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Effects of aerobic and combined exercise interventions on CD4 cell counts and VO_2max in people living with HIV: a systematic review and meta-analysis

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KEYWORDS
Aerobic exercise; Cardiorespiratory fitness; Immune function; Non-pharmacological treatment; Physical activity.

ABSTRACT

Exercise has been proposed as a non-pharmacological strategy to improve immune functions and cardiorespiratory fitness in people living with human immunodeficiency virus (HIV). This systematic review and meta-analysis evaluated the effects of aerobic and combined exercise interventions on the cluster of differentiation 4 (CD4) cell counts and maximal oxygen consumption (VO_2max). Randomized controlled trials were identified and pooled using random-effects models. Seven trials comprising 366 participants were included. Meta-analysis demonstrated a significant improvement in VO_2max following exercise interventions compared with control conditions, while a favorable but non-significant effect was observed for CD4 cell counts. Several included studies implemented combined exercise modalities (e.g., aerobic with resistance training), which may have contributed to the observed effects. These findings suggest that exercise interventions, particularly those including aerobic components, improve cardiorespiratory fitness and may provide modest immunological benefits in people living with HIV. Further adequately powered trials are required to clarify the independent effects of different exercise modalities and to determine optimal exercise prescriptions.

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Introduction

Human immunodeficiency virus (HIV) infection remains a significant global public health challenge, with an estimated 38 million people living with HIV worldwide in 2022[1]. The widespread implementation of antiretroviral therapy (ART) has dramatically improved life expectancy and reduced the incidence of opportunistic infections among people living with HIV. However, despite effective viral suppression, many patients continue to experience persistent immunological dysfunction, chronic inflammation, and comorbidities, such as cardiovascular disease, pulmonary complications, and metabolic disorders[2,3]. These factors collectively contribute to reduced physical functions and quality of life, creating a pressing need for comprehensive management strategies beyond pharmacological treatments.

Reduced CD4 cell counts are associated with impaired immune surveillance and increased susceptibility to opportunistic infections[4]. In addition, chronic inflammation, mitochondrial dysfunction, and muscle wasting in individuals living with HIV contribute to reduced aerobic capacity, increased fatigue, and diminished physical function[5-6]. These physiological alterations negatively impact quality of life and increase the risk of comorbidities[7].

Aerobic exercise has emerged as a promising non-pharmacological intervention to address these challenges by improving cardiovascular endurance, muscle strength, and immune function[8]. Numerous studies have shown that regular aerobic exercise can enhance VO^2 max and improve quality of life in HIV-infected populations[9-11]. Moreover, some evidence suggests that aerobic exercise may help stabilize or increase CD4 cell counts, potentially mitigating immune decline[12]. Despite this, results across studies have been inconsistent, and optimal exercise prescriptions including intensity, frequency, and duration, have yet to be standardized for this population.

Although previous systematic reviews have examined the role of exercise in HIV populations, most have evaluated exercise interventions broadly without clearly distinguishing between aerobic and non-aerobic modalities. Furthermore, many studies implement combined exercise programs, making it difficult to isolate the independent effects of specific exercise types. Therefore, this study aims to systematically evaluate the effects of aerobic and combined exercise interventions on CD4 cell counts and VO_2max in people living with HIV. The findings will contribute to evidence-based recommendations for incorporating aerobic exercise into comprehensive HIV management, ultimately aiming to improve patients' health outcomes and quality of life.

Materials and methods

Definition of exercise modalities

Aerobic exercise was defined as continuous, rhythmic physical activity aimed at improving cardiorespiratory endurance (e.g., walking, cycling, treadmill exercise). Non-aerobic exercise inferred to exercise modalities that primarily target on strength or anaerobic performance, including resistance or strength training. In studies involving combined exercise interventions (e.g., aerobic plus resistance training), exercise classification was based on the predominant component of the intervention, considering the primary training objective, proportion of session time, and protocol description reported in the original studies.

