Sex Differences in People Aging With HIV

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Background: To evaluate differences between older women and men with HIV regarding HIV variables, comorbidity, physical function, and quality of life (QOL).

Setting: The Modena HIV clinic.

Methods: Prospective cohort study. Cross-sectional analysis. Patients >50 years were included, stratified by sex. We recorded sociodemographic data, comorbidities, variables related to HIV infection, frailty, data on body composition, physical function, physical activity, and QOL.

Results: We evaluated 1126 older adults with HIV, of which 284 (25.2%) were women. Median age was 55 (IQR 6) years. There were significant differences between women and men in the median current $CD4^+$ T-cell and the mean CD4/CD8 ratio. There were differences regarding alcohol consumption, cardiovascular (CV) disease, hypertension, diabetes mellitus, and renal failure. Sarcopenia and slower gait speed were found more prevalent among men, but without significant differences. Significant differences were found regarding lower extremity strength measured by the chair stand test and in the short physical performance battery score. Short physical performance battery <9 was detected for 11.1% women vs. 5.6% men ($P = 0.002$). EQ5D5L score was 0.87 in women vs. 0.89 in men ($P = 0.002$).

Conclusions: In our cohort, older women represented one in 4 of the total patients. Despite the fact that women have better immunological recovery measured by CD4 T-cell count and CD4/CD8 ratio, and fewer CV disease and CV risk factors than men, their physical function and their QOL are worse. Therefore, older HIV-infected women have special characteristics, and the assessment of physical function in this group seems to be crucial.

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INTRODUCTION

The HIV population is aging, and interest in the way it happens is growing quickly. There were more than 35 million adults with HIV in 2017, of whom 18.2 million were women, which means more than half (51.8%) of the people with HIV (PWH) currently are women. In 2017, about 4400 new HIV infections a day were observed among adults aged 15 years and older, of whom almost 43% were women. In developed countries women accounted for 37% of new adult HIV infections.[1]

Despite the fact that 20%–30% of the PWH in developed countries are women and one in 3 of new adult HIV infections occur in women, few studies are centered on this specific group, most of them focused on women of reproductive age and pregnant women. Sex differences have been described within PWH regarding HIV stigma and the impact of HIV in everyday life,[2] and HIV-related coping and depression.[3] No significant differences have been found by sex regarding clinical outcomes such as immunological response, new AIDS events, or death.[4–6] Women are less likely to have advanced disease, more likely to have a higher CD4 count at antiretroviral therapy initiation, and less likely to be lost to follow-up.[7] Clinical trials have not been able to definitively establish sex differences in toxicity risk despite sex differences in toxicity having been reported for nucleoside analogues, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors.[8]

There are limited data about the specific characteristics of older women with HIV or whether they have special needs, but aging will be an issue for both men and women with HIV. According to the predictive model of Smit et al,[9] the mean age of PWH in 2030 will be 56.6 years, 73% of them will be 50 years old or above, and close to 40% will be older than 65. The main objective of our study was to evaluate differences between women and men with HIV aged 50 years plus, in HIV variables, comorbidity, physical function, and quality of life (QOL).

METHODS

Study Design and Patient Population

We performed a cross-sectional study from the prospective Modena HIV Metabolic Clinic (MHMC) cohort in Italy. Consecutive patients attending the Modena HIV clinic

were included in our analysis between June 15, 2016, and May 15, 2018. The inclusion criteria were confirmed HIV infection, age ≥50 years at the time of recruitment, and regular follow-up at the HIV clinic. Patients were stratified by sex.

Data Collection

We recorded sociodemographic data and variables related to HIV infection: risk practice; the baseline and current immunovirological status; the CDC category of HIV infection at diagnosis; and the years of known HIV duration. HIV RNA assay used was Abbott RealTime HIV-1 and the detection limit was 40 copies. Lifestyle, including current smoking and alcohol intake were self-reported.

Frailty was measured using the Frailty Index (FI), a tool computing the accumulation of age-related health deficits. We used a previously validated FI, based on 37 health variables.[10] Comorbidities were recorded by medical history, physician-diagnosed at the time of the visit or by chronic use of concomitant medications. They included hypertension, diabetes, dyslipidemia, cardiovascular disease (CVD), chronic obstructive pulmonary disease, renal failure, liver cirrhosis, HIV-associated neurocognitive disorders (HAND), AIDS malignancy, non-AIDS malignancy, vitamin D insufficiency (defined as serum 25OHD below 30 ng/mL), fragility fractures, and osteoporosis defined by dual-energy X-ray absorptiometry (DXA) as T-score in femoral neck less than −2.5.

