

# The effects of aerobic exercises on high sensitivity C-reactive protein and depression in patients living with HIV infection; a systematic review with meta-analysis

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## Research article

**Keywords:** Aerobic exercise, high sensitivity C-reactive protein, depression, HIV infection, Systematic review

**Posted Date:** October 2nd, 2019

**DOI:** <https://doi.org/10.21203/rs.2.12341/v2>

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# Abstract

Background HIV infection and chronic use of highly active antiretroviral therapy have been associated with increased expression of pro-inflammatory biomarkers (e.g. high-sensitivity C-reactive protein) and major affective disorders (e.g. depression). There is a growing research interest in aerobic exercise as an adjunct therapy on inflammatory outcomes and depression in people living with HIV (PLHIV) who are undergoing antiretroviral therapy. Synthesizing and appraising available evidence may be essential to guide practice and future research on exercise intervention to this population. This review evaluated the effects of aerobic exercises on serum levels of high-sensitivity C-reactive protein (hs-CRP) and depressive symptoms in PLHIV. Methods Cochrane Central Register of Controlled Trials, MEDLINE, PEDRO, EMBASE, AMED, CINAHL, and Web of Science were systematically searched to include clinical trials that investigated the effects of aerobic exercises on hs-CRP and/or depression in PLWH. Two reviewers independently screened all the articles for eligibility and also evaluated the risk of bias using the Cochrane Collaboration risk of bias assessment tool. Data were extracted and meta-analyses conducted using Review Manager Software. Results Six studies (261 participants) met the inclusion criteria and were included in the review. Four of the studies reported on depressive symptoms and two on hs-CRP outcome. The meta-analysis result showed a significant ( $Z=3.78$ ,  $p<0.0002$ ) decrease in depression scores in PLWH; implying that aerobic exercise interventions reduce depressive symptoms among PLWH. The two studies that reported on hs-CRP outcome, found no significant effect of aerobic exercise on hs-CRP. Overall, the GRADE evidence for this review was of moderate quality. Conclusion There was evidence that aerobic exercises of about 24-60 minutes duration, two to five times per week can lead to a significant improvement in depression level but not hs-CRP in PLWH. However, it should not be concluded as 'no evidence of effect' because the included trials do not have sufficient power to detect treatment effects. Thus, further homogenous research with enough "power" is necessary for a conclusive estimate of effects.

## Background

The use of highly active antiretroviral therapy (HAART) has to a very large extent reduced the morbidity and mortality of people living with HIV infection [1]. Despite the generally recorded improved health outcome, some studies have strongly associated HAART to specific side effects which includes elevation of inflammatory markers, for example, high-sensitivity C-reactive protein (hs-CRP) [2, 3]. Hs-CRP, a non-specific inflammatory biomarker, has been noted by both the American Heart Association and Centres for Disease Control as an independent predictor of increased coronary risk; and they recommended that individuals with hs-CRP levels greater than or equal to 3.0 milligrams per liter would likely need more intense management and treatment of heart disease [4].

Several studies have reported significant declines in hs-CRP levels following aerobic exercise interventions among older individuals [5], obese women [6] and breast cancer survivors [7]. The third National Health and Nutrition Examination Survey observed that 21% of sedentary individuals had increased hs-CRP levels compared to 13% of moderately active individuals [8]. Yet, a meta-analysis of randomized controlled trial reported a non-significant decline in hs-CRP levels among healthy subjects following an aerobic exercise intervention [9]. The existing studies that investigated the effects of aerobic exercise interventions on

circulating inflammatory biomarkers have produced inconsistent results, and no meta-analysis of effects have been conducted to explore the intervention effects of aerobic exercises on hs-CRP in PLWH.

Depression is amongst the most common neuropsychiatric disorders that burden individuals with HIV infection [10]. Depression could be as a result of the effects of the infection in the brain, shock after diagnosis, presentation of symptoms, a death of another HIV patient, loss of friends due to HIV infection status, as well as side effects of HAART [11]. Exercise has proven to have a short-term effect on depression among general population [12, 13]. However, there is no recent meta-analysis that has evaluated the effects of aerobic exercise on depression in PLWH [14].

This systematic review is therefore aimed at evaluating the effects of aerobic exercises on serum levels of high-sensitivity C-reactive protein (hs-CRP) and depression in PLWH undergoing HAART. Specifically, two questions guide this review: (a) Are aerobic exercise interventions effective in reducing hs-CRP levels in patients with HIV undergoing HAART? , and (b) Are aerobic exercise interventions effective in reducing depressive symptoms in patients with HIV infection undergoing HAART?

## **Methods**

### **Design**

This systematic review and subsequent network of meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) 2015 guideline [15, 16].

