH compared to the general Italian population.

Nevertheless, this may not be true in other geographical areas. Lastly, increased visceral adiposity has been shown to be associated with exposure to older ART regimens and low CD4 cell counts [24].

Older age, male gender and a sedentary lifestyle were common risk factors across all SO phenotypes, while an association with HIV clinical characteristics was present in SO2, SO3 and SO4. Time since HIV diagnosis was identified as a specific risk factor for these three phenotypes, presumably in collinearity with age and longer exposure to detectable HIV viremia. We still cannot exclude that immune-virological variables may impact SO, but to a lesser extent than age, sex and sedentary lifestyle which drive all SO phenotypes. Admittedly, in these analyses neither current nor cumulative exposure to different anti-retroviral therapies were explored. Instead, our data support the notion that physical activity may be a very important intervention to help prevent SO in PWH and potentially reduce CV events. The importance of accurate characterization and identification of various SO phenotypes rests on the ability to design appropriate rehabilitation programs. The WHO guidelines on physical activity and sedentary behaviours quote specific interventions for PWH to fight obesity and sarcopenia [25]. Nevertheless, it is unclear whether rehabilitation interventions for SO are simply the sum of the interventions for sarcopenia and for obesity, or if specifically designed programs will be necessary.

Chung et al, showed a significant association of SO with CAC in 1,282 subjects, independent of traditional risk factors for coronary artery disease (including age, sex, systemic hypertension, diabetes mellitus and dyslipidemia). This suggests that sarcopenia and obesity may potentiate each other to induce the development of atherosclerotic coronary artery disease, eventually leading to adverse cardiovascular events [26].

In our study, only 2 of the 4 SO phenotypes showed a statistical association with IMT and CAC: SO1 was associated with IMT and SO3 with CAC. Both SO phenotypes include VAT as an obesity criterion. This is in line with our previous report in 583 PHW where ectopic fat, including VAT, but not general adiposity measures, were associated with CAC [27]. Interestingly, both in SO1 and SO3 single measures of sarcopenia and obesity were not significantly associated with IMT and CAC, and only the combination of the two reached statistical significance, suggesting that these two phenotypes identify a condition more severe than either sarcopenia or obesity alone. Further studies may be needed to explore how skeletal muscle communicates with ectopic fat in the complex networking involving chemokines and

myokines, as well as the central and peripheral nervous system. This will allow the exploration of the connection between exercise, and cardiovascular disease, and may contribute to the understanding of a potential mechanism by which physical inactivity affects the process of metabolic diseases [28].

Some study limitations must be acknowledged. The first, and likely most important limitation, was the small number of PWH in geriatric or older-old age who would presumably have a higher SO prevalence. The inconstant availability of the radiology service to perform imaging for subclinical CVD may have inserted a selection bias. In this regard, immortal time bias cannot be excluded, as in some cases subclinical CVD might have been missed since IMT or CAC were not measured. Due to the COVID-19 pandemic, the MHMC in 2020 and 2021 experienced a loss to follow-up as all non-urgent out-patient services were rendered inoperative during the lockdown. There were too few MACE among patients in each SO phenotype, and we cannot prove that the associations we showed are predictive of long term catastrophic events. Finally, this was a single center study, and our results might not be applicable to other clinical settings. However, this paper may raise the awareness of the medical community about the presence of several phenotypes of SO in PWH, that may become highly prevalent in this special population in the future

In conclusion, the incidence and prevalence of different SO phenotypes showed a large variability among PWH followed at one tertiary center. Some of the phenotypes were associated with subclinical CVD. Future studies will be needed to explore the relationship between HIV and SO and their correlation with atherosclerotic cardiovascular events. The presence of SO and its association with markers of risk pose a special challenge for preventive and rehabilitation programs directed at reducing the risk of events and improving the outcome of those who suffered one.

Conflict of interest

JM received speaker honorarium from Gilead and ViiV. GG and CM received research grants and speaker honoraria from Gilead, ViiV, MERCK and Jansen. GG and CM attended advisory boards of Gilead, ViiV and MERCK. All other authors reported no conflicts of interest.