Data sources and search strategy

Search Strategy

A comprehensive search was conducted in MEDLINE, SCOPUS, EMBASE, IPA, CINAHL, and Cochrane Library databases from inception to January 2023. The search strategy utilized a combination of Medical Subject Headings (MeSH) and relevant keywords, including "aerobic exercise", "HIV", "CD4", and "VO_2 max". Boolean operators were applied to combine search terms as follows: ("aerobic exercise" AND "HIV" AND "CD4") and ("VO_2 max").

No language restriction was applied; however, only randomized controlled trials were included. In addition, the reference lists of all included studies and relevant reviews were manually screened to identify any further eligible articles. This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12]. The primary outcomes of interest were CD4 cell counts, as a marker of immune function, and VO_2 max, representing cardiorespiratory exercise capacity in individuals living with HIV.

The search strategy described earlier was used to identify titles and abstracts of studies potentially relevant to the objective of this review. Each abstract was independently screened by two reviewers to assess its eligibility. If at least one reviewer considered a study to be potentially eligible, the full-text article was retrieved for detailed evaluation. Both reviewers then independently reviewed the full text to determine whether it met the predefined inclusion and exclusion criteria. In the event of disagreement, the reviewers discussed their decisions and reached consensus through joint deliberation. Studies were included if they investigated the effects of aerobic exercise interventions in individuals living with HIV and reported outcomes on CD4 cell counts and VO_2 max. Studies were excluded if they were non-original publications such as commentaries, letters, reviews, surveys, or editorials. Duplicate studies using the same population were also excluded, as were studies that did not report effect estimates or lacked sufficient data to calculate the impact of the intervention.

Data extraction was conducted independently by two reviewers using a standardized data extraction form. Extracted information included the first author and year of publication, study design, sample size, participant characteristics (e.g., age, sex, HIV status), details of the exercise intervention (type, frequency, intensity, and duration), comparison or control group (if applicable), outcome measures (CD4 cell counts and VO_2 max), duration of follow-up, and key findings including effect sizes. Any discrepancies in data extraction were resolved by discussion and, if necessary, consultation with a third reviewer.

The methodological quality of the included studies was assessed using the Physiotherapy Evidence Database (PEDro) scale, which evaluates internal validity and statistical reporting. The scale includes 11 items, with a maximum score of 10 (excluding the first item, which addresses external validity). Each study was independently assessed by two reviewers. Studies were classified as high quality (scores of 6–10), moderate quality (scores of 4–5), or low quality (scores below 4). Discrepancies in scoring were resolved through discussion to reach a consensus. Although studies with low quality were not excluded, their limitations were considered during the interpretation of the overall results.

Study selection

The search strategy outlined earlier was applied to identify titles and abstracts of studies potentially relevant to this review. Each abstract was independently assessed by two reviewers. If at least one reviewer considered a study to be potentially eligible, the full-text article was retrieved for comprehensive evaluation. Both reviewers independently assessed the full-text articles to determine their eligibility based on predefined inclusion and exclusion criteria. In cases of disagreement, the reviewers discussed the rationale for their decisions and reached a consensus.

The inclusion criteria were as follows: (1) studies that implemented aerobic exercise interventions in individuals living with HIV; and (2) studies that reported outcomes for both CD4 cell counts and VO_2max. Exclusion criteria included non-original publications such as commentaries, letters, reviews, surveys, or editorials. Additionally, duplicate publications based on the same population, studies without reported effect estimates, or those with insufficient data to

calculate the impact of interventions were excluded.

Data synthesis and analysis

The risk of bias in the included studies was independently evaluated by two reviewers using the Cochrane Collaboration's Risk of Bias tool[12]. This tool assesses methodological quality based on key criteria such as random sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting, and other potential sources of bias. Any disagreements were resolved through discussion to reach consensus.

A meta-analysis was conducted using CD4 cell counts and VO_2max as the primary outcomes. Heterogeneity among studies was assessed using Cochran's Q statistic, with a *p-value* < 0.10 indicating statistically significant heterogeneity. The I^2 statistic was also calculated to quantify the proportion of total variation across studies that was due to heterogeneity rather than chance. Values of approximately 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively[13].