Body composition data were collected using whole body DXA. Body mass index was defined as weight (Kg)/height $(m)^2$. Lipodystrophy was defined following the Multicenter AIDS Cohort Study (MACS) criteria[11] and central obesity using the waist-to-hip ratio (WHR): WHR >0.9 for men and WHR >0.8 for women. The quantity of the muscle mass was determined using the Appendicular Skeletal Muscle Mass Index (ASMI) by DXA as total lean (Kg)/height $(m)^2$.[12] Sarcopenia was defined by ASMI score: ASMI <7.26 for men or <5.5 for women. Fat-free mass index was also measured.

Muscle strength was measured by hand grip strength using a calibrated handheld dynamometer and expressed in kilograms (Kg), and by the chair stand test, which measures the amount of time needed for the patient to rise 5 times from a sitting position without using his or her arms, expressed in seconds. Physical performance was measured with objective measures of gait speed and the Short Physical Performance Battery (SPPB).[13] We used the four-meter usual walking speed test, measuring speed in seconds with a manual stopwatch. The SPPB includes the assessment of gait speed, a balance test, and a chair stand test. Each component of the SPPB is scored on a scale of 0–4, based on ability to complete the task and time required for completion, with a maximum overall score of 12. We defined physical activity and its intensity according to the short version of the International Physical Activity Questionnaire (IPAQ).[14] There are 3 levels of physical activity: low, moderate, and high. Median values and interquartile ranges (IQRs) can be computed for walking (W), moderate–intensity activities (M), vigorous–intensity activities (V), and a combined total physical activity score. All continuous scores are expressed in MET-minutes/week.

Exhaustion was defined as a positive answer to either of the following questions from the Center for Epidemiologic Studies Depression Scale (CES-D)[15]: "How often in the last week did you feel everything you had to do was an effort?" and "How often in the last week did you feel everything you had to do you could not get going?" with responses of rarely or none of the time (<1 day), some or a little of the time (1–2 days), a moderate amount of the time (3–4 days), or most of the time (5–7 days).

QOL was measured by the EQ5D5L[16] and by the presence and intensity of pain, because we consider pain to be a marker of QOL. The intensity of pain was stratified as mild, moderate, or severe.

Statistical Analysis

We used descriptive statistics to examine participant characteristics, which are expressed as frequency (percent) for categorical variables, mean (SD) for normally distributed continuous variables, and median (IQR) for continuous variables with a skewed distribution. Continuous variables were compared using the *t* test for independent variables. The Mann–Whitney test was used for variables with a non-normal distribution or when the group size was small, less than 12 participants. The association between qualitative variables was assessed using the χ^2 test or the Fisher exact test when less than 5 participants fell into one of the categories of the contingency tables.

RESULTS

We evaluated 1126 older adults with HIV. One in 4 were women [284 (25.2%)]. The mean age was 56.7 years, and 10.2% were 65 years or older. Baseline characteristics are described in Table 1. Women were younger than men at HIV diagnosis. Median nadir $CD4^+$ T cell was 195 (IQR = 88–296), and 76.6% of participants had an undetectable HIV RNA without significant differences between women and men. The percentage of patients in B or C category according to CDC classification was 57.8% women vs. 52.4% men ($P = 0.001$). Immunological recovery was measured by current $CD4^+$ T-cell and CD4/CD8 ratio, and differences were found: Median current $CD4^+$ T-cell count was 758 (IQR = 367) in women and 699 (IQR = 356) in men ($P = 0.03$), and median CD4/CD8 ratio was 1.01 in women compared with 0.83 among men ($P = 0.0001$). No differences were found regarding frailty.

