

**REVIEW**


---

**THE EFFECTS OF AN EXERCISE PROGRAM ON THE  
RESPONSE OF CD4<sup>+</sup> AND CD8<sup>+</sup> T LYMPHOCYTES  
IN PEOPLE LIVING WITH HIV/AIDS (PLWHA): A  
SYSTEMATIC REVIEW**

---

*Ilva Lana Balieiro Capela<sup>1</sup>, Luciana Santiago de Oliveira<sup>1</sup>, Andressa Karoline Pinto de Lima Ribeiro<sup>2</sup>, Antonio Carlos Rosário Vallinoto<sup>1,3</sup> and Izaura Maria Vieira Cayres Vallinoto<sup>1,3</sup>*

**ABSTRACT**

People living with HIV and AIDS (PLWHA) have decreased functional capacity, muscle strength and quality of life. Furthermore, HIV/AIDS can cause some adverse effects and long-term problems, such as sarcopenia and some peripheral neuropathies. A common practice among the healthy population that helps to modify these risk factors is to practice of some kind of exercise, such as aerobic and resistance exercises. The objective of this review is to assess the possible effects of exercise on the increase in CD4<sup>+</sup> and/or CD8<sup>+</sup> T lymphocytes among PLWHA. The LILACS, IBECs, PubMed/MEDLINE, Cochrane Library, SciELO, PEDro, ScienceDirect and Bireme databases were systematically searched for randomized controlled trials. The following descriptors were used in the search in English, Portuguese and Spanish: HIV, physical functional performance, resistance training, and aerobic exercise. The methodological quality of the studies was evaluated using the PEDro scale. The data were read, analyzed, extracted, and synthesized. Of the 3,319 studies consulted, only five met the inclusion criteria. A synthesis of the five selected studies was performed, all of which were randomized controlled trials. It was concluded that aerobic and/or resistance exercise protocols have a positive effect on immunity (CD4<sup>+</sup> and/or CD8<sup>+</sup> T lymphocytes and TNF- $\alpha$ ) and on the metabolic/ biochemical profile of PLWHA.

**KEY WORDS:** HIV; AIDS; CD4; CD8; exercise.

1. Graduate Program in Biology of Infectious and Parasitic Agents, Institute of Biological Sciences, Federal University of Pará, Belém, Pará, Brazil.

2. Graduate Program in Diabetes Care and Clinical Research, João de Barros Barreto University Hospital, Federal University of Pará, Belém, Pará, Brazil.

3. Laboratory of Virology, Institute of Biological Sciences, Federal University of Pará, Belém, Pará, Brazil.

Ilva Lana Balieiro Capela ORCID: <https://orcid.org/0000-0003-1891-708X>; Luciana Santiago de Oliveira ORCID: <https://orcid.org/0000-0002-2421-0649>; Andressa Karoline Pinto de Lima Ribeiro ORCID: <https://orcid.org/0000-0002-7981-938X>; Antonio Carlos Rosário Vallinoto ORCID: <https://orcid.org/0000-0003-1135-6507>; Izaura Maria Vieira Cayres Vallinoto ORCID: <https://orcid.org/0000-0003-1408-8384>

Corresponding author: Izaura Maria Vieira Cayres Vallinoto. E-mail: [ivallinoto@ufpa.br](mailto:ivallinoto@ufpa.br)

Received for publication: 20/3/2023. Reviewed: 24/6/2023. Accepted: 4/7/2023.

## INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) was first described in 1981; it is associated with the presence of a novel retrovirus, human immunodeficiency virus (HIV), and its discovery was a milestone in the infectious diseases' history (Barré-Sinoussi et al., 1983). The HIV pandemic is a dynamic and unstable phenomenon of global importance whose occurrence in different regions of the world depends on individual and collective human behavior, among other determinants (Gallo, 2021; UNAIDS, 2021; Brazier et al., 2023).

According to Joint United Nations Program on HIV/AIDS (UNAIDS) data, as of June 2021, approximately 77.5 million people worldwide have been infected with HIV. Since the beginning of the pandemic, 34.7 million people have died from AIDS-related diseases. In total, there were approximately 1.5 million new HIV infections in the world in 2020 (UNAIDS, 2021). In Brazil, from 2007 to June 2020, 342,459 cases of HIV infection were reported in the Notifiable Diseases Information System (SINAN), with 152,029 (44.4%) cases in the Southeast region, 68,385 (20.0%) in the South region, 65,106 (19.0%) in the Northeast region, 30,943 (9.0%) in the North region, and 25,966 (7.6%) in the Center-West region. During this same period, a total of 237,551 (69.4%) cases were reported in men, and 104,824 (30.6%) cases were reported in women. In 2019, the sex ratio for HIV cases was 2.6 (M:F), i.e., 26 men for every 10 women (Brazil, 2019).

Although advances in the treatment of HIV and AIDS have reduced the number of AIDS-related cases and deaths worldwide, the caseload of novel HIV infections has remained relatively stable, resulting in a continued increase in overall prevalence. In total, 1.7 million new infections occurred worldwide. Since the discovery of antiretroviral therapy (ART), the life expectancy of people living with HIV/AIDS (PLWHA) has nearly tripled from the onset of new diagnoses (UNAIDS, 2021).