Where substantial heterogeneity was detected, possible sources were explored through subgroup analysis or sensitivity analysis. Publication bias was assessed through visual inspection of funnel plots and tested statistically using Begg's rank correlation test and Egger's regression asymmetry test. A *p-value* < 0.05 in either test was considered indicative of potential publication bias[14].

Results

Search result and included study characteristics

A total of 1,326 studies were identified as shown in Figure 1. After removing duplicates and screening for relevance, potentially eligible articles were retrieved for full-text review. Ninety-seven articles were excluded at this stage, with fourteen studies failing to meet the predefined inclusion criteria. Three studies assessed the effects of exercise interventions that included aerobic components compared with control or non-aerobic conditions on CD4 cell counts. Four studies evaluated the effects of exercise interventions with aerobic components on VO_2max. Ultimately, seven studies were included in the final analysis and the characteristics of included studies are shown in Table 1. The risk of bias for each included study is presented in Figure 2, with a summary of the overall risk of bias shown in Figure 3.

Table 1 Characteristics of included studies

Author (Year)	Country	Study Design	Participants (n)	Frequency (sessions/ week)	Intensity	Time	Type	Control Group	Outcomes Measured	Main Findings
Fillipas et al. (2006)	Australia	RCT	40 HIV men	3	Aerobic exercise 60-80% HRmax and resistance exercise 60-80% 1RM	60 minutes/session 6 months	Aerobic e and resistance exercise	Walking	CD4	↑ CD4
Hand et al. (2008)	USA	Quasi	40 HIV men and women	3	Aerobic exercise 60-70% HRmax and resistance exercise	60 minutes/session 6 weeks	Walking/cycling	Read a book, talk or watch television	VO_2max	↑ VO_2max
Mutimura et al. (2008)	Rwanda	RCT	100 HIV adults	3	60-70% HRmax	60 minutes/session	Aerobic, stabilization, and strengthening	No exercise	CD4, VO_2max	↑ VO_2max and CD4
Dolan et al. (2010)	Boston	RCT	40 HIV women	3	Aerobic exercise 60-80% HRmax and resistance exercise 60-80% 1RM	60 minutes/session 16 weeks	Home-based progressive resistance training and aerobic exercise	No exercise	CD4, VO_2max	↑ VO_2max No significant change in CD4
Ogalha et al. (2011)	Brazil	RCT	63 HIV adults	3	Aerobic exercise 70-80% HRmax	60 minutes/session 24 weeks	Combined aerobic, resisted and stretching exercises	Dietary counseling	CD4, VO_2max	↑ VO_2max and CD4
Mendes et.al. (2013)	USA	RCT	29 HIV men and 51 HIV women	3	Aerobic exercise 60-75% HRmax and resistance exercise 60-80% 1RM	40-60 minutes/session 24 weeks	Combined aerobic e and resistance exercise	No exercise	VO_2max	↑ VO_2max,
Neto et.al. (2016)	Brazil	Quasi	63 HIV adults	3	Aerobic exercise 60-70% HRmax	30-40 minutes/session	Aerobic exercise	No exercise	CD4, VO_2max	↑ VO_2max and CD4

Abbreviation: CD4, cluster of differentiation 4; VO_2max, maximal oxygen consumption; HIV, human immunodeficiency virus; ART, antiretroviral therapy.