Authors' contributions

JM, StC and GG conceptualized and designed the research protocol. JM, StC, PR and GG wrote and revised the manuscript. StC, SR and FM performed the statistical analyses. JM, CM, GS, PR and GG supervised and approved the final version of the manuscript. All authors reviewed and approved the final manuscript.

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Patient Consent Statements

The authors confirm that patient consent is not applicable to this article. This was an observational, longitudinal and retrospective study using de-identified data; therefore the IRB did not require that a consent be obtained from each patient.

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Figure 1. Cumulative incidence plot for all SO phenotypes over time.

Table 1. Demographic, anthropometric, HIV-related and clinical characteristics according to SO1 definition.

Characteristics	**Never** N = 929 (75.2%)	**At least once** N = 307 (24.8%)	**p**
Age, years, median (IQR)	53 (9)	55 (9)	<0.001
Sex, N (%)	649 (70%)	277 (90%)	<0.001
HIV duration, months, median (IQR)	265 (154)	261 (167)	0.60
Nadir CD4 cell count, c/microL median (IQR)	200 (210)	200 (220)	0.40
Current CD4 count, c/microL, median (IQR)	714 (373)	722 (377)	0.60
CD4/CD8 ratio, median (IQR)	0.88 (0.55)	0.84 (0.51)	0.40
Undetectable HIV RNA viral load, N (%)	891 (98%)	294 (98%)	0.40
Physical activity, N (%) Low Moderate Intense	 375 (41%) 453 (49%) 95 (10%)	 176 (57%) 117 (38%) 14 (4.6%)	<0.001
Weight, kg, median (IQR)	69 (16)	78 (15)	<0.001
Waist circumference, cm, median (IQR)	87 (14)	98 (13)	<0.001
BMI, kg/m^2, median (IQR)	23.5 (4.3)	26.4 (4.4)	<0.001
Weak grip, N (%)	163 (30%)	137 (68%)	<0.001
Frailty phenotype, N (%) Fit Pre-frail Frail	 267 (48%) 272 (49%) 12 (3%)	 45 (22%) 141 (70%) 15 (8%)	<0.001
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	<0.001
ASMI, kg/m^2, median (IQR) Men Women	6.94 (1.73) 7.49 (1.23) 5.73 (1.02)	7.42 (1.25) 7.51 (1.07) 5.66 (1.13)	<0.001 0.30 0.90
Frailty index, median (IQR)	0.27 (0.14)	0.31 (0.12)	<0.001
CVD, N (%)	48 (5.5%)	20 (7.3%)	0.29
ASCVD risk, median (IQR)	5 (7)	8 (9)	<0.001
Statins, N (%)	107 (12%)	45 (16%)	0.20
VAT, cm^2, median (IQR)	119 (81)	209 (70)	<0.001
IMT (>1mm), at least once, N (%)	71 (19%)	42 (28%)	0.013
CAC (>10), at least once, N (%)	288 (57%)	109 (62%)	0.3

Legend: ASCVD: atherosclerotic cardiovascular disease; ASMI: appendicular skeletal muscular index; BMI: body mass index; CAC: coronary artery calcium; CVD: cardiovascular disease; IMT: intima-media thickness; VAT: visceral adipose tissue

Table 2. Demographic, anthropometric, HIV-related and clinical characteristics according to SO2 definition.

