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ORIGINAL PAPER

Effects of a Combined Exercise Training Program on Health Indicators and Quality of Life of People Living with HIV: A Randomized Clinical Trial

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Abstract
The aim of this study was to evaluate the effects of 16 weeks of combined exercise training (CET) on muscle strength, body composition, depression, anxiety and quality of life of people living with HIV (PLHIV). Twenty-three participants completed the study, 14 in trained group (TG) and 9 in control group (CG). TG consisted of resistance and aerobic training three times a week, while the CG was exposed to recreational activities twice a week. CET promoted increased muscle strength (25% in overall strength) and aerobic capacity (+20% in training speed and +23% in VO_2 during aerobic training; $p<0.05$). In addition, TG had better quality of life and reduced depression rates (from 7 subjects with mild, moderate or severe depression to 1 post-training). In conclusion, this pilot data demonstrated that 16 weeks of CET increased muscle strength, and improved depression and quality of life indexes in a small sample of PLHIV.

Keywords HIV infection · Physical fitness · Body composition · HAART · Exercise

Resumen
El objetivo de este estudio fue evaluar los efectos de 16 semanas de entrenamiento combinado (CET) sobre la fuerza muscular, composición corporal, depresión, ansiedad y calidad de vida de las personas que viven con el VIH (PVHIV). Veintitrés participantes completaron el estudio, 14 en el grupo entrenado (TG) y 9 en el grupo control (CG). TG consistió en entrenamiento de resistencia y aeróbico tres veces por semana, mientras que el CG estuvo expuesto a actividades recreativas dos veces por semana. CET promovió una mayor fuerza muscular (25% en la fuerza general) y la capacidad aeróbica (+20% en la velocidad de entrenamiento y +23% en el VO2 durante el entrenamiento aeróbico; $p<0.05$). Además, TG tenía una mejor calidad de vida y tasas de depresión reducidas (de 7 sujetos con depresión leve, moderada o severa a 1 post entrenamiento). En conclusión, estos datos piloto demostraron que 16 semanas de CET aumentaron la fuerza muscular y mejoraron los índices de depresión y calidad de vida en una pequeña muestra de PVHIV.

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Introduction

The human immunodeficiency virus (HIV) is the etiologic agent of acquired human immunodeficiency syndrome, and is a chronic disease that weakens the immune system rendering the infected individual susceptible to opportunistic infections [1]. Currently, HIV can be successfully treated by antiretroviral therapy (ART), medications that restore the immune system and prevent HIV replication [2]. Indeed, ART dramatically reduced HIV-related mortality and morbidity but turned HIV into a chronic condition with associated comorbidities including cardiovascular disease, kidney impairment, dyslipidemia, bone loss and others [3, 4].

Muscle loss and reduced muscle strength have been recognized as important comorbidities associated to ART [5–7]. Muscle loss and weakness lead to functional disability, exercise limitation, increased risk of cardiovascular diseases, and reduced quality of life [8, 9]. In addition, these comorbidities and ART adverse effects may also be psychosocial stressors leading to depression and decreased quality of life, both of which can disrupt treatment and accelerate disease progression [10, 11].

Physical exercise can counterbalance both the adverse effects of ART and chronic HIV infection. Numerous benefits of physical exercise has been demonstrated in people living with HIV (PLHIV) including increased muscle mass and strength, and enhanced cardiorespiratory fitness, body composition, metabolic profile, psychological profile and overall health [12–15]. Combined exercise training (CET) is a novel and promising intervention for PLHIV, because it combines strength and aerobic exercises in the same training session providing significant cardiovascular and neuromuscular benefits [16]. Despite its potential benefits and increasing studies in PLHIV testing a CET intervention, recent reviews consistently confirmed the need for further studies in this area [15, 17–19]. Among the reasons cited, authors highlight the small amount of available studies and the significant sample heterogeneity [14, 17–20]. Further, some conclude that the available studies were conducted years ago, and that their results may not represent today's population, due to a shift in patient demographics and treatment [20, 21]. Finally, there is a concern about the low number of female participants in the studies, and an indication that equally balanced groups in terms of gender could increase the quality of future randomized controlled trials [12, 14, 20, 22]. Therefore, the aim of this study was to conduct a randomized clinical trial to evaluate the effect of 16 weeks of CET on muscle strength, body composition, depression, anxiety, and quality of life of PLHIV.