PLWHA have decreased functional capacity, muscle strength, quality of life, and, consequently, deterioration of cardiorespiratory fitness. Despite the improvements in the patients' health provided by antiretroviral therapy (ART), HIV/AIDS can also cause some adverse effects and long-term problems in PLWHA, such as sarcopenia and some peripheral neuropathies. Thus, HIV/AIDS infection is a multidimensional condition that can affect the functional capacity of these individuals and cause long-term disabilities in this population (Chetty et al., 2020).

The practice of physical activities, such as Pilates exercises, has been shown to have an effect on the immune response, reducing proinflammatory cytokines in people living with human T-lymphotropic virus and improving the individual's quality of life (Klautau et al. 2020). Recently, Lenask et al. (2023) showed that in females, the antigen processing and presentation pathway

with MHC II signaling was blocked by physical activity. Lim et al. (2023) concluded that in patients with diabetes, a modest level of physical activity may need to be maintained to reduce the risk of pneumonia. Additionally, Murugathasan et al. (2023) suggested that chronic moderate exercise can influence the inflammatory responses of macrophages by reprogramming their metabolic and epigenetic landscape.

Gomes et al. (2010) demonstrated the efficacy of exercise on the physiological and immunological functions of PLWHA. Aerobic and/or resistance exercises provide greater benefits to this population, with the added bonus of not presenting the toxicity that is generated by drugs and without the adverse effects of pharmacological interventions.

This systematic review was conducted to describe the current knowledge on the use of exercise from well-defined protocols as a way to help increase the number of these cells, which are important for the immune system of PLWHA. The information generated may be useful for researchers, professionals and policymakers in the development and implementation of treatment methods combined with ART to assist in the treatment of PLWHA.

## MATERIAL AND METHODS

### *Study registration*

This systematic review was registered in the PROSPERO database under the number CRD42021261512.

### *Eligibility criteria for the literature search*

Studies that evaluated the effects of resistance and/or aerobic exercise based on the PICOS (population, intervention, comparison, outcomes, study) framework were included: (P) People living with HIV/AIDS, (I) Practicing Exercise, (C) People living with HIV/AIDS and not practicing an exercise protocol, (O) Increased CD4<sup>+</sup>/CD8<sup>+</sup> T lymphocyte count, (S) Randomized clinical trials.

### *Data sources and search strategy*

The following electronic databases were searched: LILACS, IBECS, PubMed/MEDLINE, Cochrane Library, SciELO, PEDro, ScienceDirect, and BIREME (Table 1). A reference lists of the included studies were also manually searched. Scientific articles written in English, Portuguese and Spanish were included. There were no restrictions regarding the year of publication or study type. The search was conducted from May 1, 2021, to June 30, 2021.

*Table 1.* Summary of the descriptors used in the search strategy.

Data source	Descriptors
LILACS PubMed/MEDLINE BIREME SciELO	((HIV) or (acquired immunodeficiency syndrome) or (serodiagnóstico del sida) or (sorologia da aids)) and ((physical functional performance) or (rendimiento físico funcional) or (desempenho físico funcional)) and ((exercício físico) or (ejercicio) or (exercise) or (exercises) or (physical activity) or (activities physical) or (activity physical) or (physical activities))
Cochrane Library PEDro ScienceDirect IBECS	HIV and physical functional performance and physical activity

### *Study selection and data collection*

A four-stage study selection process was done: identification, selection, eligibility, and inclusion. The identification stage included all studies found during the search process. During this stage, the titles and abstracts of all identified studies were evaluated; those that met the eligibility criteria were included, while all others were excluded. In the eligibility stage, the full texts of the articles were read to confirm that they could be included in the study, and an eligibility form that contained the established inclusion criteria was used to record the reasons for exclusion at this stage. The inclusion stage contained the studies that were used in the systematic review. A consensus meeting was held between the authors to begin data collection from the selected studies. During the selection process, the articles were entered into different reference managers, which were used according to the familiarity of each author. Zotero was used by the first evaluator, and Mendeley was used by the second evaluator.

### *Data extraction*

During the data extraction process, a standard clinical form was designed to well-defined extraction from the selected studies. The following data were extracted into the form created by the authors: title, first author, country, PEDro score, age, study design, sample, use of ART, time on ART, type of intervention, variables studied, control group, outcome and results.

## *Methodological quality assessment*

The methodological quality of each study was analyzed based on the PEDro scale, which is a specific database for studies that investigate the effectiveness of physical therapy interventions. Most of its criteria are based on the Delphi scale and aim to assist users of the PEDro database regarding the methodological quality of randomized clinical trials and to assess the statistical description, that is, whether the study contains minimal statistical information so that the results can be interpreted (Shiwa et al., 2011).

The PEDro scale has a total of 11 evaluation criteria and includes two additional criteria that were not included in the Delphi scale. The final score was given by summing the number of criteria that were classified as satisfactory (1 point) and unsatisfactory (0 points) for criteria 2 to 11. Criterion 1 is not considered for the final score because it is an item that verifies the external validity of the study. The final score ranges between 0 and 10 points (Cipolat et al., 2011; Shiwa et al., 2011; Physiotherapy evidence database, 2021).