There were differences between women and men regarding alcohol consumption [mild or intense: 55 (19.4%) vs. 282 (33.5%), $P = 0.0001$], CVD [8 (2.8%) vs. 93 (11%), $P = 0.0001$], hypertension [110 (38.7%) vs. 508 (60.3%), $P = 0.0001$], diabetes mellitus [33 (11.6%) vs. 193 (22.9%), $P = 0.0001$], and renal failure [94 (33.1%) vs. 151 (17.9%), $P = 0.0001$] (Fig. 1). Only one fragility fracture was recorded, and no HAND was reported. Data related to body composition, physical function, physical activity, and QOL are represented in Figure 2. Body mass index (BMI) was within the established

TABLE 1. Baseline Characteristics, Immunology Recovery, and Frailty

	Total	Women	Men	*P*
Patients, N (%)	1126	284 (25.2)	842 (74.8)	
Age, Mean (SD)	56.7 (5.76)	55.7 (5.6)	57.09 (5.7)	0.002
Age ≥65 years, N (%)	115 (10.2)	26 (9.2)	89 (10.6)	NS
Age HIV diagnosis, Mean (SD)	32.5 (9.8)	30.4 (9.5)	33.2 (9.8)	0.0001
Risk practice for HIV infection, N (%)				0.0001
IDU	337 (29.9)	80 (28.2)	257 (30.5)	
MSM	357 (31.7)		378 (44.9)	
Heterosexual	329 (29.3)	175 (61.6)	133 (15.8)	
Others	23 (2)	7 (2.5)	16 (1.9)	
NA	80 (7.1)	22 (7.7)	58 (6.9)	
Education, N (%)				NS
Primary school	44 (4.3)	14 (5.2)	30 (3.9)	
Middle school	388 (37.6)	94 (35.1)	294 (38.5)	
High school	411 (39.9)	117 (43.7)	294 (38.5)	
University	188 (18.2)	43 (16)	145 (19)	
Years of known HIV duration, Mean (SD)	23.6 (7.3)	24.7 (6.5)	23.2 (7.5)	0.003
<10 years, N (%)	78 (7)	11 (4)	67 (8.1)	
10–20 years, N (%)	230 (20.8)	50 (18.1)	180 (21.7)	
>20 years, N (%)	797 (72.1)	216 (78)	581 (70.2)	0.017
B or C CDC category, N (%)	605 (53.7)	164 (57.8)	441 (52.4)	0.001
Nadir $CD4^+$ T-cell median (IQR)	195 (107)	191 (190)	195 (157)	NS
Undetectable HIV RNA, N (%)	862 (76)	211 (74.2)	651 (77.3)	NS
Current $CD4^+$ T-cell median (IQR)	714 (178)	758 (367)	699 (356)	0.03
CD4/CD8 ratio, Median (IQR)	0.87 (0.6)	1.01 (0.61)	0.83 (0.5)	0.0001
Frailty index, Mean (SD)	0.17 (0.09)	0.18 (0.09)	0.17 (0.09)	NS

IDU, injection drug user; MSM, men who have sex with men; NA, nonavailable; CDC, center for control diseases.

range as normal weight (BMI of 18.5 to <25). Mean central obesity measured by WHR was 1.56 (0.49) in the whole group, over the cut-off in both sex and sarcopenia was more prevalent among men than in women, but not statistically significant. No differences were found regarding lipodystrophy (82.4% in women, 85.7% in men), mean appendicular skeletal mass index [5.46 (1.12) in women, 7.06 (1.63) in men] or in mean fat free mass index [13.13 (3.7) in women, 16.41 (7.7) in men]. Regarding muscle strength, the mean hand grip strength in both men and women was over the low cut-off adjusted by BMI used by Fried to define weakness,[17] one of the 5 criteria of frailty phenotype: 17 Kg for women and 29 Kg for men. Significant differences were found regarding lower extremity strength measured by the chair stand test. Of the women, 10.5% took more than 13.70 seconds to complete the test, compared with 5.5% of the men ($P = 0.005$). Regarding physical function, there were significant differences in SPPB. The proportion of women with an SPPB score under 9 was double that of the men, despite the fact that there was not a significant difference in walking speed. No significant differences were found regarding the proportion of women and men having or not having physical activity, but differences were shown in the physical activity score measured by MET-minutes per week, being significantly lower among women. Among physically active participants, differences between women and men were found regarding the intensity of the activity: it was mild-to-moderate intensity in 91.5% of women compared with 86.9% of men and intense in 8.5% of women compared with 13.1% of men. Exhaustion was more frequent among women, as well. QOL measured by the EQ5D5L was significantly worse among women, and pain was more prevalent and severe in women than in men as shown in Figure 3. Sex remains an independent predictor of physical performance, physical activity, and QOL after adjusting results by age, age at HIV diagnosis, years of known HIV duration, CDC clinical category at HIV diagnosis, current CD4, CD4/CD8 ratio, and CVD.