Characteristics	**Never** N = 2052	**At least once** N = 131	**p**
Age, years, median (IQR)	52 (9)	54 (11)	0.022
Sex, N (%)	1470 (72%)	108 (82%)	0.007
HIV duration, months, median (IQR)	258 (171)	205 (180)	0.001
Nadir CD4 cell count, c/microL, median (IQR)	208 (220)	215 (254)	0.90
Current CD4 count, c/microL, median (IQR)	712 (364)	730 (356)	0.40
CD4/CD8 ratio, median (IQR)	0.88 (0.55)	0.88 (0.64)	0.50
Undetectable viral load, N (%)	1972 (98%)	124 (97%)	0.20
Physical activity N (%) Low Moderate Intense	 905 (44%) 959 (47%) 178 (9%)	 93 (72%) 32 (25%) 5 (3%)	<0.001
Weight, kg, median (IQR)	70 (16)	88 (15)	<0.001
Waist circumference cm, median (IQR)	89 (14)	108 (11)	<0.001
BMI, kg/m^2, median (IQR)	23.8 (4.2)	31.0 (3.6)	<0.001
Weak grip, N (%)	456 (36%)	78 (77%)	<0.001
Frailty phenotype, N (%) Fit Pre-frail Frail	 543 (43%) 577 (54%) 35 (3%)	 15 (15%) 77 (77%) 9 (8%)	<0.001
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	<0.001
ASMI, kg/m^2, median (IQR) Men Women	7.01 (1.70) 7.45 (1.17) 5.67 (1.02)	7.57 (1.22) 7.78 (1.08) 6.35 (1.29)	<0.001 <0.001 <0.001
Frailty index, median (IQR)	0.27 (0.14)	0.33 (0.13)	<0.001
ASCVD risk, median (IQR)	5 (7)	8 (9)	<0.001
CVD, N (%)	104 (5.4%)	6 (5.1%)	0.89
Statins, N (%)	193 (10.0%)	17 (14%)	0.024
VAT, cm^2, median (IQR)	142 (105)	239 (66)	<0.001
IMT (>1mm) at least once, N (%)	126 (18%)	16 (32%)	0.011
CAC (>10) at least once, N (%)	436 (61%)	34 (68%)	0.30

Legend: ASCVD: atherosclerotic cardiovascular disease; ASMI: appendicular skeletal muscular index; BMI: body mass index; CAC: coronary artery calcium; CVD: cardiovascular disease; IMT: intima-media thickness; VAT: visceral adipose tissue

Table 3. Demographic, anthropometric, HIV-related and clinical characteristics according to SO3 definition.

Characteristic	**Never**, N = 626	**At least once**, N = 191	**p**
Age, years, median (IQR)	53 (8)	57 (9)	<0.001
Male sex, N (%)	439 (70%)	176 (92%)	<0.001
Time since HIV diagnosis, years, median (IQR)	260 (141)	291 (121)	0.004
Nadir CD4 cell count, c/microL, median (IQR)	200 (203)	163 (197)	0.005
Current CD4 count, c/microL, median (IQR)	713 (388)	713 (420)	0.12
CD4/CD8 ratio, median (IQR)	0.93 (0.57)	0.81 (0.54)	0.006
Undetectable HIV RNA viral load, N (%)	598 (98%)	183 (99%)	0.50
Physical activity, N (%) Low Moderate Intense	 267 (43%) 298 (48%) 60 (9%)	 107 (56%) 77 (41%) 6 (3%)	<0.001
Weight, kg, median (IQR)	70 (18)	75 (13)	<0.001
Waist circumference, cm, median (IQR)	88 (16)	95 (10)	<0.001
BMI, kg/m^2, median (IQR)	24.2 (4.8)	24.7 (3.7)	0.084
Weak grip, N (%)	120 (36%)	49 (37%)	0.80
Frailty phenotype, N (%) Fit Pre-frail Frail	 155 (47%) 166 (50%) 10 (3%)	 30 (23%) 98 (75%) 3 (2%)	<0.001
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	0.036
ASMI, kg/m^2, median (IQR) Men Women	7.29 (1.84) 7.65 (1.12) 5.72 (1.14)	6.86 (1.05) 6.91 (0.95) 5.27 (0.78)	0.002 <0.001 0.14
Frailty index, median (IQR)	0.29 (0.13)	0.31 (0.11)	<0.001
CVD, N (%)	32 (5.5%)	17 (9.7%)	0.05
ASCVD risk, median (IQR)	5 (7)	10 (12)	<0.001
Statins, N (%)	66 (11%)	36 (20%)	0.002
VAT, cm^2, median (IQR)	124 (93)	195 (80)	<0.001
IMT (>1mm), at least once, N (%)	62 (21%)	25 (25%)	0.40
CAC (>10), at least once, N (%)	210 (54%)	94 (71%)	<0.001

Legend: ASCVD: atherosclerotic cardiovascular disease; ASMI: appendicular skeletal muscular index; BMI: body mass index; CAC: coronary artery calcium; CVD: cardiovascular disease; IMT: intima-media thickness; VAT: visceral adipose tissue

Table 4. Demographic, anthropometric, HIV-related and clinical characteristics according to SO4 definition.

