

This is a pre print version of the following article:

Sarcopenic Obesity Phenotypes in Patients With HIV: Implications for Cardiovascular Prevention and Rehabilitation / Milic, J., Calza, S., Cantergiani, S., Albertini, M., Gallerani, A., Menozzi, M., Barp, N., Todisco, V., Renzetti, S., Motta, F., Mussini, C., Sebastiani, G., Raggi, P., Guaraldi, G.. - In: CANADIAN JOURNAL OF CARDIOLOGY. - ISSN 0828-282X. - 39:11(2023), pp. S359-S367. [10.1016/j.cjca.2023.08.027]

*Terms of use:*

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

18/06/2026 06:34

(Article begins on next page)

# Journal Pre-proof

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

Jovana Milic, MD, PhD, Stefano Calza, PhD, Samuele Cantergiani, MD, Maddalena Albertini, MD, Altea Gallerani, MD, Marianna Menozzi, MD, Nicole Barp, MD, Vera Todisco, MD, Stefano Renzetti, PhD, Federico Motta, MSc, Cristina Mussini, MD, Giada Sebastiani, MD, Paolo Raggi, MD, PhD, Giovanni Guaraldi, MD



PII: S0828-282X(23)01646-X

DOI: <https://doi.org/10.1016/j.cjca.2023.08.027>

Reference: CJCA 4794

To appear in: *Canadian Journal of Cardiology*

Received Date: 22 June 2023

Revised Date: 15 August 2023

Accepted Date: 18 August 2023

Please cite this article as: Milic J, Calza S, Cantergiani S, Albertini M, Gallerani A, Menozzi M, Barp N, Todisco V, Renzetti S, Motta F, Mussini C, Sebastiani G, Raggi P, Guaraldi G, Sarcopenic Obesity Phenotypes in Patients With HIV: Implications for Cardiovascular Prevention and Rehabilitation, *Canadian Journal of Cardiology* (2023), doi: <https://doi.org/10.1016/j.cjca.2023.08.027>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2023 Published by Elsevier Inc. on behalf of the Canadian Cardiovascular Society.

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

Short title: Sarcopenic obesity in people living with HIV

Jovana Milic, MD, PhD<sup>1</sup>, Stefano Calza, PhD<sup>2</sup>, Samuele Cantergiani, MD<sup>3</sup>, Maddalena Albertini, MD<sup>3</sup>, Altea Gallerani, MD<sup>3</sup>, Marianna Menozzi, MD<sup>3</sup>, Nicole Barp, MD<sup>3</sup>, Vera Todisco, MD<sup>3</sup>, Stefano Renzetti, PhD<sup>4</sup>, Federico Motta, MSc<sup>5</sup>, Cristina Mussini, MD<sup>1,3</sup>, Giada Sebastiani, MD<sup>6</sup>, Paolo Raggi, MD, PhD<sup>7</sup>, Giovanni Guaraldi, MD<sup>1,3</sup>

<sup>1</sup> Department of Surgical, Medical, Dental and Morphological Sciences, University of Modena and Reggio Emilia, Italy

<sup>2</sup> Department of Molecular and Translational Medicine, University of Brescia, Italy

<sup>3</sup> Department of Infectious Diseases, Azienda Ospedaliero-Universitaria, Policlinico of Modena, Modena, Italy

<sup>4</sup> Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy

<sup>5</sup> Department of Physical, Computer and Mathematical Sciences, University of Modena and Reggio Emilia, Modena, Italy

<sup>6</sup> Division of Gastroenterology and Hepatology and Division of Infectious Diseases, McGill University Health Centre, Montreal, Canada

<sup>7</sup> Department of Medicine, Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada

### **Correspondence:**

Giovanni Guaraldi, MD

Department of Surgical, Medical, Dental and Morphological Sciences

University of Modena and Reggio Emilia

Largo del Pozzo, 71

41124 Modena, Italy

T: +39 059 422 5318

M: +39 335 33 34 34

Email: giovanni.guaraldi@unimore.it

**Word count:** 3148 (without abstract); **Abstract:** 249; **Number of tables:** 7; **Number of figures:** 1; **References:** 28; **Supplemental material:** 1 table

**Keywords:** sarcopenia; obesity; sarcopenic obesity; people living with HIV; HIV; subclinical cardiovascular disease

Journal Pre-proof

**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)  $\geq 30$  kg/m<sup>2</sup> or (ii) visceral adipose tissue (VAT)  $\geq 160$  cm<sup>2</sup>. 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)  $\geq 1$  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<sup>2</sup>. 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  $\geq 1$ , 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 (I-ASMI) <7.26 /<5.45 kg/m<sup>2</sup> for men/women, assessed by DEXA;
- SPPB score <11.

Obesity was defined as one or both of the following:

- BMI  $\geq$  30 kg/m<sup>2</sup>;
- VAT  $\geq$  160 cm<sup>2</sup>.

