Body Composition Changes in Response to Moderate or High-Intensity Exercise Among Older Adults with or without HIV Infection

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Abstract

Background: People with HIV (PWH) have increased risk for adiposity and sarcopenia, despite effective antiretroviral therapy. Our objective was to compare the effects of prescribed exercise on body composition in older PWH and uninfected controls.

Setting: Academic medical center

Methods: Sedentary PWH (n=27) and uninfected controls (n=28) aged 50-75 completed 24 weeks of cardiovascular and resistance exercise. Participants completed 12 weeks of moderate-intensity exercise then were randomized to moderate- or high-intensity exercise for 12 additional weeks. Total lean (LEAN) and fat mass (FAT) and visceral adipose tissue area (VAT) were measured using DXA at baseline and 24 weeks; baseline and intervention differences were

compared by HIV serostatus using multivariable regression analyses adjusted for baseline values, age, and exercise adherence.

Results: At baseline, PWH had significantly lower FAT (P=0.003), but no significant differences in LEAN or VAT compared to controls (P>0.20). Changes over 24 weeks were not significantly different by HIV serostatus, though controls tended to gain more LEAN (0.8 kg [0, 1.6; P=0.04] than PWH (0.6 kg [−0.2, 1.4; P=0.12]) and lose less FAT and VAT (controls (−0.9 [−1.8, 0.0] kg; −10.3 [−19.6, 1.0] cm^2; both P = 0.03 vs PWH −2.0 [−2.9, −1.1] kg; −17.7 [−27.1, −8.2] cm^2; both P< 0.001). Exercise intensity differences were not apparent for LEAN, FAT, or VAT.

Conclusion: Exercise reduced total and visceral fat in older PWH and controls. Minimal gains in lean mass suggest that greater emphasis on resistance exercise may be needed to effectively increase muscle in PWH.

Introduction

Antiretroviral therapy (ART) has decreased mortality for people with HIV (PWH) and, with newer ART agents, AIDS-associated complications including muscle wasting or lipoatrophy are less frequent compared to the early years of ART. With age, many people with HIV experience age-related changes in body composition, including sarcopenia (loss of muscle mass and function) and increased central adiposity. Studies by our group and others have found that age-related sarcopenia and adiposity are associated with impairments in physical function among older adults with HIV[1–3]. Furthermore, emerging data suggest that ART regimens that include integrase strand transfer inhibitors (INSTIs)[4–6] may be associated with greater weight gain than other ART classes. Thus interventions to simultaneously reduce sarcopenia and obesity are needed to improve the health of adults aging with HIV.

The U.S. Department of Health and Human Services (DHHS)[7] recommends regular aerobic and resistance exercise to increase muscle mass and function and reduce body fat in healthy older adults and adults with chronic health conditions; evidence for these adaptations in older PWH has been equivocal[8,9]. Even with effectively suppressed HIV-1, exposure to earlier generation ART [10,11] that were toxic to mitochondria or newer ART[12–14] associated with weight gain, chronic inflammation, comorbidities, and viral reservoirs[14–16] could interfere with the potential beneficial effects of exercise in PWH.

We have previously reported that older PWH had similar improvements in physical function as controls without HIV following a 24-week, moderate- or high-intensity exercise training intervention[17]. Here, in this secondary analysis, we sought to compare the adaptations in body composition in response to exercise in older PWH and controls, and to identify what, if any, adaptations were unique to older PWH. Further, we evaluated whether the changes in body composition were related to circulating testosterone and insulin-like growth factor 1 (IGF-1) because of their anabolic effects on skeletal muscle and changes with aging.

Methods

The Exercise for Healthy Aging Study enrolled PWH and HIV-uninfected controls from April 2014 to May 2017 (NCT02404792). The inclusion and exclusion criteria and study design have been published previously[17]. Briefly, participants were aged 50 to 75 years, sedentary (< 60 minutes of physical activity per week for preceding 6 months by self-report), had a body mass index (BMI) between 20 and 40 kg/m^2, and no contraindications to exercise. PWH were on stable ART with undetectable HIV-1 RNA for >2 years and CD4+ T-cell count > 200 cells/μL. The study procedures were approved by the Colorado Multiple Institution Review Board. Written informed consent was obtained from all participants.