Characteristic	**Never**, N = 2193	**At least once**, N = 31	**p**
Age, years, median (IQR)	52 (9)	56 (13)	0.041
Male sex, N (%)	1,561 (71%)	28 (90%)	0.019
Time since HIV diagnosis, months, median (IQR)	255 (173)	165 (231)	0.042
Nadir CD4 cell count, c/microL, median (IQR)	210 (220)	249 (200)	0.70
Current CD4 count, c/microL, median (IQR)	715 (367)	688 (379)	0.50
CD4/CD8 ratio, median (IQR)	0.88 (0.55)	0.87 (0.61)	0.70
Undetectable HIV RNA viral load, N (%)	2123 (99%)	30 (100%)	0.90
Physical activity, N (%) Low Moderate Intense	 990 (45%) 1003 (46%) 189 (9%)	 22 (71%) 8 (26%) 1 (3%)	0.018
Weight, kg, median (IQR)	70 (17)	87 (16)	<0.001
Waist circumference, cm, median (IQR)	89 (15)	108 (6)	<0.001
BMI, kg/m2, median (IQR)	24.0 (4.3)	30.6 (1.7)	<0.001
Weak grip, N (%)	449 (37%)	13 (65%)	0.011
Frailty phenotype, N (%) Fit Pre-frail Frail	 505 (42%) 665 (55%) 38 (3%)	 3 (15%) 16 (80%) 1 (5%)	0.080
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	0.10
ASMI, kg/m2, median (IQR) Men Women	7.13 (1.72) 7.51 (1.17) 5.71 (1.09)	7.06 (0.56) 7.07 (0.47) 5.31 (0.78)	0.70 0.008 0.90
Frailty index, median (IQR)	0.27 (0.14)	0.35 (0.16)	<0.001
CVD, N (%)	108 (5.1%)	4 (13%)	0.11
ASCVD risk, median (IQR)	5 (7)	9 (16)	0.003
Statins, N (%)	200 (9.6%)	7 (24%)	0.019
VAT, cm2, median (IQR)	159 (113)	195 (98)	0.30
IMT (>1mm) at least once, N (%)	139 (18%)	5 (42%)	0.052
CAC (>10) at least once, N (%)	454 (61%)	9 (75%)	0.40

Legend: ASCVD: atherosclerotic cardiovascular disease; ASMI: appendicular skeletal muscular index; BMI: body mass index; CAC: coronary artery calcium; CVD: cardiovascular disease; IMT: intima-media thickness; VAT: visceral adipose tissue

Table 5. Poisson models for predictors of different sarcopenic obesity phenotypes.

Variable	Sarcopenic obesity 1 (weak grip + VAT)			Sarcopenic obesity 2 (weak grip + BMI)		
	IRR	**95%CI**	**p**	**IRR**	**95%CI**	**p**
Age at baseline	1.04	1.03 – 1.05	<0.001	1.02	1.01 – 1.04	0.003
Male sex	5.05	3.45 – 7.74	<0.001	2.84	1.89 – 4.44	<0.001
Current CD4 cell count	1.00	1.00 – 1.00	0.20	1.00	1.00 – 1.00	0.50
CD4/CD8 ratio	0.98	0.77 – 1.23	0.90	1.13	0.83 – 1.50	0.40
Baseline time since HIV infection	1.00	0.99 – 1.02	0.40	0.97	0.95 – 0.98	<0.001
Low physical activity	1.89	1.46 – 2.45	<0.001	5.90	4.02 – 8.83	<0.001
Variable	**Sarcopenic obesity 3 (ASMI + VAT)**			**Sarcopenic obesity 4 (ASMI + BMI)**		
	IRR	**95%CI**	**p**	**IRR**	**95%CI**	**p**
Age at baseline	1.05	1.04 – 1.07	<0.001	1.06	1.03 – 1.10	<0.001
Male sex	4.95	3.02 – 8.77	<0.001	3.49	1.38 – 11.7	0.02
Current CD4 cell count	1.00	1.00 – 1.00	0.40	1.00	1.00 – 1.00	0.90
CD4/CD8 ratio	0.94	0.67 – 1.27	0.70	1.44	0.79 – 2.37	0.20
Baseline time since HIV infection	1.02	1.01 – 1.04	0.01	0.95	0.92 – 0.99	0.005
Low physical activity	1.77	1.26 – 2.49	0.001	8.43	3.48 – 23.2	<0.001

Table 6. Impact of each sarcopenia and obesity phenotype alone and in combination (SO phenotypes) on IMT >1 mm evaluated with Poisson regression models. The interaction term between sarcopenia and obesity was also assessed.