Methods

Experimental Design

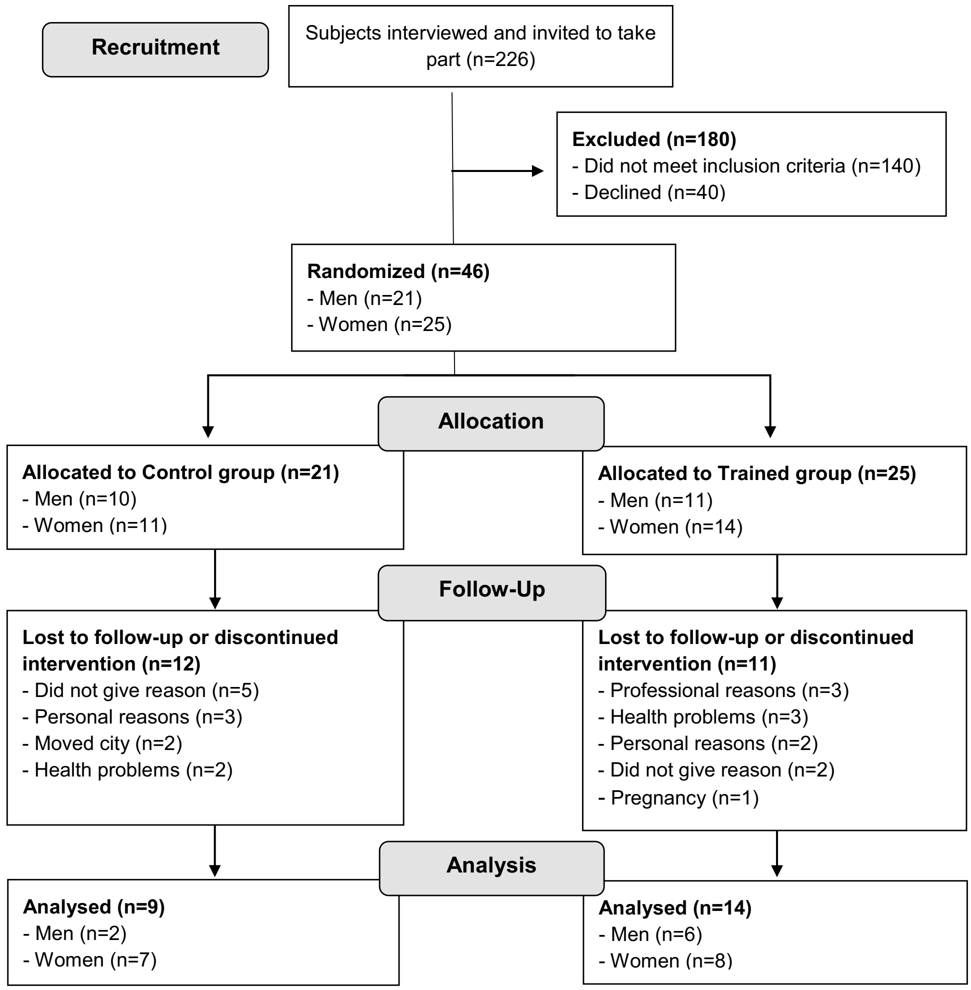
PLHIV taking ART for at least 1 year were invited to participate in a 16-week CET program (aerobic training + strength training). Forty-six subjects were initially randomized to the trained group (TG, $n=25$) or control group (CG, $n=21$). The numbers were generated by a random number generator (www.random.org) and placed in individual sealed and opaque envelopes. Men and women were randomized separately, to maintain the same proportion in each group. Given the nature of the intervention (physical exercise), subjects and trainers were not blinded. Evaluations were performed in the pre- and post-training periods (baseline and 16-weeks after baseline), and all the subjects who completed both data collection visits were included in analysis ($n=23$). For the pre- and post-training evaluations, subjects made six visits to the laboratory at each timepoint, on non-consecutive days (separated by 48 h) as follows: Visit 1) anthropometric, body composition, and isokinetic strength (1st session) assessments; Visit 2) anxiety, depression, quality of life, and isokinetic strength (2nd session) assessments; Visits 3, 4 and 5) dynamic muscle strength and dietary intake assessments.

Subjects

Subjects were recruited at the Hospital of the State University of Londrina and the Integrated Center for Infectious Diseases of Londrina, Brazil, through posters, flyers and by team members during clinical care. To be eligible, subjects must have had a documented HIV diagnosis, be between the ages of 18 and 60 years, and taking ART for at least 1 year. Subjects were excluded if they reported participation in a planned, structured and repetitive physical exercise program to condition any part of the body (i.e. load and volume progression, as well as fixed frequency and duration) in the last 6 months, had been taking hormones or anabolic steroids, had any systemic infection (e.g., influenza, pneumonia, throat infection) in the 30 days prior to enrollment, or had any other medical contraindication. The study was conducted at the State University of Londrina and was initiated after approval by the Ethics Committee for Research Involving Human Subjects of this university (#319.837) and Clinical Trials registering (#RBR-7hf8jw). Participation was voluntary, and all subjects were informed of the benefits and risks of the investigation prior to signing an informed consent document.

Forty-six subjects (21 men and 25 women) were enrolled in the study, but only 23 of them completed the post-training

Fig. 1 CONSORT flow diagram of participant recruitment and allocation



evaluations (TG, $n = 14$, 8 women; CG, $n = 9$, 7 women; drop-out rate of 50%) and were included in the analysis. The main causes for attrition were personal and professional reasons along with health problems not related to exercise training (Fig. 1). The TG subjects' adherence ranged from 67.4% (32 sessions) to 100% (48 sessions), with a mean of 87.4%, while the CG adherence ranged from 25.0% (8 sessions) to 65.6% (21 sessions), with a mean of 42.1%.

Training Protocol

The training protocol consisted of 16 weeks of CET, performed three times a week on non-consecutive days, and was organized in four stages with 4 weeks each as shown in Table 1. CET was supervised by experienced and licensed exercise physiologists, and each trainer was responsible for a maximum of three subjects. The order of execution (aerobic training or strength training first) was random, due to the equipment availability.

Aerobic training was performed on treadmills using heart rate monitors to control the desired cardiovascular intensity.

Table 1 Combined exercise training program for 16 weeks

Weeks	Aerobic training		Strength training		
	Duration (min)	Intensity	Exercises	Sets	Repetitions
1–4	15	50–60% HRR	6	2	12–15 MR
5–8	20	50–60% HRR	6	3	8–12 MR
9–12	20	60–65% HRR	6	3	8–12 MR
13–16	20	60–65% HRR	6	3	8–10 MR

HRR heart rate reserve, *MR* maximum repetitions

The aerobic training consisted in a continuous walk in the first 4 weeks that was increased progressively using heart rate reserve (HRR) as demonstrated in Table 1. Subjects were instructed to start jogging when it was necessary to keep the desired cardiovascular intensity. HRR was calculated at weeks 1, 5, 9 and 13 (the first weeks of each training stage) and was used to determine each subject's aerobic training prescription. To calculate the HRR, we used the predicted maximal heart rate (HRmax, 220 – age) and the resting heart rate (HRrest, which was obtained with the participants resting in a chair for 10 min, while recording the heart rate for the final 5 min). The target heart rate during training was calculated through the equation:

$$\text{Aerobic training heart rate} = (\text{HRmax} - \text{HRrest}) \times \text{intensity} + \text{HRrest}$$

where HRmax = predicted maximal heart rate; HRrest = resting heart rate.

Strength training was composed of bench press, leg press, pulldown, leg curl, arm curl, and sit-up exercises, performed in that order. At week 9, we replaced the pulldown and leg curl exercises with seated cable rows and hack squat, and modified the strength exercise order (subjects performed lower limbs exercises first and then upper limb exercises) both to increase training intensity [23]. Subjects used fixed loads through the sets (i.e. all the sets of an exercise performed with the same load), and the loads were consistent with the stipulated number of repetitions. Loads were adjusted weekly, based on the results obtained through the application of maximum repetitions tests [24]. Subjects also performed three sets of 20–30 repetitions of sit-ups at the end of every session. Rest time was 60 to 90 s between sets and 2–3 min between exercises. Exercise session duration ranged from 50 to 70 min. Subjects were instructed to not participate in any other exercises during the duration of the study.