The authors applied the scale independently, and disagreements were resolved through discussion and consensus. Studies with scores equal or greater than 5 on the scale were considered to have high methodological quality (Cipolat et al., 2011; Physiotherapy evidence database, 2021).

## RESULTS

In total, 3,319 articles were found. Of these, 1,959 were duplicates, and 650 were excluded because they were book chapters, conference abstracts, or other types of publication not considered as scientific studies. A total of 708 articles were analyzed by reading the title and the abstract, and 568 were excluded because they did use exercise as the intervention, they did not examine CD4<sup>+</sup> and/or CD8<sup>+</sup> T lymphocyte counts as the immunological outcome variables, or they did not examine humans. Of the 142 articles remaining for full-text evaluation, 122 did not meet the inclusion criteria and they were excluded because they did not examine the association between physical training with CD4<sup>+</sup> and/or CD8<sup>+</sup> T lymphocyte counts. Twenty articles were selected because they met the inclusion criteria, but 15 were excluded because they were not randomized clinical trials. Ultimately, five studies were included in this review. A flowchart of the study selection process is shown in Figure.

The included studies were determined to have high methodological quality, according to the PEDro scale evaluation, as they obtained total scores  $\geq 6$  on a scale from 0 to 10, according to the score of each item in the instrument (Table 2).

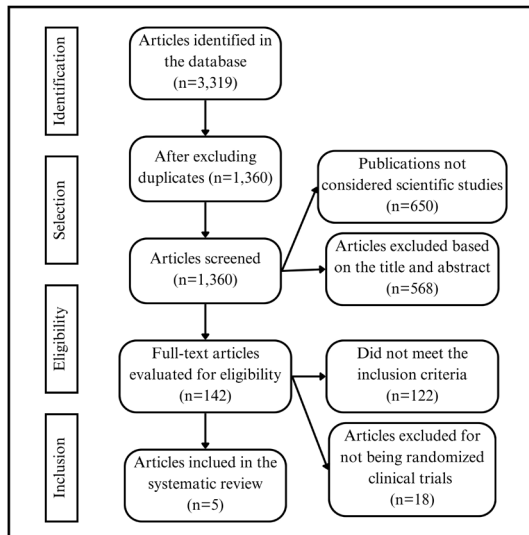


Figure. Flowchart of included studies on exercise and HIV.

Table 2. Methodological quality assessment using the PEDro scale.

Study	Quality assessment	PEDro score
Ogalha et al. (2011)	1. Yes 2. Yes 3. No 4. Yes 5. No 6. No 7. No 8. Yes 9. Yes 10. Yes 11. Yes	6/10
Ghayomzadeh et al. (2019)	1. Yes 2. Yes 3. No 4. Yes 5. No 6. No 7. No 8. Yes 9. Yes 10. Yes 11. Yes	6/10
Dianatinasab et al. (2018)	1. Yes 2. Yes 3. No 4. Yes 5. No 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes	8/10
Soares et al. (2022)	1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes	10/10
Zanetti et al. (2020)	1. Yes 2. Yes 3. Yes 4. Yes 5. No 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes	10/10

1: Eligibility criteria\*; 2: Random allocation; 3: Concealed allocation; 4: Comparability at baseline; 5: Blinded subjects; 6: Blinded therapists; 7: Blinded assessors; 8: Adequate follow-up; 9: Intention-to-treat analysis; 10: Between-group comparisons; 11: Point estimates and variability. \*Criterion 1 does not contribute to the total score (physiotherapy evidence database).

A summary of the included studies on the effects of aerobic and/or resistance physical training on the CD4<sup>+</sup> T and/or CD8<sup>+</sup> T lymphocyte counts of PLWHA was performed. Two studies used combined aerobic and resistance exercise (80%), and 1 study (20%) used resistance exercise in at least one of the groups (Table 3). All selected articles were published in English. The manuscripts were then read, the data were extracted, and the variables were synthesized. The data extracted from the studies are shown in Table 4.

The study by Ogalha et al. (2011) compared aerobic and resistance exercise according to anthropometric and laboratory variables and quality of life in PLWHA. The sample was divided into two groups, with 35 sedentary patients in the intervention group and 35 sedentary patients in the control group (receiving only nutritional counseling). The training protocol lasted 24 weeks. In that study, the intervention group showed decreases in body fat and resting heart rate and increases in CD4<sup>+</sup> T lymphocyte levels, vitality, and quality of life compared to the control group.

The study by Ghayomzadeh et al. (2019) investigated the effect of aerobic, resistance, and flexibility exercises on anthropometric and laboratory variables, cardiorespiratory capacity, and quality of life. The sample was divided into two groups, with 12 sedentary patients in the resistance training group (RES) and six sedentary patients in the control group (CG). The results of eight weeks of training were an increase in the CD4<sup>+</sup> T lymphocyte count of  $\approx 28\%$  (111 cells/mm<sup>3</sup>) in the RES group, while the CG showed a decrease of  $\approx 17\%$ , but the difference was not significant. The effects on body fat percentage reduction, lean mass percentage increase, and fat mass reduction were significant.