Sarcopenic obesity 1 (weak grip + VAT)				**Sarcopenic obesity 2 (weak grip + BMI)**			
Variable	**IRR**	**95%CI**	**p**	**Variable**	**IRR**	**95%CI**	**p**
Weak grip + VAT (SO1)	1.05	1.01 - 1.09	0.024	Weak grip + BMI (SO2)	1.04	0.95 - 1.12	0.30
Weak grip	0.97	0.90 – 1.05	0.50	Weak grip	1.02	0.98 – 1.06	0.40
VAT	0.99	0.95 – 1.04	0.80	BMI	1.13	1.03 – 1.22	0.003
Weak grip * VAT (interaction)	1.01	1.00 – 1.02	0.20	Weak grip * ASMI (interaction)	0.99	0.97 – 1.00	0.11
Sarcopenic obesity 3 (ASMI + VAT)				**Sarcopenic obesity 4 (ASMI + BMI)**			
Variable	**IRR**	**95%CI**	**p**	**Variable**	**IRR**	**95%CI**	**p**
ASMI + VAT (SO3)	1.02	0.97 - 1.07	0.40	ASMI + BMI (SO4)	1.12	0.88 – 1.31	0.20
ASMI	0.99	0.93 – 1.05	0.80	ASMI	1.01	0.97 – 1.05	0.50
VAT	0.99	0.94 – 1.05	0.80	BMI	1.07	0.99 – 1.14	0.07
ASMI * VAT (interaction)	1.00	1.00 – 1.01	0.11	ASMI * BMI (interaction)	1.01	0.98 – 1.02	0.50

Legend: ASMI: appendicular skeletal muscular index; BMI: body mass index; IMT: intima-media thickness; VAT: visceral adipose tissue

Table 7. Impact of each sarcopenia and obesity phenotype alone and in combination (SO phenotypes) on CAC score >10 evaluated with Poisson regression models. The interaction term between sarcopenia and obesity was also assessed.

Sarcopenic obesity 1 (weak grip + VAT)				**Sarcopenic obesity 2 (weak grip + BMI)**			
Variable	**IRR**	**95%CI**	**p**	**Variable**	**IRR**	**95%CI**	**p**
Weak grip + VAT (SO1)	1.01	0.99 - 1.03	0.40	Weak grip + BMI (SO2)	1.02	0.98 - 1.05	0.40
Weak grip	1.01	0.97 – 1.04	0.60	Weak grip	0.99	0.97 – 1.01	0.50
VAT	1.02	1.00 – 1.05	0.02	BMI	1.00	0.96 – 1.04	0.90
Weak grip * VAT (interaction)	1.00	0.99 – 1.00	0.50	Weak grip * ASMI (interaction)	1.00	1.00 – 1.01	0.60
Sarcopenic obesity 3 (ASMI + VAT)				**Sarcopenic obesity 4 (ASMI + BMI)**			
Variable	**IRR**	**95%CI**	**p**	**Variable**	**IRR**	**95%CI**	**p**
ASMI + VAT (SO3)	1.03	1.01 - 1.05	0.01	ASMI + BMI (SO4)	1.03	0.96 – 1.10	0.30
ASMI	1.00	0.97 – 1.02	0.70	ASMI	1.01	0.99 – 1.03	0.30
VAT	1.01	0.98 – 1.03	0.60	BMI	1.01	0.98 – 1.05	0.40
ASMI * VAT (interaction)	1.00	1.00 – 1.01	0.12	ASMI * BMI (interaction)	1.00	0.99 – 1.01	0.80

Legend: ASMI: appendicular skeletal muscular index; BMI: body mass index; CAC: coronary artery calcium; VAT: visceral adipose tissue