Study Procedures

Prior to training and at week 12, peak cardiorespiratory capacity (VO$_2$ peak) was measured using a graded treadmill test. Maximum muscle strength was measured using the one-repetition maximum (1-RM; maximum weight that can be lifted only one time) at baseline and every 3 weeks. Participants attended supervised exercise sessions three times/week for 24 weeks at the University of Colorado-Anschutz Medical Campus Exercise Research Laboratory. Each session included treadmill walking and four weight-assisted machine (Cybex) exercises (bench press, leg press, lateral pulldown, and a rotating 4th exercise). Exercise time gradually increased to a target of 50 minutes/session. The first 12 weeks targeted moderate intensity (40–50% VO$_2$ peak) treadmill walking and 3 sets of 8 repetitions of moderate intensity resistance exercises (60–70% 1-RM) each session. At week 12, participants were randomized to continue moderate-intensity training or advance to high-intensity training (60–70% of week 12 VO$_2$ peak and > 80% 1-RM). Participants were encouraged to consume a healthy diet but no specific or personalized dietary guidance was given.

Body Composition Measures

Before and at week 24 of exercise training, total body bone-free lean mass (LEAN), fat mass (FAT), and visceral adipose tissue (VAT) area were measured by dual-energy x-ray absorptiometry (DXA) using either the Hologic Discovery W (Apex 4.0.1; n=42) or Horizon W (Apex 5.6.05; n=13) instrument (Hologic, Inc., Bedford MA). Each participant had pre- and post-training measures on the same instrument. In our laboratory, the coefficient of variation (95% CI) for LEAN and FAT are 0.7% (0.5, 0.8%) and 1.7% (1.3, 2.1%), respectively. Appendicular lean mass (ALM) was calculated as the sum of the limb lean mass (kg), then normalized to height in meters-squared (ALM/m^2). VAT area included the fat within the abdominal muscle walls of the abdominal cavity, between the superior border of the pelvis and the inferior border of the rib cage. (Hologic Series User Guide, Whole Body Examination, MAN-03644 Revision 006). DXA scan reports were reviewed by one investigator (CMJ) for quality assurance.

At baseline and 24 weeks, BMI was calculated using body mass from DXA divided by baseline height squared (kg/m^2), with height measured using a wall-mounted stadiometer. Participants were classified as sarcopenic using the criteria of Baumgartner et al: ALM/m^2 < 7.26 for men and < 5.45 for women [18]. Lipodystrophy among the PWH was determined at

baseline using the criteria of Bonnet et al (ratio of percent fat of the trunk to percent fat of the lower limbs ≥ 1.961 for males; ≥ 1.329 for females)[19].

Anabolic hormones

Fasted blood samples were collected at baseline and 24 weeks for measurement of total testosterone (T; males only) and IGF-1. Serum sex hormone binding globulin (SHBG) and albumin were measured and used to calculate free T[20]. Serum was separated and stored at −80°C for batch analyses. All samples from the same participant were analyzed in the same batch. T was measured using liquid chromatography-tandem mass spectrometry. The intra- and inter-assay co-efficients of variation (CVs) were < 2% and < 8%, respectively. SHBG and IGF-1 were measured by chemiluminescence (SHBG: Beckman Coulter; intra- and inter-assay CVs 3.6% and 5.7%, respectively; IGF-1: Immunodiagnostics Systems; intra- and inter-assay CVs 2.0% and 9.5%, respectively). Albumin was measured by enzymatic assay (Beckman Coulter; intra- and inter-assay CVs 2.3% and 4.9%, respectively).

Comorbidity Assessment

The Veterans Aging Cohort Risk Index (VACS Index) was used to quantify comorbidities at baseline, with higher scores indicating greater comorbidity. The VACS index reliably predicts HIV and non-HIV related mortality[21].

Statistical analyses

Study data were managed using the secure, web-based software platform Research Electronic Data Capture (REDCap) hosted at the University of Colorado[22,23]. The primary body composition outcome was the change from baseline in LEAN. The effect of exercise intensity was considered a secondary outcome given the limited duration of the higher intensity training and the time necessary to measure changes in body composition. Additional outcomes, including differences in free T and IGF-1 levels, were considered complementary. The randomization to exercise intensity arms was balanced by HIV serostatus, gender, and age. Log transformations were performed due to right skew, as appropriate, and results reported as geometric means. Baseline measures were compared via t-tests or Fischer's Exact Test.

The primary predictor was HIV serostatus. All models were adjusted for the respective baseline value, age, and exercise adherence, with percent exercise adherence calculated as [1- (72 sessions - # sessions attended)/72 sessions] x 100. Exercise intensity models were similarly adjusted for baseline values, age and percent adherence. Separate models tested the effect of adjusting for VACS (in place of age) and baseline free T (males only), and a sensitivity analysis compared responses by use of testosterone supplementation. Additionally, we implemented a model that adjusted for DXA instrument. Two-sided tests are reported assuming a 0.05 significance level. Outcomes were considered complementary and reported without adjustment for multiple comparisons[24–26]. Results are expressed as the mean and 95% confidence interval unless otherwise specified. Analyses utilized R (v. 3.4.2) and SAS (v. 9.4).