DISCUSSION

PWH are considered older adults when in their 50s due to their accentuated aging and an early immunosenescence clinically noticeable by their premature presence of comorbidity, geriatric syndromes, and frailty.[18] The population of our study can be considered "the youngest of the older adults" since most of them were in their 50s and just around 10% were 65 years or older. They were quite a fit population as well, according to the FI, which was below 0.2 in both women and men. These facts make the results particularly interesting. They highlight that there are already differences between women and men in their paths of aging in the early aging stage, despite their apparent good health conditions.

In our cohort of HIV adults aged 50 years old or above, women represented one in 4 of the total patients. Despite the

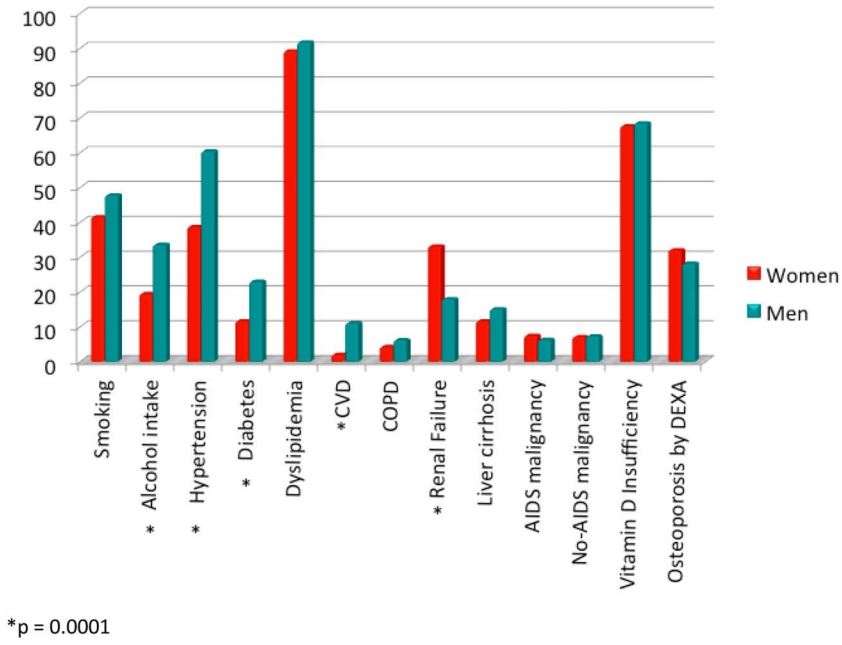

FIGURE 1. Comorbidity. Comorbidities recorded by medical history, physician-diagnosed at the time of the visit, or by chronic use of concomitant medications. COPD, Chronic obstructive pulmonary disease. full color online

fact that women have better immunological recovery measured by CD4 T-cell count and CD4/CD8 ratio, and fewer CVD and cardiovascular (CV) risk factors than men, their physical function and their QOL are worse.

Better immunological recovery in women has been previously described. In the SCOLTA (surveillance cohort long-term toxicity of antiretrovirals) project,[19] women were younger at the start of antiretroviral treatment, as in our study, and had better immune response measured by CD4 T cell despite a nonsignificantly lower initial $CD4^+$ level. Other studies have shown that women achieve better immune recovery after long-term HAART and were less likely to die.[20,21] Very recently published data from the GEPPO cohort have also shown that women older than 65 years old displayed better CD4+/CD8+ ratio in comparison to men.[22] It has already been well established that the CD4/CD8 ratio is a surrogate marker of immune senescence[23] and is associated with markers of age-related disease in virally suppressed HIV-infected patients with immunological recovery.[24] We found a significantly better CD4/CD8 ratio in women than in men and at the same time, less burden of comorbidity, specifically CVD, in women.