The CG completed two recreational session meetings per week on nonconsecutive days. The meetings were composed of light activities such as stretching, recreational games and dancing. This control condition was designed to maintain contact with subjects during the training period to minimize attrition, without promoting physical fitness improvements.

Medical Characteristics

With their permission, medical records were obtained from the participants' health services and were used to abstract the following data: year of HIV diagnosis; latest measures of HIV viral load, CD4+, and CD8+ lymphocyte counts (average time between last exam date and beginning of training was 2.3 ± 1.6 months); year of initiation of ART; and the composition of the current ART regimen. These data were obtained in the pre-training period and were used descriptively.

Anthropometry and Body Composition

Total body mass was measured with an electronic Urano (Canoas, RS, Brazil) scale with resolution of 0.1 kg and height was measured with a stadiometer with 0.1 cm resolution. Body mass index (BMI) was calculated as body mass (kg) divided by height (m^2).

Lean and fat body mass were measured using bioelectrical impedance (Xitron® Hydra ECF/ICF 4200, Xitron Technologies, San Diego, USA), in accordance with the procedures described by Sardinha et al. [25]. Prior to completing the bioelectrical impedance, subjects were asked to fast for 12 h, not engage in any strenuous physical exercise, avoid foods or drinks containing caffeine in the last 24 h, urinate 30 min prior the test, and remove any metal accessories. The procedure was conducted with subjects laying in a supine position with their legs and arms apart, and four electrodes were placed on the right side of the body.

Fitness Variable Measurements

Dynamic muscle strength was assessed using the 1 repetition maximum test (1RM) for bench press, leg press and arm curl exercises. For each exercise, subjects warmed-up with light loads followed by 2 min of rest; subjects were submitted to three maximum repetition trials with three to 5 min of rest between them [5]. Tests were conducted on three nonconsecutive days. The execution technique of each exercise was standardized and monitored by an exercise physiologist to ensure proper and consistent execution. We reported the 1RM value of each exercise (bench press, leg press and arm curl) and also the 1RM total, which was obtained by adding up the values of the three exercises.

Isokinetic strength evaluation was carried out at speed of 60°/s for knee extension in the concentric mode on a Biodex® Multi-Joint System – PRO dynamometer (Biodex Medical Systems Inc., Shirley, USA), in accordance with procedures described by Terreri et al. [26]. After 5 min of warming up on a cycle ergometer in a self-selected load, participants were positioned and stabilized on the dynamometer chair. Test range was determined according to the range of motion of the subject that was being evaluated, and calibration and gravitational correction were performed. Before the test, the subjects performed four submaximal repetitions to familiarize themselves with the movement and testing procedures. The protocol consisted in a set of three repetitions performed bilaterally, and the choice of which leg to test first was made randomly. Verbal encouragement to motivate maximum effort during the test was consistent across subjects. Subjects first performed a familiarization session and then a testing session, which occurred after a minimum of 48 h after the familiarization session (time range 48 to 72 h) and at the same time of day. We reported the peak torque normalized by body mass and the mean power.

To determine the subjects' evolution during the CET program (Fig. 2), we calculated the velocity and the VO_2 in the aerobic training component, as well as the load and