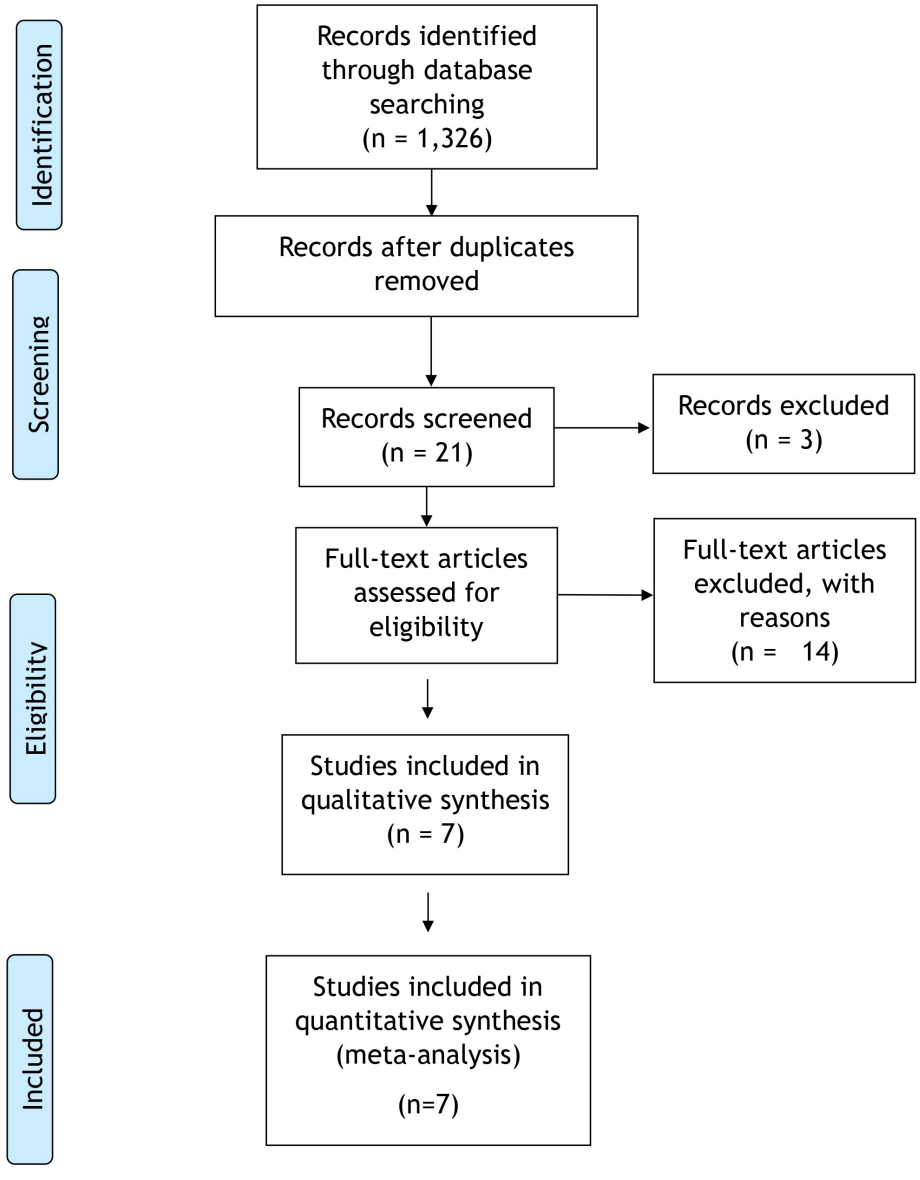


Figure 1 Search and selection of the studies for systematic review and meta-analysis by PRISMA