The study by Dianatinasab et al. (2018) investigated the effect of aerobic, resistance, and flexibility training for 12 weeks in sedentary individuals living with HIV, evaluating the CD4<sup>+</sup> T lymphocyte count and health status using the General Health Questionnaire-28 (GHQ-28). The sample was divided into two groups, with 14 participants in the exercise group who underwent 12 months of aerobic, resistance, and flexibility training and 16 in the control group who did not receive any type of intervention beyond the normal routine services at the site. The results showed no significant differences in the reduction in the CD4<sup>+</sup> T lymphocyte count, but a significant improvement in mental health was observed in the intervention group compared to the control group.

Table 3. Detailed intervention programs of the studies.

Author	Modality	Duration	Frequency	Protocol
Ogalha et al. (2011)	Aerobic, resistance, and flexibility training	24 weeks	3 × a week	Aerobic and resistance exercises at training intensity of approximately 75% of the maximum heart rate (MHR).
Ghayomzadeh et al. (2019)	Resistance training (RES)	8 weeks	3 × a week	Color-coded elastic band with repetition maximum test in 2 phases. Phase 1: a training circuit with only one elastic band for the main muscle groups of the upper and lower limbs until failure. Phase 2: training volume further increased, combining bodyweight with the resistance bands employing multijointed exercises, such as squats and dips.
Dianatnasab et al. (2018)	Aerobic, resistance, and flexibility training	12 weeks	3 × a week	Warm-up: stretching, light running and flexibility for 20 min; 45 min of aerobic exercise on a stationary bicycle (40-45% MHR). Strengthening exercises with 3 sets of 8 repetitions with 50-55% workload. Workload increased by 5% every 2 weeks, but aerobic exercise was constant during the 12 weeks. The sessions ended with a stretching period of 5-15 min.



Soares et al. (2022)	Control (CON), daily undulating periodization (DUP) and non-periodized training (NPT)	12 weeks 3 × a week	DUP group: 1 <sup>st</sup> day of the week: 3 sets of 4-6 repetitions at 90% of 1RM and rest of 180 s between sets; then, high-intensity interval aerobic training with 7 sets of 30 s and velocity corresponding to 90% of tHR and 60 s of passive recovery; 2 <sup>nd</sup> day: 3 sets of 15-20 repetitions performed at 50% of 1RM and 60 s of rest between sets; then, intermittent aerobic training with 5 sets of 120 s at 75% of tHR and 60 s of active recovery at 45-50% HRmax; 3 <sup>rd</sup> day: 3 sets of 8-12 repetitions at 70% of 1RM with 90 s rest between sets; then, continuous aerobic training for 20 min at 70% of tHR. NPT group: Resistance training consisted of 3 sets of 8-12 repetitions at 70% of 1RM and 90 s interval between sets; then, aerobic training was performed for 20 min at 70% of tHR.
Zanetti et al. (2020)	Placebo (PL), statins (STA), placebo + aerobic and resistance exercise training [ET] (PLET), and statins + ET (STAET)	12 weeks 3 × a week	Nonlinear periodized resistance training: 1 <sup>st</sup> session: 3 sets of 4-6 repetition maximum (RM) and interval of 180 s; 2 <sup>nd</sup> session: 3 sets of 15-20 RM and 45 s interval; 3 <sup>rd</sup> session: 3 sets of 8-12 RM and 90 s interval. Periodized polarized training program performed on a treadmill: 1 <sup>st</sup> session: 7 sets of 30 s with intensity of 85-90% of tHR and 1 min of passive recovery; 2 <sup>nd</sup> session: 6 sets of 2 min at 70% of tHR and 1 min of recovery at 50% of tHR; 3 <sup>rd</sup> session: 25 min at 60% of tHR.

**Table 4.** Characteristics and results from the studies.

Author	Location/ year	Sample size/age	Study design	Measuring instrument	Use of ART	Results
Ogalha et al. (2011)	Bahia, Brazil (2011)	Sample: 70≥18 years old	Randomized clinical trial	Laboratory evaluation: count of leukocytes, hemoglobin, platelets, fasting total cholesterol, viral load, and CD4 <sup>+</sup> /CD8 <sup>+</sup> T lymphocyte counts, among others Anthropometric evaluation: BMI, skinfolds Stress test: treadmill Quality of life assessment: SF-36	Mandatory use	Reduction in body fat and resting heart rate, increase in CD4 <sup>+</sup> T lymphocytes, vitality and quality of life
Ghayomzadeh et al. (2019)	Tehran, Iran (2017)	Sample: 18≥18 years old	Randomized clinical trial	TCD4 <sup>+</sup> cell count, body anthropometry including bioelectrical impedance, analysis of lean body mass and body fat percentage, BMI, and waist-to-hip ratio.	Use for at least 3 months	Reduction in body fat percentage, increase in lean mass percentage, reduction in fat mass and increase in CD4 <sup>+</sup> T lymphocyte count ≈28% (111 cells/m <sup>3</sup> ) in the RES, while the CG showed a decrease of ≈17%.
Dianatinasab et al. (2018)	Shiraz, Iran (2013)	Sample: 30≥18 years old	Randomized clinical trial	TCD4 <sup>+</sup> cell count and health status by the GHQ-28	Study does not report	No significant differences were found in the reduction in CD4 <sup>+</sup> T lymphocyte count, but there was a significant improvement in mental health in the experimental group compared to the control group.