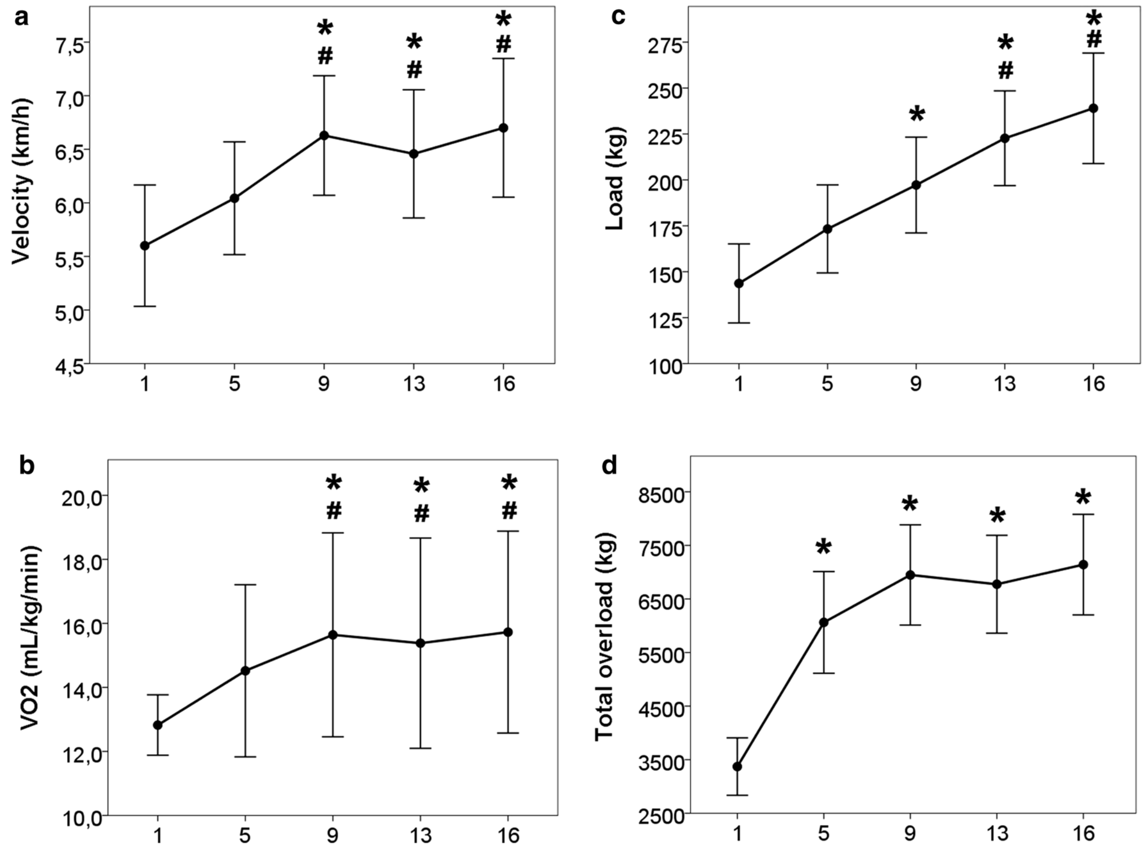


Fig. 2 Evolution of combined exercise training at weeks 1, 5, 9, 13 and 16. Bars represent 95% of the confidence interval. **a** Average velocity used in aerobic training, **b** oxygen consumption (VO_2) in aerobic training, **c** Total load used in strength training, **d** Total strength training overload (load x repetitions). *$p < 0.05$ versus week 1; $^{\#}p < 0.05$ versus week 5 by ANOVA one-way followed by Bonferroni post hoc test

the total overload in strength training. The velocity was the average used by all subjects. The VO_2 was estimated through the American College of Sports Medicine equations [27], which consist of summing the resting + horizontal + vertical components. The total load was obtained by summing the loads used in all exercises. The total overload was calculated by multiplying loads × repetitions. Moreover, as CET was divided into four stages with 4 weeks each, we examined changes during the first week of each stage (weeks 1, 5, 9 and 13) and in the last week of the CET program (week 16).

Anxiety, Depression and Quality of Life

Three validated and widely used questionnaires were used to measure indices of anxiety (the Beck Anxiety Inventory), depression (Beck Depression Inventory) and health-related quality of life (World Health Organization Quality of Life instrument, WHOQOL-HIV Bref). The WHOQOL-HIV is a multidimensional instrument related to a subject's perception about their quality of life in six domains: physical, psychological, level of independence, social relationships, environment and spirituality/religion/personal beliefs [28]. All questionnaires were administered by a licensed psychologist in their Portuguese versions [29–32] and were scored and interpreted based on the recommended scoring procedures.

Dietary Intake

A 24-h dietary recall was used to assess food intake, and the recalls were completed during interviews conducted by licensed nutritionists on 3 days, including 2 weekdays and 1 weekend day. The software DietPro 5.1 (A.S. Sistemas, Viçosa, MG, Brazil) was used to quantify the mean intake of energy and macronutrients.

Statistical Analyses

Data normality was checked through the Shapiro–Wilk test; Levene's test was used to analyze the homogeneity of variances; Independent *t* test was used to examine differences in baseline scores between CG and TG. Fitness parameters (aerobic training velocity, VO_2, total training load and overload) through 16-weeks of CET were compared using one-way analysis of variance (ANOVA), followed by Bonferroni post hoc test. To determine the effects of training in strength and body composition variables, the post-training values were compared between groups using an analysis of covariance (ANCOVA), where the post-training values were considered dependent variables, the group allocation was the independent variable, and the baseline values were the covariates. Additionally, the magnitude of the differences was calculated from the effect sizes using the Cohen method, where a Cohen's d value lower than 0.2 was classified as 'trivial', between 0.2 and 0.49 was 'small', between 0.5 and 0.79 was 'medium', and 0.8 and higher was 'large' [33]. Depression and anxiety scores were compared using Fisher's exact test. Statistical significance was set at $p \leq 0.05$, and data was analyzed using a SPSS for Windows Version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Participants were 45.5 ± 7.2 years old, had a BMI of 26.0 ± 5.7 kg/m^2, and were living with HIV for 13.5 ± 4.2 years. Regarding immunologic characteristics, CD4+ lymphocytes count was 712.4 ± 472.3 cells/mm^3, CD8+ lymphocytes count was 1157.3 ± 582.3 cells/mm^3, and approximately 80% of the subjects were undetectable for HIV viral load (< 40 copies/mm^3). In addition, participants were taking ART for 12.1 ± 4.7 years, and the most common schemes were: (a) Nucleoside Reverse Transcriptase Inhibitor + Protease Inhibitor ($n = 13$), and (b) Nucleoside Reverse Transcriptase Inhibitor + Non-nucleoside Reverse Transcriptase Inhibitor ($n = 12$). There were no significant differences ($p > 0.05$) between intervention groups on the above cited variables. Moreover, there were no differences on any of the baseline values (muscle strength, body composition, anxiety and depression rates, quality of life, and dietary intake; $p > 0.05$).

Figure 2 presents the evolution of speed and VO_2 in aerobic training along with total load and overload of strength training during the CET program. The average aerobic training speed increased significantly ($p < 0.05$) from week 1 (5.6 km/h) to 9 (6.6 km/h; + 18%). There was also a significant increase in VO_2 during aerobic training from week 1 (12.8 mL/kg/min) to 9 (15.6 mL/kg/min; + 22%). Considering strength training, the total training load increased ($p < 0.05$) progressively from week 1 (144 kg) to 9 (197 kg; + 37%), and from week 5 (173 kg) to 13 (222 kg; + 28%). The total strength training overload at weeks 5 (6062 kg, + 80%), 9 (6948 kg, + 106%), 13 (6774 kg, + 101%) and 16 (7141 kg, + 112%) were higher ($p < 0.01$) than week 1 (3371 kg).

Figure 3 demonstrates the comparisons of the dynamic and isokinetic strength variables for CG and TG in the pre- and post-training periods. CET significantly increase ($p < 0.05$) dynamic strength measured using chest press, leg press and arm curl, which did not occur in CG. Cohen´s coefficient demonstrated a large increase for bench press (Pre = 36.9 vs. Post = 41.3 kg, + 12%, Cohen´s $d = 1.00$), leg press (Pre = 149.6 vs. Post = 193.8 kg, + 30%, Cohen´s d = 2.84), arm curl (Pre = 24.8 vs. Post = 26.9 kg, + 8%, Cohen´s $d = 1.37$) and 1RM total (Pre = 211.3 vs. Post = 262.0 kg, + 24%, Cohen´s d = 2.88). No significant differences were found for peak torque and mean power in the isokinetic test.