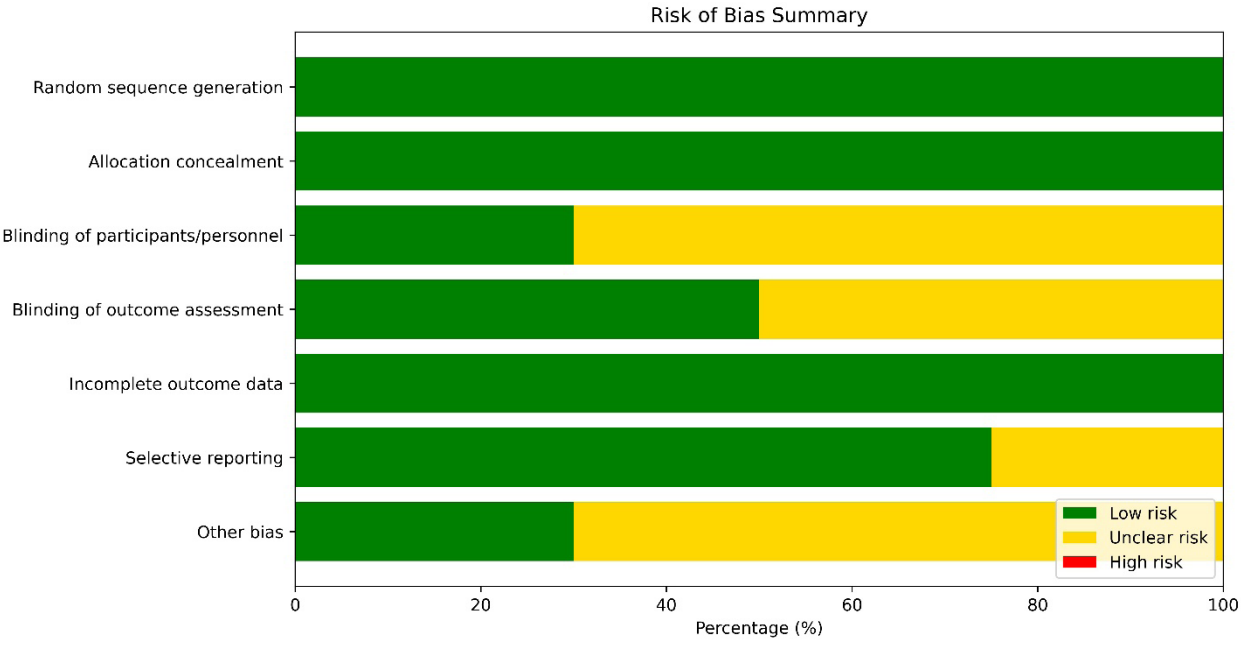


Figure 2 Risk of bias summary presented as percentages across included studies

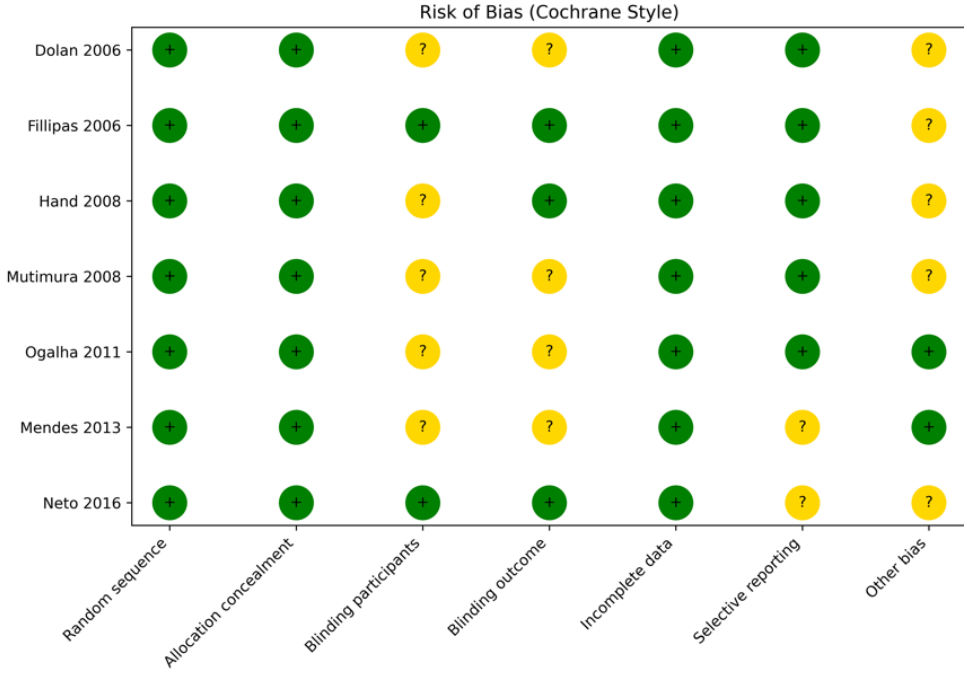


Figure 3 Risk of bias of included studies. Green (+) indicates low risk, yellow (?) unclear risk, and red (−) high risk