Soares et al. (2022)	Uberaba, Brazil (2020)	Sample: 41/18 to 60 years old	Randomized clinical trial	<p>Level of physical activity: IPAQ; Immunological markers: TCD4<sup>+</sup>, TCD8<sup>+</sup> and TCD45<sup>+</sup> cell counts; Anthropometric profile: BMI and body mass; Tetrapolar bioimpedance: lean body mass and body fat mass (BFM), body fat percentage (% BF), intracellular (IW) and extracellular (EW) water, muscle strength, cardiorespiratory fitness, functional aerobic impairment, and lower limb strength.</p>	Use for more than one year	<p>After 12 weeks, DUP was more effective in improving muscle strength, muscle power and aerobic capacity compared to NPT. In addition, an increase in the number of CD4<sup>+</sup> T lymphocytes was observed only in the DUP group. Both training protocols were effective in increasing %FFM and decreasing %BFM compared to the CG.</p>
Zanetti et al. (2020)	Uberaba, Brazil (2018)	Sample: 72/18 to 60 years old	Randomized, double-blind, placebo-controlled clinical trial	<p>Hemodynamic profile: blood pressure; Biochemical: fasting glucose (FG), glycated hemoglobin (HbA1c), fasting insulin (FI), creatine kinase (CK), and lactate levels; Inflammatory: tumor necrosis factor alpha (TNF-<math>\alpha</math>) and adiponectin levels; Immune: TCD4<sup>+</sup>/CD8<sup>+</sup> cell counts and viral load.</p>	Continuous use for at least one year	<p>There was an improvement in the hemodynamic profile, a reduction in lactate and TNF-<math>\alpha</math>, and an increase in adiponectin levels and CD4<sup>+</sup>/CD8<sup>+</sup> T lymphocyte counts in the ET groups (PLET and STAET).</p>

The study by Soares et al. (2022) investigated the effects of daily undulating periodization (DUP) and non-periodized training (NPT) programs on the physical activity level, which was assessed using the short version of the International Physical Activity Questionnaire (IPAQ). CD4<sup>+</sup>, CD8<sup>+</sup> and CD45<sup>+</sup> T lymphocyte counts were measured as immunological markers. The anthropometric profile was measured by assessing the following parameters. Body mass index (BMI) and body mass were calculated. Fat-free mass (FFM), body fat mass (BFM), body fat percentage (%BF), intracellular (IW) and extracellular (EW) water were evaluated by tetrapolar bioimpedance. Muscle strength was measured by the 1RM test. Cardiorespiratory fitness was measured using the modified Bruce test on a treadmill. Functional aerobic impairment was calculated from the predicted VO<sub>2</sub> max. Lower limb strength was measured by a jump platform.

The individuals evaluated were of both sexes, diagnosed with HIV infection, on ART for more than one year, 18-60 years of age, and sedentary (30 min of physical activity per day, three days a week) or did not systematically exercise over the previous six months. The study protocol was performed for 12 weeks with a frequency of three times a week every other day, and aerobic training was performed in volume and intensity, according to the training heart rate (tHR). The sample was divided into three groups: 13 patients in the DUP group, 13 in the NPT group, and 15 in the control group (CG). After 12 weeks, DUP was more effective in improving muscle strength, muscle power, and aerobic capacity than NPT. In addition, an increase in the number of TCD4<sup>+</sup> cells were observed only in the DUP group. Both training protocols were effective in increasing %FFM and decreasing %BFM compared to the CG.

In the study by Zanetti et al. (2020), 72 patients with HIV were randomly allocated to four groups: 21 participants in the placebo group (PL), 21 in the statins group (STA), 20 in the placebo and aerobic and resistance exercise training (ET) group (PLET), and 20 in the statins and ET group (STAET). The ET intervention consisted of nonlinear periodized resistance training, in which in the first session of each week, the participants performed three sets at the individual's 4-6 repetition maximum (RM), with a resting interval of 180 s; in the second session, they performed three sets at 15-20 RM, with a resting interval of 45 s; in the third session, three sets at 8-12 RM, with a resting interval of 90 s; and a periodized polarized training program, which was performed on a treadmill and varied in session volume and intensity, according to the training heart rate (tHR). In the first session, the participants performed seven sets of 30 s at an intensity of 85-90% of tHR and 1 min of passive recovery; in the second session, they performed six sets of 2 min at 70% of tHR and 1 min of recovery at 50% tHR; and in the third session, the participants performed 25 min at 60% of tHR. The training was performed three times a week for 12 weeks, and the recruited patients were sedentary (30 min of physical activity per day, three days in a week) or did not exercise.

After the intervention, there was an improvement in the hemodynamic profile, reduction in lactate and in TNF- $\alpha$ , and an increase in adiponectin levels and CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocyte counts in the ET groups (PLET and STAET).

## DISCUSSION

During the literature search, it was observed that the protocols used in the studies were not well defined, as most of them lacked a control group and they did not examine the use of therapies combined with ART. Thus, only randomized clinical trials were included since their degree of recommendation is level A according to the Oxford Center for Evidence-Based Medicine classification (AMB-CFM, 2002).