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  $\geq 1$  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)/ $\mu\text{L}$ , 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)  $\text{cm}^2$ , ASMI in men=7.50 (1.15)  $\text{kg}/\text{m}^2$ , ASMI in women = 5.71 (1.09)  $\text{kg}/\text{m}^2$ . 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 endpoints were markers of subclinical CVD. Specifically,  $IMT \geq 1$  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  $IMT \geq 1$  mm (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  $IMT \geq 1$  mm, while weak grip, high VAT and the interaction between weak grip and VAT were not (Table 3, panel A). Obesity, defined as  $BMI \geq 30$  kg/m<sup>2</sup> (IRR = 1.13, 95% CI: 1.03, 1.22,  $p = 0.003$ ) was associated with  $IMT \geq 1$  mm, 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  $\geq 30$  kg/m<sup>2</sup>, 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 immunovirological 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.

**Funding**

The authors received no funding to collect the information that form the basis of this research and to produce this manuscript.

**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.

## References

1. United Nations Department of Economic and Social Affairs (DESA)/Population Division. World population prospects. Available at: <https://population.un.org/wpp/>; Last access: 8 August 2023.
2. Malafarina V, Úriz-Otano F, Iñesta R, Gil-Guerrero L. Sarcopenia in the elderly: Diagnosis, physiopathology and treatment. *Maturitas* **2012**; 71:109–114. Available at: <https://doi.org/10.1016/j.maturitas.2011.11.012>.
3. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* **2019**; 48:16–31.
4. Tanimoto Y, Watanabe M, Sun W, et al. Sarcopenia and falls in community-dwelling elderly subjects in Japan: Defining sarcopenia according to criteria of the European Working Group on Sarcopenia in Older People. *Arch Gerontol Geriatr* **2014**; 59:295–299.
5. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* **2002**; 50:889–896.
6. Gariballa S, Alessa A. Sarcopenia: prevalence and prognostic significance in hospitalized patients. *Clin Nutr* **2013**; 32:772–776.
7. Kim JH, Lim S, Choi SH, et al. Sarcopenia: an independent predictor of mortality in community-dwelling older Korean men. *J Gerontol A Biol Sci Med Sci* **2014**; 69:1244–1252.
8. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International. *Circulation* **2009**; 120:1640–1645.
9. Frühbeck G, Toplak H, Woodward E, Yumuk V, Maislos M, Oppert J-M. Obesity: the gateway to ill health - an EASO position statement on a rising public health, clinical and scientific challenge in Europe. *Obes Facts* **2013**; 6:117–120.
10. Kalinkovich A, Livshits G. Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. *Ageing Res Rev* **2017**; 35:200–221.
11. Bellanti F, Romano AD, Lo Buglio A, et al. Oxidative stress is increased in sarcopenia and associated with cardiovascular disease risk in sarcopenic obesity. *Maturitas* **2018**; 109:6–12.
12. Kang S-Y, Lim GE, Kim YK, et al. Association between Sarcopenic Obesity and Metabolic Syndrome in Postmenopausal Women: A Cross-sectional Study Based on the Korean National Health and Nutritional Examination Surveys from 2008 to 2011. *J bone Metab* **2017**; 24:9–14.
13. Freitas P, Carvalho D, Santos AC, et al. Prevalence of obesity and its relationship to clinical lipodystrophy in HIV-infected adults on anti-retroviral therapy. *J Endocrinol Invest* **2012**; 35:964–970.
14. Nduka CU, Uthman OA, Kimani PK, Stranges S. Body Fat Changes in People Living with HIV on Antiretroviral Therapy. *AIDS Rev* **2016**; 18:198–211.
15. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. *N Engl J Med* **2019**; :NEJMoa1902824. Available at: <http://www.nejm.org/doi/10.1056/NEJMoa1902824>.
16. Achhra AC, Mocroft A, Reiss P, et al. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: The D: A: D study. *HIV Med* **2016**; 17:255–268.