Despite no significant changes in body composition ($p > 0.05$; Table 2), the CG demonstrated an increase in fat deposits (11% increase in % of body fat considered 'large' according to Cohen's d value) which was not observed in the TG.

Table 3 presents the classification of WHOQOL-HIV and Beck Inventories for depression and anxiety scores determined for the CG and the TG in the pre- and post-training periods. CET significantly improved ($p < 0.05$) the quality of life scores in the level of independence domain, which did not occur in the CG. CET also significantly decreased ($p < 0.05$) depression rates. Six (85%) of the trained PLHIV have their depression score reduced from mild, moderate or severe to minimal. No significant difference was observed for anxiety scores (p = 0.06).

Lastly, there were no differences ($p > 0.05$) between groups regarding energy and macronutrients (carbohydrate, protein and lipid values) intake, indicating that the dietary pattern of subjects in both groups was similar, and it had little influence on the results presented.

Discussion

Our results demonstrated that 16 weeks of CET increased muscle strength, and improved quality of life and depression scores among this small sample of PLHIV. In addition, PLHIV showed improvements in strength and aerobic training components during training sessions, demonstrating better exercise capacity at the end of the program. The high drop-out rate observed in this study was a concern (drop-out rate of 50%), but this pilot data demonstrates the potential of CET to act as a complementary strategy to HIV treatment by minimizing adverse effects caused by ART.

Functional decline including frailty is recognized as an important comorbidity associated with ART use [34]. It has been demonstrated that functional decline, sarcopenia and frailty may occur prematurely among relatively young

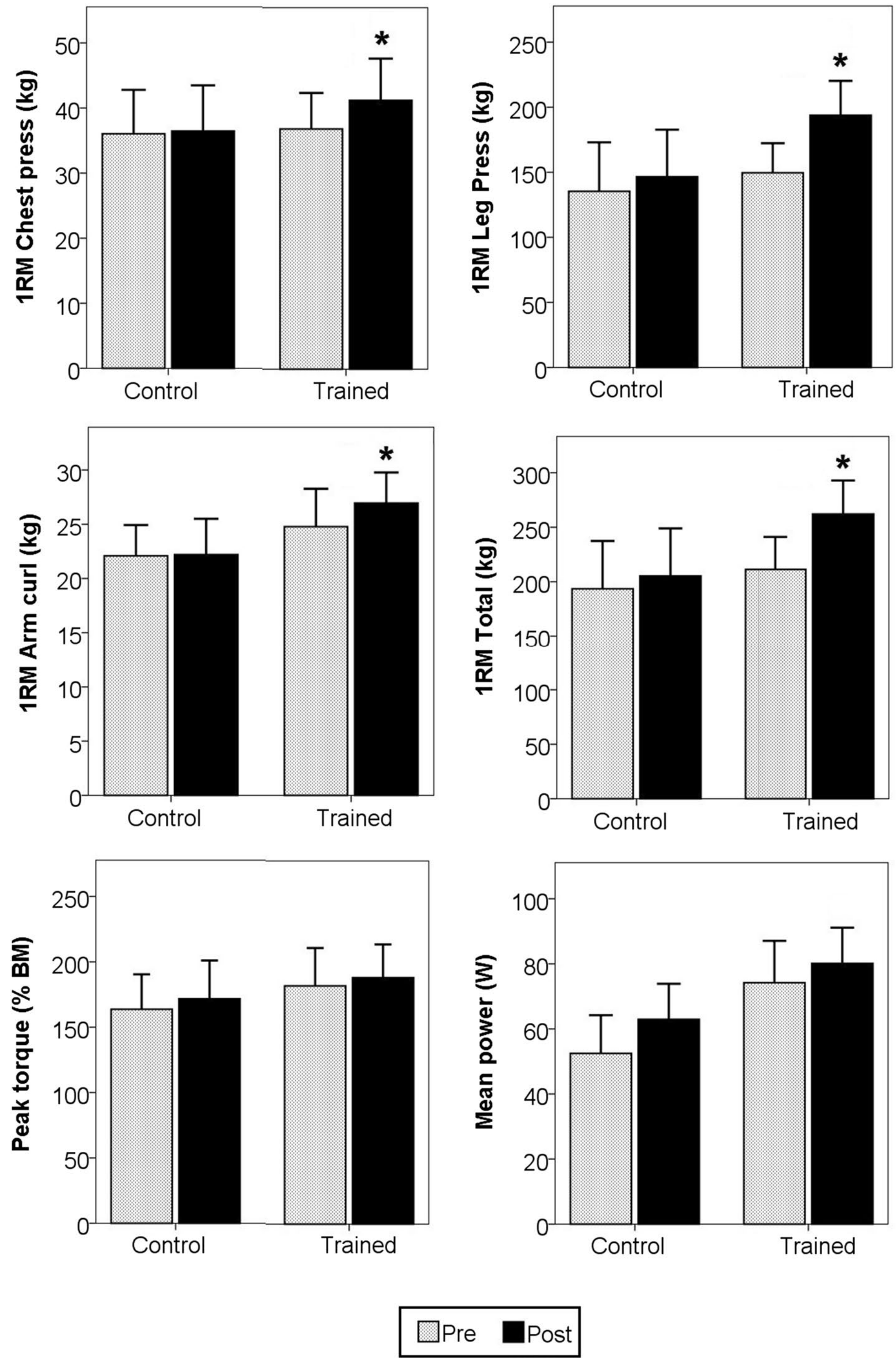


Fig. 3 Dynamic and isokinetic strength determined pre and post 16 weeks of combined exercise training. Lines represent 95% of the confidence interval. *$p < 0.05$ between groups (ANCOVA) at the post-training period, when controlled for the baseline value. 1RM = 1 Repetition Maximum Test; (% BM) = absolute values of peak torque corrected by body mass and expressed as percentage of this

PLHIV compared to people living without the infection [35, 36]. This early muscle mass and muscle strength losses lead to frailty in PLHIV, and has been related to ART-mediated muscle mitochondrial toxicity which culminates in functional impairment and increased mortality [34–36]. Oliveira et al. [5] studied 44 PLHIV and 25 people living without the infection, and found that HIV infection was associated with impaired dynamic and isokinetic strength. Richert et al. [37] analyzed the *French Agency for AIDS and Hepatitis Research CO3 Aquitaine Cohort* ($n = 324$, 89% on ART) and demonstrated that half of their subjects performed poorly on locomotor tests related to lower limb muscle strength compared to data established in the general population. Also, aerobic capacity was reduced in PLHIV taking ART compared to predicted values [38].