No studies were found that met the criteria adopted by this review that specifically addressed the CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocyte counts in individuals performing resistance and/or aerobic training, as all the studies always included other additional variables to be analyzed and associated for comparison of effects between groups.

Of the five studies selected for this review, only one used resistance training as a protocol, and the others used combined resistance and aerobic training but with different volume and intensity protocols. The duration of the protocols varied between eight and 24 weeks of training; however, the frequency was the same in all studies, which was three nonconsecutive days per week.

The study by Ogalha et al. (2011) used protocols for therapy combined with resistance, aerobic, and flexibility exercise, evaluating laboratory variables such as leukocyte, hemoglobin, and platelet counts, fasting total cholesterol, viral load, and CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocyte counts. Anthropometric variables were also measured: BMI and skinfolds; treadmill stress test; and quality of life (assessed by the SF-36). The study participants were required to use ART, but the minimum time of drug use was not mentioned, which was a limitation. As a result, this study showed improvement in the body fat reduction, resting heart rate, CD4<sup>+</sup> T lymphocyte count, vitality, and quality of life. Erlandson et al. (2018) applied a protocol with resistance and aerobic training, in which an improvement in physical performance was observed at the end of the 12-week protocol, with a significant increase in muscle strength. In that study, the limitation was no evaluation of the CD4<sup>+</sup> T lymphocyte count.

The study conducted by Gomes et al. (2008) analyzed the CD4<sup>+</sup> T lymphocyte count and the life satisfaction index using a resistance, aerobic, and flexibility exercise protocol in individuals living with HIV and using ART. As a result, no significant changes in the CD4<sup>+</sup> T lymphocyte levels were observed in either group, despite the clear increase in the T-cell count in the experimental group, whose positive percentage variation in terms of the absolute count exceeded 12%, while in the control group, it decreased by

approximately 14%. Additionally, the intervention was able to significantly improve the perceived satisfaction with life of people with HIV/AIDS without causing immunological losses.

The study by Ghayomzadeh et al. (2019) used progressive elastic band resistance exercise as a training protocol, combining these bands with bodyweight exercises to increase intensity. This study evaluated body composition and CD4<sup>+</sup> T lymphocyte count, and the results were: a reduction in percentage body fat, an increase in percentage lean mass, a reduction in fat mass, and an increase in the CD4<sup>+</sup> T lymphocyte count of ≈28% in the RES group, while the CG group showed a decrease of ≈17%.

Vaiyapuri et al. (2014) conducted a study to evaluate functional capacity, quality of life, and CD4<sup>+</sup> T lymphocyte count using only progressive resistance exercise for the main muscle groups. As a result, progressive resistance exercise was able to increase the functional capacity and CD4<sup>+</sup> T lymphocyte count and consequently improve the quality of life of the population that performed the exercise protocol. The limitation of the study was that it included patients who were not using ART, which may have interfered with the results. The study by Ghayomzadeh et al. (2019) adopted the mandatory use of ART for at least three months as an inclusion criterion, and the results may therefore be more reliable.

Dianatinasab et al. (2018) also studied the use of aerobic exercise combined with resistance and flexibility exercise at the end of therapy, as it was done in the study by Ogatha et al. (2011), but it did not report the use of ART as mandatory in all individuals included in the experimental group, which might also be a limitation. The findings of that study did not show significant differences in the reduction in CD4<sup>+</sup> T lymphocyte count, showing only improvement in mental health in the experimental group. Thus, the use of ART is important to help increase the CD4<sup>+</sup> T lymphocyte count in individuals living with HIV.

In the study by Soares et al. (2022), it was used a resistance and aerobic exercise protocol combined with daily undulating periodization (DUP) and non-periodized training (NPT) programs for 12 weeks. DUP was observed to be more effective in improving muscle strength, muscle power, and aerobic capacity than NPT. In addition, an increase in the number of CD4<sup>+</sup> T lymphocytes was observed only in the DUP group. Both training protocols were effective in increasing %FFM and decreasing %BFM compared to the CG.

Lazzarotto et al. (2016) conducted a study evaluating the effects of concurrent training on immunity and physical fitness in PLWHA, evaluating the CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocyte counts and cardiorespiratory capacity after 12 weeks of training. The authors observed that concurrent training with single sets resulted in a significant increase in TCD4<sup>+</sup> cells, a nonsignificant difference in TCD8<sup>+</sup> cells, and a decrease in viral load or maintenance of

undetectable viral load in the study participants. Concurrent training with single sets may be a safe therapeutic strategy for these individuals since it did not cause deleterious effects on the immune system or increase the viral load.

Similar results were found in the study by Garcia et al. (2014), who investigated the influence of combined resistance and aerobic training on the immunological, physical, and biochemical parameters of individuals living with HIV. The protocol consisted of a circuit with 12 interrupted exercises with an interval of 90 s, and after the complete circuit, the sequence was repeated three times. After resistance exercise, aerobic exercise was performed by means of a 400-m treadmill run for 30 min. The results showed that the combined exercise (resistance and aerobic) induced a significant increase in the number of CD4<sup>+</sup> T lymphocytes, as well as in the CD4<sup>+</sup>/CD8<sup>+</sup> T-cell ratio, which reflects a relevant benefit to the immune system of individuals infected with HIV. The protocol was performed with individuals who used ART for a prolonged period of time, but this study did not establish a specific ART use timeframe.