Aerobic exercise and CD4 cell count

Three studies assessed the effects of aerobic exercise compared to non-aerobic exercise (control group) on CD4 cell counts[9-11]. There was no evidence of heterogeneity among these studies (I^2 = 0.0%; *p*-value = 0.854), as shown in Figure 4. Funnel plot analyses indicated no apparent publication bias (Egger's test *p*-value = 0.117; Begg's test *p*-value = 0.317). The pooled results showed that participants in the aerobic exercise group had a greater improvement in CD4 cell counts compared to the non-aerobic group, although this difference was not statistically significant (mean difference = -2.92 cells/mm^3; 95% confidence interval: -12.56 to 6.73).

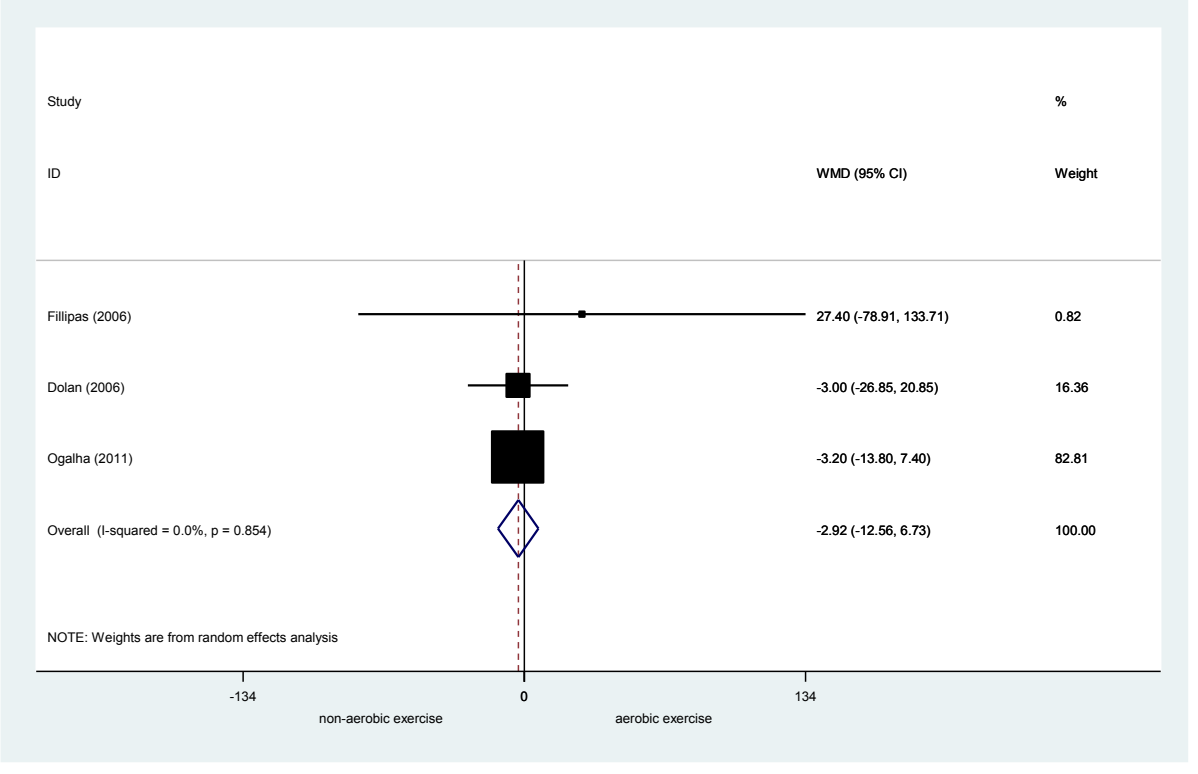


Figure 4 Forest plot showing the effects of exercise interventions on CD4 cell counts in people living with HIV