Results

Sixty-nine participants began the study and 56 completed, of whom 55 contributed body composition data before and after exercise training (27 PWH [15 high-intensity, 13 moderate-intensity], 28 HIV-uninfected controls [14 high-intensity, 14 moderate-intensity]). Of the completers, baseline characteristics are provided in Table 1. Compared to controls, more PWH had a higher VACS score (P= 0.02). The prevalence of current smoking, use of testosterone supplementation, and statin use were not significantly different in PWH and controls (P>0.2). Adherence to the exercise intervention (median, [IQR]) was 89% [82, 92%] in PWH and 87% [81, 92%] in controls.

Baseline Body Composition

At baseline (Table 2), PWH had lower BMI (P=0.018) and FAT (P=0.003) than controls whereas LEAN, ALM/m^2, and VAT area were not significantly different between groups (P>0.20). Four PWH and one control met criteria for sarcopenia, and 7 of 27 PWH had lipodystrophy.

Changes in Body Composition

The main effect of HIV status was not significant for any changes in BMI and body composition after adjustment for baseline values, age, and exercise adherence (Figure 1; P>0.09). The decrease in BMI was significant for PWH (−0.48 [−0.87, −0.08]kg/m^2; P=0.02) but not controls (−0.15 [−0.54, 0.24]kg/m^2; P=0.43). LEAN increased in controls (0.8 [0, 1.6]kg; P=0.04) and PWH (0.6 [−0.2, 1.4]kg; P=0.12) but reached significance only in controls. Increases in ALM/m^2 approached significance (P=0.06), with similar changes in each group (PWH, 0.14 [−0.01, 0.30]kg/m^2; controls 0.14 [−0.01, 0.29]kg/m^2). After the intervention, two of the four PWH and the one control no longer met criteria for sarcopenia.

Total and visceral adiposity decreased within both groups in response to the intervention. FAT decreased 2.0 kg (−2.9, −1.1 kg; P < 0.001) in PWH and 0.9 kg (−1.8, −0.06 kg; P=0.04) in controls, but the between group difference was not significant (P=0.09). VAT decreased 18 cm^2 (−27, −8.2 cm^2; P< 0.001) in PWH and 10 cm^2 (−20, −1.0 cm^2; P= 0.03) in controls. The between group difference in the changes in VAT was not significant (P=0.28).

Exercise intensity in weeks 13–24 (high vs. moderate) was not related to any changes to body composition (P>0.12). Inclusion of the VACS Index in the any of the models did not meaningfully alter the estimates of the intervention on body composition outcomes (10% difference in the estimates). Greater exercise adherence was significantly associated with changes in FAT (−0.1 kg [−0.2, 0], P=0.008), but did not meaningfully change the effect estimates. Adjustment for DXA instrument did not appreciably alter the body composition results.

Anabolic hormones

At baseline, serum total T was significantly greater in male PWH than controls (P=0.006) but free T was not different between groups (P=0.35; Supplemental Table). When

participants using testosterone supplementation were excluded from the analyses, total T remained significantly greater in PWH (P=0.002) and free testosterone tended to be greater in PWH than controls (P=0.063). In response to the intervention, the decreases in free T were not significant within (PWH, P=0.27; controls, P= 0.68) or between groups (P=0.62). When testosterone supplementation was excluded from the analysis, free T decreased significantly within PWH (P=0.02) and controls (P< 0.001) but these changes were not different between groups (P=0.32). Baseline free T was not significantly associated with the changes in body composition (P= 0.21 to 0.36) in males. Baseline IGF-1 did not differ between PWH and controls (P=0.472), the changes in IGF-1 from baseline to week 24 were not significant within PWH (P=0.10) or controls (P=0.73), and the changes due to training were not significantly different between PWH and controls (P=0.16).

Discussion

The goals of this study were to 1) compare the adaptations in body composition in response to exercise in older PWH and controls; 2) identify whether any adaptations were unique to older PWH; and 3) evaluate the whether the changes in body composition were related to systemic testosterone and IGF-1. The side-by-side comparisons of PWH and uninfected controls in a supervised resistance and cardiovascular endurance exercise intervention that was consistent with the 2008 U.S. DHHS recommendations[7] provided a rigorous examination of body composition adaptations among older adults with and without HIV infection. Overall, we found that HIV infection did not significantly interfere with the reduced adiposity seen with training, but may blunt increases in lean mass.