Several studies have focused on the burden of comorbidity in PWH. Regarding CVD in particular, data published so far are scarce, but show a higher CVD risk among HIV-positive women than HIV-negative women, with a hazard ratio of 2.8 after adjusting for CV risk factors.[25] The prevalence of early and premature menopause is variable, but higher than in HIV-negative women,[26] which, added to HIV-related factors and lifestyle-related risk factors (cigarette smoking and illicit drug abuse), can explain this fact. However, few studies have been designed to explore sex differences in the risk of CVD among PWH. We found fewer CVD and CV risk factors in women than in men. On the contrary, some studies previously demonstrated CVD rates to be higher in HIV-positive women than in HIV-positive men, but most of these studies were conducted in women in their 30s during periods of high antiretroviral therapy toxicity.[27–30] All studies revealed that the most significantly increased relative risk of CVD within HIV- infected women occurred when they were younger than 50 year old.[31] Our women's mean age was 55.7 years. There are differences in body composition, fat distribution, and hormonal control with aging that make older women a special group with specific characteristics, not allowing for the assumption of the findings about CVD research in young HIV-infected women, nor from HIV-infected male studies.[32]

In current clinical practice, the assessment of older PWH is still focused on viral load suppression, immunological recovery, and comorbidity, and it is uniform (ie, without specific approaches for men or women). However, much is presently being said about the fourth 90,[33] as PWHs' health status and life expectancy have largely improved. There is no consensus about the outcomes used to define QOL, or whether healthy aging instead of QOL should be the measure of success in treating HIV.[34] However, the whole scientific community agrees that new outcomes beyond immunovirological recovery are required to provide better person-centered care to middle-aged adults with HIV. Beyond mortality, good physical function is a key issue for achieving and sustaining healthy aging and a good QOL. Our results demonstrated differences between physically fit older women and men with HIV regarding physical function and QOL.

One of the most relevant results of our study was that physical function was worse in women. This can be considered normally expected as in the general population men perform better than women across all ages;[35] however, this loss of physical function in women with HIV occurs at a younger age. We also found interesting differences related to which has been described for general population. In the