Our data demonstrated that participants evolved in strength and aerobic training capacity over a short period

Table 2 Comparison of body composition variables between pre- and post-training periods

Variables	Control group ($n=9$)			Trained group ($n=14$)		
	Pre	Post	Δ% (ES)	Pre	Post	Δ% (ES)
Body mass (kg)	62.7 ± 16.4	63.8 ± 16.5	1.8 (0.85)	67.9 ± 9.5	67.7 ± 9.4	− 0.4 (0.14)
BMI (kg/m^2)	25.6 ± 5.0	25.9 ± 5.0	1.6 (0.56)	25.9 ± 3.4	25.7 ± 3.5	− 0.5 (0.20)
LBM (kg)	43.2 ± 12.1	42.3 ± 11.9	− 2.2 (0.59)	47.9 ± 8.3	47.9 ± 9.0	0.5 (0.03)
Fat mass (kg)	19.5 ± 9.8	21.5 ± 9.2	13.5 (1.08)	20.1 ± 8.1	19.7 ± 7.3	− 3.5 (0.10)
Fat %	30.4 ± 10.8	33.2 ± 9.9	11.4 (1.05)	29.2 ± 10.7	28.9 ± 9.8	− 3.9 (0.04)

Data are presented as mean ± standard deviation

ES effect size (Cohen´s *d*), *BMI* body mass index, *LBM* lean body mass

Table 3 Comparison of quality of life scores (WHOQOL-HIV Bref) and Beck Inventory for depression and anxiety classification between pre- and post-training periods

	Control group ($n=9$)			Trained group ($n=14$)		
	Pre	Post	Δ% (ES)	Pre	Post	Δ% (ES)
Quality of life						
Physical	12.1 ± 2.1	11.7 ± 2.1	− 1.9 (0.21)	12.0 ± 2.2	12.1 ± 1.8	3.5 (0.06)
Psychological	10.8 ± 3.1	11.5 ± 3.3	10.9 (0.25)	12.7 ± 1.8	12.9 ± 1.6	2.8 (0.14)
Level of independence	12.4 ± 3.2	12.2 ± 2.1	− 1.8 (0.10)	13.5 ± 2.5	14.7 ± 2.1*	10.9 (0.73)
Social relationships	14.1 ± 2.9	13.9 ± 2.9	− 0.3 (0.08)	14.9 ± 2.4	15.0 ± 2.4	1.9 (0.07)
Environment	11.9 ± 2.8	11.5 ± 3.0	− 3.1 (0.24)	12.9 ± 2.7	13.6 ± 2.6	7.7 (0.36)
Spirituality	13.2 ± 4.7	12.8 ± 3.8	− 2.9 (0.16)	10.8 ± 3.2	9.6 ± 1.9	− 4.6 (0.39)
Anxiety						
Minimal anxiety (%)	2 (22.2)	4 (44.4)	$p=0.31$	6 (42.9)	11 (78.6)	p = 0.06
Mild, moderate or severe anxiety (%)	7 (77.8)	5 (55.6)		8 (57.1)	3 (21.4)	
Depression						
Minimal depression (%)	2 (22.2)	5 (55.6)	$p=0.17$	7 (50.0)	13 (92.9)	p = 0.01
Mild, moderate or severe depression (%)	7 (77.8)	4 (44.4)		7 (50.0)	1 (7.1)	

*$p<0.05$ between groups (ANCOVA) at the post-training period, when controlled for the baseline value (continuous variables). *ES* effect size (Cohen´s *d*). Data are presented as mean ± standard deviation for quality of life scores, and as absolute (relative) cases for anxiety and depression scores

of time, when comparing the beginning of CET with the subsequent training sessions. CET has become the exercise regimen of choice against chronic disease comorbidities because it combines strength, aerobic capacity enhancements and significant changes in body composition in a relative short period of time [16]. This is particularly relevant since decreased levels of muscle strength and aerobic capacity are associated with overall health and increased risk of mortality and hospitalization [39–41]. Studies have also demonstrated that the risk and the cost of hospitalization among PLHIV progressively increase in the presence of one or more comorbidities (e.g. dyslipidemia, hypertension, as well as renal, liver, and chronic pulmonary comorbidities) [42]. Thus, is reasonable to affirm that CET is a novel and promising tool to counteract ART-associated comorbidities and to reduce the cost of PLHIV treatment. Noteworthy, although the CG participants attended a few recreational sessions during our study, it was insufficient to promote strength gains or beneficial changes in other variables.

The improvements in physical fitness observed in our study appear to be followed by positive maintenance of body fat mass. Even though it was not statistically significant, the results indicate a relevant clinical importance. Today, PLHIV taking ART often present with decreased muscle loss, but also experienced several metabolic and lipid disorders, that together can lead to an increased risk for cardiovascular disease [43]. Similar to the general population, overweight or obesity has growing among PLHIV. As an example in the same ethnic group, Kroll et al. [44] demonstrated in a Brazilian cohort of 345 PLHIV, 8.3% were classified as obese, 34.2% were overweight, and 5.2% were malnourished. Thus, our intervention also promoted slightly beneficial effects on fat mass (compared to the 11% increase in % of body fat observed in CG). We believe that body composition analysis in our study was limited by the use of bioelectrical impedance, which is not the most accurate measurement technique. A similar intervention study showed a reduction in body fat measured using dual energy X-ray absorptiometry [45]. Future research using larger sample sizes and more precise measurement techniques (i.e., dual energy X-ray absorptiometry) is needed to evaluate the effects of CET interventions on body fat mass in PLHIV.