First, we found similar, highly favorable reductions in total body and visceral fat in both PWH and HIV-uninfected controls that could reduce long-term cardiometabolic disease risk. The reduction in VAT area (using DXA) in PWH was comparable to that reported in a systematic review of supervised exercise trials in middle-aged adults without HIV infection (15.3 ± 40.4 cm^2; using computed tomography)[27]. The reduced BMI in PWH following the exercise intervention was attributed to a decrease in fat mass and maintenance of lean mass.

Second, the reduction in fat mass and visceral fat that we found was consistent with three other recent studies of younger (average ages 46–49 years) PWH who completed combined aerobic and resistance exercise training. Notably, none of these studies included an HIV-uninfected group for comparison. Guariglia et al[28] found that fat mass decreased approximately 1.5 kg (9%) and android fat mass (measured by DXA) decreased 0.2 g (10%) in PWH (N=25) during 16 weeks of exercise training. Cutrono et al[8] found that waist circumference decreased approximately 0.5 inch in PWH after 12 weeks of combined moderate-intensity exercise. In a study of PWH with lipodystrophy (N=26), Bonato et al[9] found that DXA-measured fat mass decreased approximately 0.1 kg, lean mass increased 1.8 kg (both P<0.05), and waist circumference decreased by 1.0 cm (P=0.05) from baseline to 12 weeks of exercise. The participants in Bonato et al[9] were also guided to consume 2000 kcal/day, including 15–30% of energy as protein and 20–30% as fat during the intervention, which may explain the greater increase in lean mass compared to the PWH in our study (0.6 kg). Although PWH acknowledge the importance of exercise and diet for their overall

health, evidence-based interventions are needed to promote and then maintain these behavior changes over the long-term[29].

Weight loss is often accompanied by reductions in muscle mass, with the concern for potential long-term functional consequences. Our findings of maintenance or modestly increased lean mass reassured that aerobic and resistance exercise among older PWH can improve cardiometabolic risk with decreased fat mass while also preserving lean mass and improving physical function, as we previously reported[17]. Appendicular lean mass adjusted for height, an index of sarcopenia, improved in both groups, albeit not significantly, and three of five participants who were sarcopenic at baseline became non-sarcopenic after training. The blunted increase in lean mass in PWH may be related to persistent mitochondrial dysfunction due to previous exposure to thymidine analogues or HIV-infection [30–32]. Neither greater comorbidity (VACS Index) nor prevalence of smoking explained the limited increase in lean mass in PWH. The anabolic hormonal milieu, albeit limited to circulating free testosterone in males and IGF-1 in all participants, did not have detectable effects on the changes in body composition. The exercise intervention included only four resistance exercises, three of which involved large muscle groups. Hence, the stimulus for skeletal muscle hypertrophy was also modest. Exercise recommendations for older PWH may need to place greater emphasis on resistance exercise to increase muscle mass, although improvements in physical function indicate improved muscle quality.

Lastly, greater loss of fat mass in PWH and controls was not related to exercise intensity, but was significantly associated with exercise adherence. As we have previously published, however, higher intensity exercise did not deter adherence to training and resulted in greater improvements in some physical function outcomes[17]. The association of greater exercise adherence with improved outcomes is not surprising and could be a motivating message for PWH to start and maintain an exercise habit. The DHHS guidelines for exercise[7,33] can and should be recommended for older PWH, particularly with the growing prevalence of obesity and physical function impairments in this population, however barriers to starting and maintaining a regular exercise habit in older PWH are substantial[34]. We have described[35] several behavior change strategies that health care providers can recommend to encourage and maintain physical activity behaviors among PWH. A program of supervised exercise training that transitions to self-managed exercise may improve the uptake and maintenance of exercise in older PWH[36], thereby leading to favorable changes in body composition.

The side-by-side comparisons of PWH and uninfected controls in a supervised exercise intervention provides a rigorous examination of the effects of resistance and cardiovascular endurance exercise on body composition among older adults with and without HIV, however several limitations of the study should be highlighted. The study sample was predominantly male, thus limiting generalization to women aging with HIV. The study was not adequately powered to rule out an interaction of exercise intensity and HIV status on body composition. The operational definition of sarcopenia[18] included lean tissue mass but no indicator of muscle quality[37,38]. Lastly, the effects of dietary changes outside of the exercise intervention cannot be discerned. Participating in supervised exercise may have prompted conscious or unconscious dietary habits that could have contributed to changes in body composition. As

the primary focus of this study was on changes in physical function, we did not collect detailed dietary logs throughout the intervention.