Aerobic exercise and exercise capacity

Four studies evaluated the effects of aerobic exercise versus non-aerobic exercise on VO_2max[10,12,14]. Moderate heterogeneity was observed among these studies (I^2 = 43.1%; *p*-value=0.153), as illustrated in Figure 5. Funnel plots did not reveal any significant publication bias (Egger's test *p*-value=1.00; Begg's test *p*-value=0.3154). The meta-analysis demonstrated that aerobic exercise significantly improved VO_2max compared to non-aerobic exercise (mean difference=3.68 mL/kg/min; 95% confidence interval: 2.96 to 4.41)

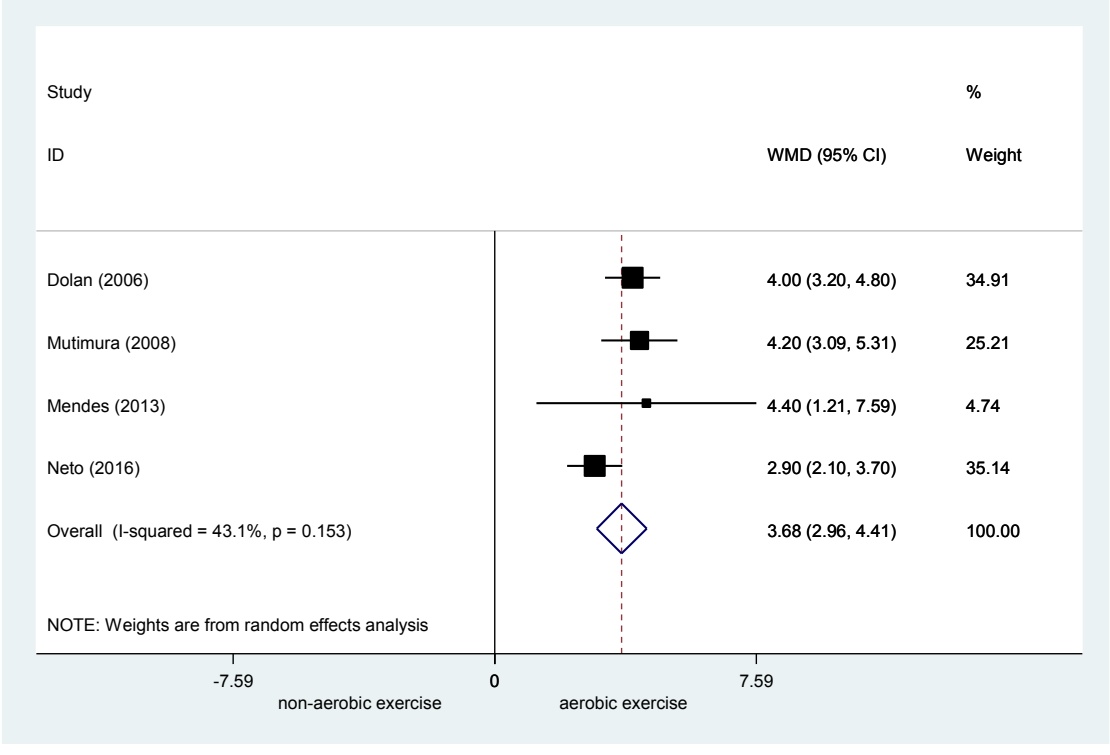


Figure 5 Forest plot showing the effects of exercise interventions on VO_2max in people living with HIV.

Discussion

This meta-analysis evaluated the effects of aerobic exercise on immune function, represented by CD4 cell counts, and cardiorespiratory fitness, measured by VO_2max, in individuals living with HIV. Our findings align with previous studies indicating that aerobic exercise has the potential to enhance physical fitness and may contribute to immunological benefits [15]. Although the increase in CD4 cell counts observed was not statistically significant, the trend suggests that regular aerobic exercise could support immune system maintenance or improvement, which is crucial for HIV patients who are often immunocompromised[16-17].