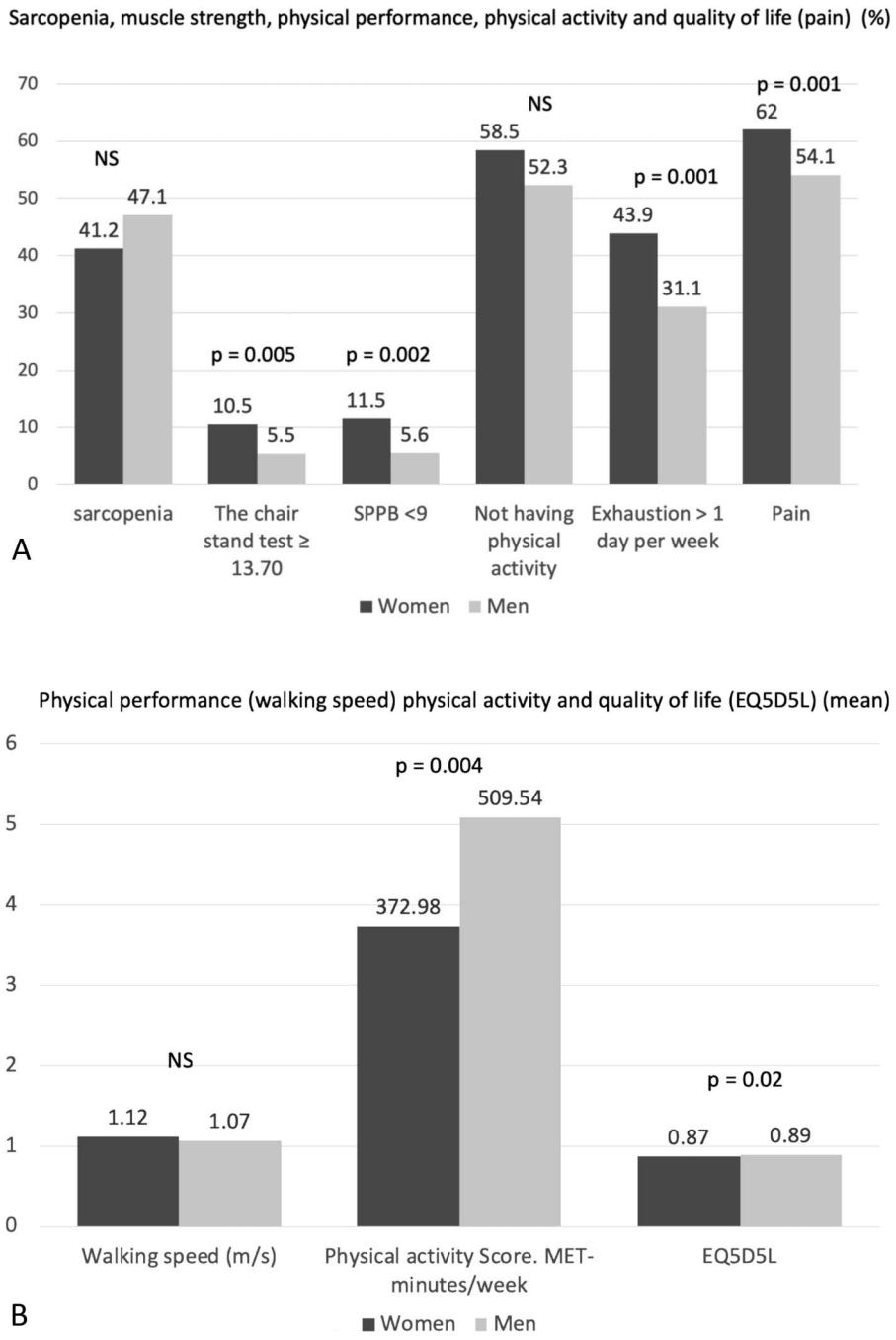

FIGURE 2. Body composition, physical function, physical activity, and QOL. A, Sarcopenia, muscle strength, physical performance, physical activity, and QOL (pain). Percentage of patients with sarcopenia. Lower extremity strength measured by the percentage of patients who took more than 13.70 seconds to complete the chair stand test. Lower physical performance measured by the percentage of patients with SPPB score under 9. The proportion of patients not having physical activity. The proportion of patients with pain. B, Physical performance (walking speed), physical activity, and QOL (EQ5D5L). Mean walking speed (meters per second). Mean physical activity score measured by MET-minutes per week. Mean EQ5D5L.

older HIV-negative population, 15 years older than our study's population, women perform worse on the SPPB, gait speed, and the chair stand test[36] and sarcopenia has been demonstrated to be more common in older women than in older men[37] In our study, the percentage of women with an SPPB score lower than 9, which means functional impairment, was double that in men, despite the fact that walking speed tended to be faster in women and sarcopenia tended to be more prevalent among men. However, women needed significantly more time (in seconds) to complete the chair stand test. This highlights the idea that low muscle strength overtakes the role of low muscle mass as a principal determinant of physical performance.[38] It has been demonstrated in the general population that strength is better than mass in predicting adverse outcomes.[39,40] Because of this, the definition of sarcopenia has recently changed to include this concept, and in the revised guidelines,[38] muscle strength comes to the forefront. In our study, sarcopenia was defined in quantity of the muscle mass (ASBMI score), and the quality of the muscle was measured separately by the muscle strength and the physical performance. Despite the lack of evidence for loss in skeletal muscle mass, fatigue and some

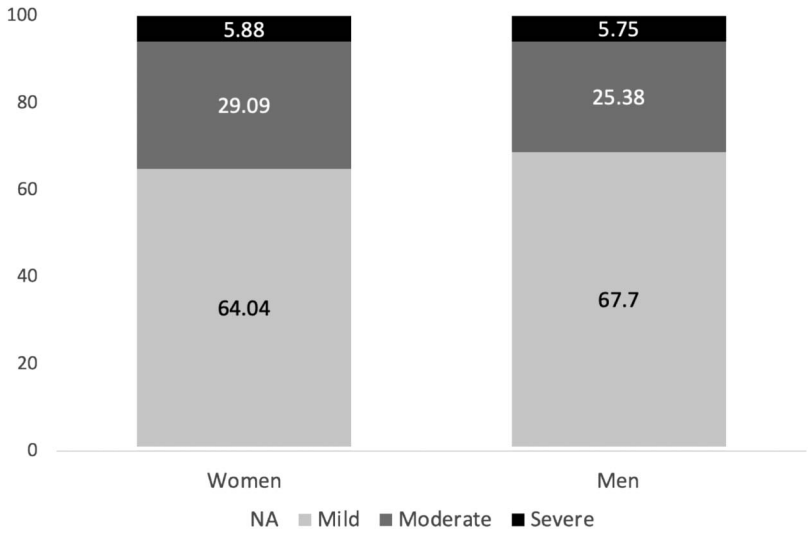

FIGURE 3. Intensity of pain as a marker of QOL. Proportion of patients with mild, moderate, or severe pain.

deficits in physical function have been demonstrated among asymptomatic older HIV-infected people.[41] Sarcopenia in PWH is age-related and HIV-related due to the elevated inflammation and immune activation.[41] We found higher quantity of muscle mass in women than in men, but worse quality of muscle in physical performance. Reduced physical performance has independent effects on mortality among PWH.[42] An independent association between HIV infection and reduced physical performance has been demonstrated previously,[42–44] but we are now demonstrating differences by sex that make women more vulnerable than men regarding physical function.