In summary, our findings provide evidence that moderate- to high-intensity cardiovascular and resistance exercise reduces abdominal and total body adiposity and maintains lean mass in middle-aged and older PWH. Larger studies with greater racial, ethnic, and gender diversity are needed to confirm the present findings, and to determine if there is a dose-response between exercise intensity and body composition changes in older PWH. The etiology of the suggested attenuated response of lean mass to exercise among PWH is unknown, but may be due to primary muscle pathology, altered myokine/cytokine responses, or mitochondrial dysfunction. A more intensive resistance exercise intervention (e.g., additional exercises, longer duration, or greater frequency) or adjuvant therapies (e.g., high protein diet) may be needed to increase lean mass in older PWH. Lastly, behavior change strategies to promote long-term adherence to exercise are imperative to sustaining improvements in physical function and body composition beyond the duration of supervised interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding

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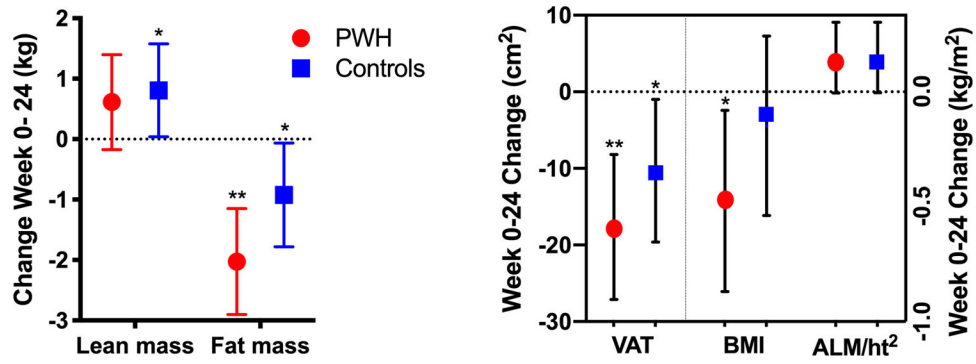
Fig 1.
Changes in body composition in response to the intervention, adjusted for baseline values, age, and exercise adherence. * P < 0.05; ** P < 0.001 for changes within groups. ALM, appendicular lean mass; BMI, body mass index; PWH, people with HIV; VAT, visceral adipose tissue area.

Table 1.

Participant Characteristics (median [IQR] or %)

	People with HIV (n=27)	Uninfected Controls (n=28)
Age (years)	56 [52, 61]	61 [54, 64]
Gender (% male)	93	93
Race (% white)	70	89
Non-Hispanic (%)	85	86
Current Smoker (%)	15	11
Testosterone use (% males)	20	8
Statin use (%)	48	43
VACS-1 > 20 points (%)	59[*]	25[*]
Unintentional weight loss[a] (n)	6	1
Years since HIV diagnosis	23 [17, 28]	---
CD4 count (cells/μL)	546 [416, 772]	---
ART duration (years)	17 [9, 19]	---
Current use INSTI (%)	59	---
Current use TAF (%)	4	---
Current or prior use of thymidine analogues (%)	68	---

[a]Year prior to intervention, self-report.

[*]P<0.05 for between group difference

ART, antiretroviral therapy; BMI, body mass index; INSTI, integrase strand transfer inhibitors; TAF, tenofovir alafenamide fumarate; VACS-1, Veterans Administration Comorbidity Score-1

Table 2.

Baseline Body Composition by HIV Serostatus [Mean (95% CI) or %]

	People with HIV (n=27)	Uninfected Controls (n=28)	P-value
Body Mass Index (kg/m^2)	26.9 (25.3, 28.4)	29.6 (27.9, 31.3)	0.018
Total Body Lean Mass (kg)	57.7 (54.2, 61.1)	60.0 (56.4, 63.6)	0.34
ALM/m^2	8.6 (8.1, 9.1)	8.9 (8.5, 9.3)	0.26
Fat Mass (kg)	20.6 (17.7, 23.6)	27.2 (24.0, 30.4)	0.003
VAT area (cm^2)	184 (151, 217)	211 (184, 237)	0.20
Sarcopenia[a] (%)	15	4	0.19
Lipodystrophy[b] (%)	26	—	

[a] According to the criteria of Baumgartner et al (1998).

[b] According to the criteria of Bonnet et al (2005).

ALM/m^2, appendicular lean mass relative to height; VAT, visceral adipose tissue