17. Surial B, Mugglin C, Calmy A, et al. Weight and Metabolic Changes After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in People Living With HIV : A Cohort Study. *Ann Intern Med* **2021**; 174:758–767.
18. Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* **2011**; 40:423–429.
19. Wang Y-C, Bohannon RW, Li X, Sindhu B, Kapellusch J. Hand-Grip Strength: Normative Reference Values and Equations for Individuals 18 to 85 Years of Age Residing in the United States. *J Orthop Sports Phys Ther* **2018**; 48:685–693.
20. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte MJ, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* **1990**; 15:827–832.
21. Kramer CK, Zinman B, Gross JL, et al. Coronary artery calcium score prediction of all cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. *BMJ* **2013**; 346:f1654.
22. Lawless JF and CN. Some Simple Robust Methods for the Analysis of Recurrent Events. *Technometrics* **1995**; 37(2): 158.
23. Debroy P, Lake JE, Sim M, et al. Lean mass declines consistently over 10 years in people living with HIV on antiretroviral therapy, with patterns differing by sex. *Antivir Ther* **2019**; 24:383–387.
24. Koethe JR. Adipose Tissue in HIV Infection. *Compr Physiol* **2017**; 7:1339–1357.
25. WHO Guidelines on physical activity and sedentary behaviour, 2020. Available at: <https://www.who.int/publications/i/item/9789240015128>. Accessed 20 July 2023.
26. Chung GE, Park HE, Lee H, et al. Sarcopenic Obesity Is Significantly Associated With Coronary Artery Calcification. *Front Med* **2021**; 8:1–8.
27. Orlando G, Guaraldi G, Zona S, et al. Ectopic fat is linked to prior cardiovascular events in men with HIV. *J Acquir Immune Defic Syndr* **2012**; 59:494–497.
28. Chen W, Wang L, You W, Shan T. Myokines mediate the cross talk between skeletal muscle and other organs. *J Cell Physiol* **2021**; 236:2393–2412. Available at: <https://doi.org/10.1002/jcp.30033>.

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

Journal Pre-proof

**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	375 (41%)	176 (57%)	<0.001
Moderate	453 (49%)	117 (38%)	
Intense	95 (10%)	14 (4.6%)	
Weight, kg, median (IQR)	69 (16)	78 (15)	<0.001
Waist circumference, cm, median (IQR)	87 (14)	98 (13)	<0.001
BMI, kg/m <sup>2</sup> , 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	267 (48%)	45 (22%)	<0.001
Pre-frail	272 (49%)	141 (70%)	
Frail	12 (3%)	15 (8%)	
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	
ASMI, kg/m <sup>2</sup> , median (IQR)	6.94 (1.73)	7.42 (1.25)	<0.001
Men	7.49 (1.23)	7.51 (1.07)	0.30
Women	5.73 (1.02)	5.66 (1.13)	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 <sup>2</sup> , 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	905 (44%)	93 (72%)	<0.001
Moderate	959 (47%)	32 (25%)	
Intense	178 (9%)	5 (3%)	
Weight, kg, median (IQR)	70 (16)	88 (15)	<0.001
Waist circumference cm, median (IQR)	89 (14)	108 (11)	<0.001
BMI, kg/m <sup>2</sup> , 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	543 (43%)	15 (15%)	<0.001
Pre-frail	577 (54%)	77 (77%)	
Frail	35 (3%)	9 (8%)	
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	<0.001
ASMI, kg/m <sup>2</sup> , median (IQR)	7.01 (1.70)	7.57 (1.22)	<0.001
Men	7.45 (1.17)	7.78 (1.08)	<0.001
Women	5.67 (1.02)	6.35 (1.29)	<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 <sup>2</sup> , 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	267 (43%)	107 (56%)	<0.001
Moderate	298 (48%)	77 (41%)	
Intense	60 (9%)	6 (3%)	
Weight, kg, median (IQR)	70 (18)	75 (13)	<0.001
Waist circumference, cm, median (IQR)	88 (16)	95 (10)	<0.001
BMI, kg/m <sup>2</sup> , 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	155 (47%)	30 (23%)	<0.001
Pre-frail	166 (50%)	98 (75%)	
Frail	10 (3%)	3 (2%)	
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	0.036
ASMI, kg/m <sup>2</sup> , median (IQR)	7.29 (1.84)	6.86 (1.05)	0.002
Men	7.65 (1.12)	6.91 (0.95)	<0.001
Women	5.72 (1.14)	5.27 (0.78)	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 <sup>2</sup> , 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 (%)			0.018
Low	990 (45%)	22 (71%)	
Moderate	1003 (46%)	8 (26%)	
Intense	189 (9%)	1 (3%)	
Weight, kg, median (IQR)	70 (17)	87 (16)	<0.001
Waist circumference, cm, median (IQR)	89 (15)	108 (6)	<0.001
BMI, kg/m <sup>2</sup> , median (IQR)	24.0 (4.3)	30.6 (1.7)	<0.001
Weak grip, N (%)	449 (37%)	13 (65%)	0.011
Frailty phenotype, N (%)			0.080
Fit	505 (42%)	3 (15%)	
Pre-frail	665 (55%)	16 (80%)	
Frail	38 (3%)	1 (5%)	
Short Physical Performance Battery, median (IQR)	12.00 (1.00)	11.00 (2.00)	0.10
ASMI, kg/m <sup>2</sup> , median (IQR)	7.13 (1.72)	7.06 (0.56)	0.70
Men	7.51 (1.17)	7.07 (0.47)	0.008
Women	5.71 (1.09)	5.31 (0.78)	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, cm <sup>2</sup> , 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