Interestingly, in our study, no significant differences were found regarding the proportion of women and men having or not having physical activity, but differences were shown in the physical activity score measured by MET-minutes per week, being significantly lower among women. Therefore, despite a trend of better muscle quantity, worse muscle quality in strength and physical performance was found among women, and lower intensity in physical activity. Because of the methodology of our study, we are not able to establish causality, but these results could be demonstrated in further studies specifically designed for this purpose. The impact of a decline in physical activity is huge on skeletal muscle mass and strength. It is known that muscle disuse, rather than the effect of aging by itself, is responsible for a remarkably greater relative loss of muscle strength when compared with the loss of muscle mass.[45] It has been suggested that sex may influence the rate of disuse atrophy[46,47] but this is still unclear. What is a fact is that different cut-offs have been determined for women and men to define sarcopenia in low skeletal muscle mass; however, there are no differences in the scores to measure physical performance between women and men. A significant and fast decline in muscle mass has been reported in PWH,[48] but also that PWH could improve physical performance with exercise in the same manner as elder individuals with sarcopenia,[49] even if these gains are unaccompanied by an increase in muscle mass.[50] Exercise training preserves strength and muscle mass in PWH under HAART,[51] and both moderate-intensity and high-intensity exercise have demonstrated significant improvements in physical function in PWH.[52] In all of these studies and in the 2 systematic reviews and meta-analyses centered on physical activity and exercise among PWH recently published[53,54] the great majority of participants were men, and no specific conclusions or comments about older women with HIV were made.

According to our results, despite the fact that our population was aging quite well, physical function needs to be routinely tested to detect those at risk of functional decline, which will allow health care providers to establish preventive actions and early interventions. Such testing is especially necessary among women with HIV in their 50s. In our study, the intensity of physical activity was shown as a likely key factor affecting the physical performance of older women with HIV. Therefore, physical activity must first be incorporated into the routine clinical records of older adults (those in their 50s and older) with HIV, especially for women. Its intensity has to be measured to design a personalized exercise regimen.

The other most relevant result of our study is that the QOL of women was worse than that of men. A recent study that examined such sex differences directly found higher life satisfaction among women.[55] The study population was younger than ours, with a mean age of 42.7 years, and the measures used to assess QOL were focused on psychosocial dimensions of HIV-related QOL (HIVQOL). Similar to our study, others evaluated items such as somatic symptoms as indicators of QOL and found higher prevalence of fatigue or pain among women[56] as indicators of worse QOL. There are relevant issues that specifically affect women's QOL, making it worse than that of men, such as social support and stigma.[56–58] However, some studies did not find differences in QOL by sex when focusing on self-reported QOL.[59] We studied pain and its intensity as an indicator of QOL, and it was more prevalent and its intensity higher in women. The prevalence of pain among PWH has been described as high,[60] and its relationship with anxiety, depression, and lower QOL is well known.[61,62]

The main limitation of our study is that because of the methodology used, a cross sectional study, we cannot establish a relationship of causality between variables. Noteworthy is the minimum, but significant difference in the amount of years lived with HIV between women and men, which is higher among women. Our hypothesis is that there could be an interaction between a patient's sex and duration of HIV infection that affects the aging outcomes, but we are not able to prove this with the data available. It was also a one-center study in Italy, so further studies are needed to extrapolate the results. One of the major strengths of this study is the detailed and comprehensive phenotyping encompassing HIV-related issues, comorbidity, comprehensive body composition, physical function, and physical activity evaluation using objective measurements. As far as we know, this is the first study designed to globally compare these various aspects of ageing between older women and men with HIV.

Therefore, older women with HIV have special characteristics and specific needs different than those of men with HIV. Helping HIV-positive women age well should be our main goal. This requires a global assessment including physical function, pain, and QOL, and bridging the gap between clinical research and clinical care[63] by proactively providing the routine clinical care these new outcomes that HIV-positive women need at the right time.

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