The CET also improved psychosocial indicators including health-related quality of life and depression. Regarding anxiety, five (62%) of the trained PLHIV have their anxiety score reduced from mild, moderate or severe to minimal, with a *p*-value of 0.06, which may be worthy of further investigation in subsequent more highly powered studies. PLHIV deal with challenging psychosocial stressors that can lead to the development of depression and anxiety. In a systematic review, Lowther et al. [46] demonstrated depression prevalence rates between 34 to 42% and 21 to 40% for anxiety, indicating that PLHIV present higher rates of depression and anxiety compared to individuals with other chronic diseases, such as cancer, diabetes and multiple sclerosis. In the general population, the prevalence of depression ranges from 1.3 to 9.7%, and anxiety ranges from 4.4 to 18.1% [46]. Such psychosocial problems among PLHIV are associated with low adherence to ART, which can lead to treatment failure and to disease progression [10, 46], and also may be associated with low adherence to exercise [47]. In contrast, even small increases in muscle strength and aerobic capacity together with changes in body composition may improve PLHIV's self-confidence. Also, engaging in group-based exercise may give participants opportunities to establish contact with other PLHIV and to provide additional peer support. The supportive atmosphere among the participants could provide a place where they can enjoy themselves without fear of stigma and rejection, which reduces social isolation and hopelessness [22]. Thus, our results demonstrated that a group-based CET may help to minimize the effects of stigma, to promote positive social relationships, and to improve subjects' independence and quality of life, aspects that may improve ART treatment adherence.

Attrition is the main limitation of the present study (dropout rate of 50%). The reduced sample may have compromised the statistical power to detect differences between groups specially regarding lean and body fat changes. Attrition has been demonstrated to be common in interventions involving PLHIV, with an overall drop-out rate of 29.3%, which is higher than other populations with chronic diseases [48]. Causes for non-adherence to exercise among PLHIV are poorly described, but psychological characteristics appear to differentiate between adherent and non-adherent patients; some results indicate that those with better perceived well-being are more likely to show interest in further improvements [47]. In our sample, it is possible that the lack of remuneration and/or logistical barriers may have impacted subjects' compliance and adherence. Given the high attrition rate, we performed a per-protocol analysis [49]. Despite this pilot data demonstrates the effectiveness of CET to improve some health outcomes, future studies should focus attention on improving subjects' adherence and retention to this promising exercise format. Also, research is needed to replicate findings from this study in larger, well-powered samples.

Our study also had several noteworthy strengths that must be considered. First, despite the increased CET research, different reviews highlight the few available studies and the lower quality attributed to these studies, since some of them fail to include a randomized control group [14, 17–20]. Also, studies include a lower proportion of female participants [12, 14, 20, 22]. Thus, we tried to address these issues in our protocol. Moreover, we strongly controlled exercise volume and load progression along the intervention, to keep exercise stimulus challenging and effective during the entire training period [23].

In conclusion, this pilot data demonstrated that 16 weeks of CET increased muscle strength, and improved depression and quality of life indexes in a small sample of PLHIV, showing its potential to ameliorate important disturbances experienced by this population. Also, CET appears to be an engaging exercise model for PLHIV, since it combines strength and aerobic exercises in same training session, generating physiological adaptations from these two types of exercise. Thus, CET is a safe and an effective complementary intervention for the health promotion of PLHIV.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Imran M, Manzoor S, Saalim M, et al. HIV-1 and hijacking of the host immune system: the current scenario. APMIS. 2016;124:817–31.
2. Gueler A, Moser A, Calmy A, et al. Life expectancy in HIV-positive persons in Switzerland. AIDS. 2016;31:1.
3. Eyawo O, Franco-Villalobos C, Hull MW, et al. Changes in mortality rates and causes of death in a population-based cohort of