Zanetti et al. (2020) conducted a similar study with a protocol combining resistance and aerobic training, and one of the most important findings was the observation of increased CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocyte counts in the PLET and STAET groups, which evidenced an immune system improvement through ET. These results are similar to those of the study conducted by Maduagwu et al. (2015), in which aerobic training for 12 weeks was associated with a significant increase in CD4<sup>+</sup> T-cell counts and metabolic profile improvement in patients undergoing the intervention when compared to the control group. In the study conducted by Bessa et al. (2017), after a 12-week resistance training program, there was an increase in the CD4<sup>+</sup> T lymphocyte count. All the studies cited above included ART use as an inclusion criterion, ranging from three months to one year of treatment.

The mechanisms by which exercise increases immune cell counts remain unclear. However, it is speculated that exercise has an action on lymphoid organs, especially the spleen, causing positive regulation of CD4<sup>+</sup> T lymphocytes (Gleeson et al., 2011). Thus, in addition to the positive effects on physiological functioning, PLWHA benefit from an improvement in the immune system.

Much has been published recently on the effects of exercise on PLWHA. However, some studies have limitations regarding the standardization of medications administered in terms of their ART protocols and their use as an inclusion criterion, which may affect the results provided by an exercise protocol.

In the present review from five studies, only one study did not adopt ART as a criterion, negatively affecting the study outcome. Therefore, it is suggested that in future studies, the ART protocol should be standardized and clearly reported in the methods section so that the benefits found to be provided by exercise can be corroborated.

Nevertheless, it is concluded that aerobic and/or resistance exercise protocols have a positive effect on immunity (CD4<sup>+</sup> and/or CD8<sup>+</sup> T lymphocytes and TNF- $\alpha$ ) and on the metabolic/biochemical profile of PLWHA.

## ACKNOWLEDGMENTS

We would like to thank the National Council for Scientific and Technological Development (CNPq), Process n. 301869/2017-0.

## CONFLICT OF INTEREST

The authors declare that there is no conflicts of interest to disclose.

## REFERENCES

1. AMB-CFM. Associação Médica Brasileira e Conselho Federal de Medicina. *Projeto Diretrizes*. Brasília, 2002. 9p. Available in: [http://www.portalmedico.org.br/diretrizes/100\\_diretrizes/Texto\\_Introdutorio.pdf](http://www.portalmedico.org.br/diretrizes/100_diretrizes/Texto_Introdutorio.pdf) Access at: 25.may.2021.
2. Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vézinet-Brun F, Rouzioux C, Rozenbaum W, Montagnier L. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 220: 868-871, 1983.
3. Bessa A, Lopez JC, DI Masi F, Ferry F, Costa E Silva G, Martins Dantas EH. Lymphocyte CD4<sup>+</sup> cell count, strength improvements, heart rate and body composition of HIV-positive patients during a 3-month strength training program. *J Sports Med Phys Fitness* 57: 1051-1056, 2017.
4. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis - DCCI. *Boletim Epidemiológico -AIDS e DST Número Especial. Dez, 2019*. Available in: <http://www.aids.gov.br/pt-br/pub/2019/boletim-epidemiologico-de-hiv-aids-2019>. Access at 20.dec.2019.
5. Brazier E, Maruri F, Wester CW, Musick B, Freeman A, Parcesepe A, Hossmann S, Christ B, Kimmel A, Humphrey J, Freeman E, Enane LA, Lancaster KE, Ballif M, Golub JE, Nash D, Duda SN; International epidemiology Databases to Evaluate AIDS (IeDEA) consortium. Design and implementation of a global site assessment survey among HIV clinics participating in the International epidemiology Databases to Evaluate AIDS (IeDEA) research consortium. *PLoS One* 18: e0268167, 2023.
6. Chetty L, Cobbing S, Chetty V. Physical activity and exercise for older people living with HIV: a protocol for a scoping review. *Syst Rev* 9: 60, 2020.
7. Cipolat S, Pereira BB, Ferreira FV. Fisioterapia em Pacientes com Leucemia: Revisão Sistemática. *Rev Bras Cancerol* 57: 229-236, 2011.