It is important to note that several included studies implemented combined exercise interventions. Therefore, the observed effects cannot be attributed solely to aerobic exercise. The inclusion of mixed exercise modalities may have contributed synergistically to improvements in both cardiorespiratory fitness and immune function. Exercise may influence immune function through multiple mechanisms, including reductions in systemic inflammation, improved immune cell circulation, and enhanced metabolic regulation. Improvements in VO_2max reflect enhanced cardiovascular efficiency, which is associated with better functional capacity and reduced morbidity in people living with HIV. Additionally, factors such as age, sex, and antiretroviral therapy regimens may influence both CD4 responses and exercise capacity, highlighting the need for individualized exercise prescriptions. Despite promising findings, heterogeneity in intervention protocols and participant characteristics should be considered when interpreting results. The inclusion of combined exercise interventions may have introduced heterogeneity and should be considered when interpreting the findings.

Reduced CD4 cell counts and impaired exercise capacity contribute to physical deconditioning, leading to decreased functional ability and increased risk of secondary complications such as cardiopulmonary disease, metabolic syndrome, and opportunistic infections[18-19]. Exercise interventions, particularly aerobic training, are known to mitigate these risks by improving cardiovascular endurance, muscle strength, and overall physical function. Moreover, exercise has psychological benefits, including reduced fatigue and improved mood, which further enhance quality of life in HIV populations[15].

Despite these promising findings, the optimal exercise prescription regarding intensity, frequency, duration, and modality remains to be clearly defined. Individual factors such as disease stage, comorbidities, and baseline physical fitness must be considered to tailor safe and effective programs. Future randomized controlled trials with larger sample sizes and longer follow-up periods are needed to establish evidence-based guidelines that can be integrated into routine clinical care.

Limitations of the current meta-analysis include the relatively small number of eligible studies and some variability in study design and intervention protocols. Additionally, heterogeneity in participant characteristics such as age, sex, and antiretroviral therapy regimens could influence the outcomes. There is also a scarcity of studies simultaneously reporting on both immunological and functional outcomes, highlighting the need for more comprehensive research in this area.

Importantly, education and motivation remain critical components for ensuring adherence to exercise programs among people living with HIV. Healthcare providers, including physical therapists, play a vital role in promoting aerobic exercise as a safe, accessible, and effective adjunct therapy that complements pharmacological treatments.

Conclusion

This systematic review and meta-analysis suggest that exercise interventions, particularly those including aerobic components, significantly improve cardiorespiratory fitness and may provide modest benefits for immune function in individuals living with HIV. However, due to the inclusion of combined exercise interventions, the independent effects of aerobic exercise should be interpreted with caution. Further research is required to establish optimal exercise prescription.

Take home messages

Exercise interventions, particularly those including aerobic components, significantly improve cardiorespiratory fitness. Exercise training demonstrates a favorable, although non-significant, effect on CD4 cell counts, suggesting potential immunological benefits. Aerobic exercise should be considered a safe and effective adjunct to standard HIV care.

Conflicts of interest

The authors declare no conflict of interest.

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Author contributions

Sarayoot Mongkol: Conceptualization, methodology, literature search, data curation, formal analysis, risk of bias assessment, interpretation of data, writing-original draft, writing-review and editing.

Chuenpak Saleesing: Supervision, conceptualization, methodology, literature search, writing-review and editing.

Ettipad Jaiyen: Conceptualization, methodology, and literature search

Tichaporn Sookkue: Formal analysis, methodology, interpretation of data, risk of bias assessment, writing-review and editing.

Sukanya Kreeinthong: Supervision, conceptualization, critical revision of the manuscript, project administration, writing-review and editing.

Data availability

All data analyzed in this study are derived from previously published articles and are available within the article and its supplementary materials. No new datasets were generated or analyzed.

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