persons living with and without HIV from 1996 to 2012. BMC Infect Dis. 2017;17:174.
4. Smit M, Brinkman K, Geerlings S, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. Lancet Infect Dis. 2015;15:810–8.
5. Oliveira VHF, Wiechmann SL, Narciso AMS, Webel AR, Deminice R. Muscle strength is impaired in men but not in women living with HIV taking antiretroviral therapy. Antivir Ther. 2018. https://doi.org/10.3851/IMP3159.
6. Aziz SAA, Mcstea M, Bashah NSA, et al. Assessment of sarcopenia in virally suppressed HIV-infected Asians receiving treatment. AIDS. 2018;32:1.
7. Echeverría P, Bonjoch A, Puig J, et al. High prevalence of sarcopenia in HIV-infected individuals. Biomed Res Int. 2018. https://doi.org/10.1155/2018/5074923.
8. Mhariwa PC, Myezwa H, Galantino ML, Maleka D. The relationship between lower limb muscle strength and lower extremity function in HIV disease. S Afr J Physiother. 2017;73:1–6.
9. Erlandson KM, Wu K, Koletar SL, et al. Association between frailty and components of the frailty phenotype with modifiable risk factors and antiretroviral therapy. J Infect Dis. 2017;215:933–7.
10. Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. JAIDS J Acquir Immune Defic Syndr. 2011;58:181–7.
11. Langebeek N, Kooij KW, Wit FW, et al. Impact of comorbidity and ageing on health-related quality of life in HIV-positive and HIV-negative individuals. AIDS. 2017;31:1471–81.
12. O'Brien KK, Tynan A, Nixon SA, Glazier RH. Effectiveness of progressive resistive exercise (PRE) in the context of HIV: systematic review and meta-analysis using the Cochrane Collaboration protocol. BMC Infect Dis. 2017;17:268.
13. Dirajlal-Fargo S, Webel AR, Longenecker CT, et al. The effect of physical activity on cardiometabolic health and inflammation in treated HIV infection. Antivir Ther. 2015;20:237–45.
14. Pérez Chaparro CGA, Zech P, Schuch F, Wolfarth B, Rapp M, Heiβel A. Effects of aerobic and resistance exercise alone or combined on strength and hormone outcomes for people living with HIV. A meta-analysis. PLoS ONE. 2018;13:e0203384.
15. Kamitani E, Sipe TA, Higa DH, Mullins MM, Soares J. Evaluating the effectiveness of physical exercise interventions in persons living with HIV: overview of systematic reviews. AIDS Educ Prev. 2017;29:347–63.
16. Farias D, Dutra M. Combined exercise in HIV treatment: prospects for non pharmacological therapy. J AIDS Clin Res. 2016;7:6–8.
17. Ibeneme SC, Irem FO, Iloanusi NI, et al. Impact of physical exercises on immune function, bone mineral density, and quality of life in people living with HIV/AIDS: a systematic review with meta-analysis. BMC Infect Dis. 2019;19:340.
18. Gomes Neto M, Conceição CS, Carvalho VO, Brites C. Effects of combined aerobic and resistance exercise on exercise capacity, muscle strength and quality of life in HIV-infected patients: a systematic review and meta-analysis. PLoS ONE. 2015;10:e0138066.
19. Lopez J, Richardson E, Tiozzo E, et al. The effect of exercise training on disease progression, fitness, quality of life, and mental health in people living with HIV on ART: a systematic review. J Clin Transl Res. 2015;1:129–39.
20. Nosrat S, Whitworth JW, Ciccolo JT. Exercise and mental health of people living with HIV: a systematic review. Chronic Illn. 2017;13:299–319.
21. Jaggers JR, Hand GA. Health benefits of exercise for people living with HIV. Am J Lifestyle Med. 2016;10:184–92.
22. O'Brien KK, Tynan A-M, Nixon SA, Glazier RH. Effectiveness of aerobic exercise for adults living with HIV: systematic review and meta-analysis using the Cochrane Collaboration protocol. BMC Infect Dis. 2016;16:182.
23. Ratamess NA, Alvar BA, Evetoch TK, et al. American college of sports medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sport Exerc. 2009;41:687–708.
24. Ribeiro AS, Avelar A, Nascimento MA, et al. What is the actual relative intensity of a resistance training program for men and women ? Isokinet Exerc Sci. 2014;22:217–24.
25. Sardinha LB, Lohman TG, Teixeira PJ, Guedes DP, Going SB. Comparison of air displacement plethysmography with dual-energy X-ray absorptiometry and 3 field methods for estimating body composition in middle-aged men. Am J Clin Nutr. 1998;68:786–93.
26. Terreri ASAP, Greve JMD, Amatuzzi MM. Avaliação isocinética no joelho do atleta. Rev Bras Med do Esporte. 2001;7:170–4.
27. American College of Sports Medicine. ACSM'S guidelines for exercise testing and prescription. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2013.
28. World Health Organization. WHOQOL-HIV instrument users manual: scoring and coding for the WHOQOL-HIV instruments. Geneva: World Health Organization; 2002.
29. Beck A, Steer R. Beck Anxiety Inventory Manual. San Antonio: Psychological Corporation; 1993.
30. Gorenstein C, Andrade L. Validation of a Portuguese version of the Beck Depression Inventory and the State-Trait Anxiety Inventory in Brazilian subjects. Braz J Med Biol Res. 1996;29:453–7.
31. Zimpel RR, Fleck MP. Quality of life in HIV-positive Brazilians: application and validation of the WHOQOL-HIV, Brazilian version. AIDS Care. 2007;19:923–30.
32. Beck A, Steer R, Brown G. Manual for Beck Depression Inventory II (BDI-II). San Antonio: Psychological Corporation; 1996.
33. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale: Lawrence Erlbaum Associate; 1988.
34. Desquilbet L, Jacobson LP, Fried LP, et al. HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. J Gerontol Ser A Biol Sci Med Sci. 2007;62:1279–86.
35. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis. 2011;53:1120–6.
36. Pathai S, Bajillan H, Landay AL, High KP. Is HIV a model of accelerated or accentuated aging? J Gerontol Ser A Biol Sci Med Sci. 2014;69:833–42.
37. Richert L, Dehail P, Mercié P, et al. High frequency of poor locomotor performance in HIV-infected patients. AIDS. 2011;25:797–805.
38. Gomes Neto M, Conceicao CS, Ogalha C, Brites C. Aerobic capacity and health-related quality of life in adults HIV-infected patients with and without lipodystrophy. Braz J Infect Dis. 2016;20:76–80.
39. Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol Med Sci. 2006;61:72–7.
40. Cawthon PM, Fox KM, Grandra SR, et al. Do muscle mass, muscle density, strength and physical function similarly influence risk of hospitalization in older adults? J Am Geriatr Soc. 2009;57:1411–9.
41. Kokkinos P, Myers J. Exercise and physical activity: clinical outcomes and applications. Circulation. 2010;122:1637–48.
42. Cammarota S, Citarella A, Manzoli L, Flacco ME, Parruti G. Impact of comorbidity on the risk and cost of hospitalization in HIV-infected patients: real-world data from Abruzzo Region. Clin Outcomes Res. 2018;10:389–98.
43. Giannarelli C, Klein RS, Badimon JJ. Cardiovascular implications of HIV-induced dyslipidemia. Atherosclerosis. 2011;219:384–9.

44. Kroll AF, Sprinz E, Leal SC, Labrêa MDG, Setúbal S. Prevalence of obesity and cardiovascular risk in patients with HIV/AIDS in Porto Alegre, Brazil. Arq Bras Endocrinol Metabol. 2012;56:137–41.
45. Guariglia DA, Pedro RE, Deminice R, Rosa FT, Peres SB, Franzói De Moraes SM. Effect of combined training on body composition and metabolic variables in people living with HIV: a randomized clinical trial. Cytokine. 2018;111:505–10.
46. Lowther K, Selman L, Harding R, Higginson IJ. Experience of persistent psychological symptoms and perceived stigma among people with HIV on antiretroviral therapy (ART): a systematic review. Int J Nurs Stud Elsevier Ltd. 2014;51:1171–89.
47. Petróczi A, Hawkins K, Jones G, Naughton DP. HIV patient characteristics that affect adherence to exercise programmes: an observational study. Open AIDS J. 2010;4:148–55.
48. Vancampfort D, Mugisha J, Richards J, et al. Dropout from physical activity interventions in people living with HIV: a systematic review and meta-analysis. AIDS Care. 2017;29:636–43.
49. Armijo-Olivo S, Warren S, Magee D. Intention to treat analysis, compliance, drop-outs and how to deal with missing data in clinical research: a review. Phys Ther Rev. 2009;14:36–49.