8. Dianatinasab M, Fararouei M, Padehban V, Dianatinasab A, Alimohamadi Y, Beheshti S, AminiLari Z, AminiLari M. The effect of a 12-week combinational exercise program on CD4 count and mental health among HIV infected women: A randomized control trial. *J Exerc Sci Fit* 16: 21-25, 2018.
9. Erlandson KM, MaWhinney S, Wilson M, Gross L, McCandless SA, Campbell TB, Kohrt WM, Schwartz R, Brown TT, Jankowski CM. Physical function improvements with moderate or high-intensity exercise among older adults with or without HIV infection. *AIDS* 32: 2317-2326, 2018.
10. Gallo RC. Some reflections on HIV/AIDS research after 40 years. *Am J Physiol Lung Cell Mol Physiol* 321: L1057-L1058, 2021.
11. Garcia A, Fraga GA, Vieira RC Jr, Silva CM, Trombeta JC, Navalta JW, Prestes J, Voltarelli FA. Effects of combined exercise training on immunological, physical and biochemical parameters in individuals with HIV/AIDS. *J Sports Sci* 32: 785-792, 2014.
12. Ghayomzadeh M, SeyedAlinaghi S, Shamsi MM, Rezaei S, Earnest CP, Akbarnejad S, Taj L, Mohraz M, Navalta JW, Ghasemi P, Voltarelli FA. Effect of 8 Weeks of Hospital-Based Resistance Training Program on TCD4+ Cell Count and Anthropometric Characteristic of Patients With HIV in Tehran, Iran: A Randomized Controlled Trial. *J Strength Cond Res* 33: 1146-1155, 2019.
13. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol* 11: 607-615, 2011.
14. Gomes RD, Borges JP, Lima DB, Farinatti PTV. Efeito do exercício físico na percepção de satisfação de vida e função imunológica em pacientes infectados pelo HIV: Ensaio clínico não randomizado. *Braz J Phys Ther* 14: 390-395, 2010.
15. Gomes SF, da Silva CM. Perfil dos idosos infectados pelo HIV/AIDS: uma revisão. *Vitalle Rio Grande* 20: 107-122, 2008.
16. Klautau AV, da Silva Pinto D, Santana BB, Freitas Queiroz MA, Rangel da Silva ANM, Vieira Cayres-Vallinoto IM, Ishak R, Rosário Vallinoto AC. Pilates exercise improves the clinical and immunological profiles of patients with human T-cell lymphotropic virus 1 associated myelopathy: A pilot study. *J Bodyw Mov Ther* 24: 1-8, 2020.
17. Lazzarotto AR, Bazzo KO. Treinamento concorrente na imunidade e aptidão física de pacientes HIV/AIDS. *Rev Bras Med Esporte* 22: 153-156, 2016.
18. Lesnak JB, Hayashi K, Plumb AN, Janowski AJ, Chimenti MS, Sluka KA. The impact of sex and physical activity on the local immune response to muscle pain. *Brain Behav Immun* 111: 4-20, 2023.
19. Lim Y, Kim HJ, Yoon SS, Lee SJ, Lee MH, Park H, Park SJ, Jeong S, Han HW. Exercise Frequency Reduction Is Associated With Higher Risk of Infection in Newly Diagnosed Diabetes: A Nationally Representative Cohort Study. *J Korean Med Sci* 38: e176, 2023.
20. Murugathasan M, Jafari A, Amandeep A, Hassan SA, Chihata M, Abdul-Sater AA. Moderate exercise induces trained immunity in macrophages. *Am J Physiol Cell Physiol* 2023: 1-44, 2023.
21. Ogalha C, Luz E, Sampaio E, Souza R, Zarife A, Neto MG, Netto E, Brites C. A randomized, clinical trial to evaluate the impact of regular physical activity on the quality of life, body morphology and metabolic parameters of patients with AIDS in Salvador, Brazil. *J Acquir Immune Defic Syndr* 57: S179-S185, 2011.
22. Physiotherapy evidence database. *Escala PEDro*. 2021. Available in: <http://www.pedro.org.au/portuguese/downloads/pedro-scale>. Access at: 19.may.2021.
23. Shiwa SR, Costa LO, Moser AD, Aguiar IC, Oliveira LV. PEDro a base de dados de evidências em fisioterapia. *Rev Fisiot Mov* 24: 523-533, 2011.

24. Maduagwu SM, Kaidal A, Gashau W, Balami A, Ojiakor AC, Denué BA, Kida I. Effect of Aerobic Exercise on CD4 Cell Count and Lipid Profile of HIV Infected Persons in North Eastern Nigeria. *J AIDS Clin Res* 6: 508, 2015.
25. Soares VL, Soares WF, Zanetti HR, Neves FF, Silva-Vergara ML, Mendes EL. Daily Undulating Periodization Is More Effective Than Nonperiodized Training on Maximal Strength, Aerobic Capacity, and TCD4+ Cell Count in People Living With HIV. *J Strength Cond Res* 36: 1738-1748, 2022.
26. UNAIDS. Joint United Nations Programme on HIV/AIDS. *Estatísticas globais sobre HIV*. 2021. Available in: < [https://unaid.org.br/wp-content/uploads/2021/06/2020\\_11\\_19\\_UNAIDS\\_FactSheet\\_PORT\\_Revisada-Final.pdf](https://unaid.org.br/wp-content/uploads/2021/06/2020_11_19_UNAIDS_FactSheet_PORT_Revisada-Final.pdf)>. Access at: 10.jun.2021.
27. Vaiyapuri A, Ivor PD'S, Jagatheesan Alagesan, K Rajendran. Effect of Progressive resistance training on functional capacity, quality of life and CD4 count in people with HIV/AIDS. *Int J Physiother Res* 2: 626-630, 2014.
28. Zanetti HR, Mendes EL, Gonçalves A, Lopes LT, Roever L, Silva-Vergara ML, Neves FF, Resende ES. Effects of exercise training and statin on hemodynamic, biochemical, inflammatory and immune profile of people living with HIV: a randomized, double-blind, placebo-controlled trial. *J Sports Med Phys Fitness* 60: 1275-1282, 2020.