### **Search strategy**

A search strategy was developed with health-research librarian, and piloted (see Appendices I, II, III, IV) following the guidelines specified by the Cochrane Handbook for Systematic Reviews [17], and the guidance for undertaking reviews in health care by the Centre for Reviews and Dissemination [18]. The following databases were searched from inception until September 2018, to include studies that reported the effects of aerobic exercise on hs-CRP level and depression scores: Cochrane Central Register of Controlled Trials, PubMed (MEDLINE), PEDRO, EMBASE, Allied and Complementary Medicine Database (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science Core collection. The following search terms were adapted for each database: HIV OR seropositive OR HAART OR anti-retroviral therapy, highly active OR anti-HIV agents AND aerobic exercise OR physical activity OR acute exercise OR exercise training OR physical exertion OR sports AND C-reactive protein OR acute-phase proteins OR reactants OR glycoproteins OR blood proteins OR immunoproteins AND depression OR depressive symptoms OR emotional depression OR depressive syndrome OR neurotic depression OR melancholia OR affective disorders OR adjustment disorders. Additionally, the reference lists of the included articles were hand searched. Attempts were made to collect unpublished data, we searched the National Library of Medicine's clinical trial registry, directory of open-access repository websites and conference proceedings. However, there was only two ongoing trials [19, 20] still at the recruiting of participants stage that aim to evaluate the effect of aerobic exercise on depression and/or hs-CRP level among PLWH receiving HAART.

### **Eligibility criteria**

The following eligibility criteria were applied in selecting studies.

An article was included in the review if;

- a) The **study population** were adults ( $\geq 18$  years old) with HIV infection receiving HAART.
- b) The **intervention** was aerobic exercise, defined as physical activity of low to high intensity requiring free oxygen and utilization of oxygen to sufficiently meet energy demands during exercise through aerobic metabolism [21]. No particular restriction was considered regarding a particular form of aerobic exercise, dose, frequency, intensity, and duration of intervention or follow up period after intervention. As many such interventions may be complex, including several components, other interventions in addition to aerobic exercise including medications, nutrition, and health education were also included as long as the effect of aerobic exercise intervention could be determined.
- c) The **primary outcome** measure was the hs-CRP level, and/or the **secondary outcome** was any measures of depression especially generic validated tools (i.e. depression tool not developed for a specific condition, e.g. Cardiac Depression Scale). Examples of generic depression validated tools include, but not limited to; Centre for Epidemiological Studies-Depression Scale, Montgomery-Asberg Depression Scale, Becks Depression Inventory score, and Positive and Negative Affect Schedule.
- d) The **control or comparator** can be any control including non-exercise or resistance exercise.
- e) The **setting** in which the study was conducted were any of the following: hospital (e.g. inpatient, acute or outpatient), rehabilitation homes, community or long-term care.
- f) The article was randomized controlled trials (RCTs), and non-RCTs including quasi-RCTs, controlled clinical trials, pre-test post-test clinical trials.

**An article was excluded if:**

- a) The intervention was not aerobic exercise based on the definition provided above.
- b) It was an opinion paper, qualitative studies, narrative reviews, systematic reviews, letter to the editors or commentaries.
- c) If the control group was not clearly defined.

### **Study record, selection process and data management**

Eligibility questions and forms for the screening of the studies included within the review were developed, piloted and refined as appropriate. Literature search results were exported into RefWorks for deduplication and was later exported into Microsoft Excel (Microsoft Excel. Redmond, Washington: Microsoft, 2010. Computer Software) to facilitate the management and selection of articles for inclusion. The selection of the article was done in two phases: title and abstract screening, followed by full text assessment. While two reviewers (E.M.A and E.M.U) independently screened all titles and abstract, another two reviewers (O.A.E and I.B.N) conducted full text assessment according to the study selection criteria. The kappa for title/abstract and full text

screening were 0.83 and 0.82 respectively, suggesting almost perfect agreement [22]. Disagreements at any screening stage were resolved through discussion with other authors (U.O.A, M.E.K).

## **Data collection process**

### **Risk of Bias Assessment in Individual Studies**

Two authors (O.J.A, E.M.A.) independently assessed the risk of bias of the included articles. The Cochrane Collaboration Tool for Risk of Bias Assessment (Table 8.5a of the Cochrane Handbook for Systematic Reviews of Interventions) was used to assess the articles in six key domains: 1) selection bias (random sequence generation, allocation concealment); 2) performance bias (blinding of personnel and participants); 3) detection bias (blinding of outcome assessments); 4) bias due to attrition (incomplete outcome data, including dropouts and withdrawals); 5) reporting bias (selective reporting); and 6) other bias (other sources of bias not elsewhere addressed) [17]. Articles were rated as 'high risk' or 'low risk' following a well-described procedure (Table 8.5.d of the Cochrane Handbook for Systematic Reviews of Interventions) [17, 23]. Then, summary assessment for each important outcome (across domains) within and across studies was made (Table 8.7.a of the Cochrane Handbook for Systematic Reviews of Interventions) [17, 23]. Again, any disagreement in the decision between reviewers was resolved by discussion and consultation with the third author (O.A.E.).

## **Data extraction items**

Four authors (E.M.A, O.J.A, I.B.N, M.E.K ) used a standardized extraction form to extract the articles' metadata including authors name, country the study was conducted, participants' characteristics, study setting, sampling method, sample size, intervention characteristics (e.g. components of the intervention, who delivered the intervention, the duration of the intervention and follow-up) (where available), attrition rate, aspects of outcome assessed, the outcome measurement, study findings (e.g. p value, confidence intervals mean and standard deviation), conclusions and funding sources).

## **Data synthesis and assessment of heterogeneity**

To address the review objectives, the quantitative study outcomes were extracted and presented in a proof table. Mean differences were used for the uniform outcomes with 95% of CI. A meta-analysis was conducted to find pooled effect sizes across the included studies, using a random-effects model depending on the level of heterogeneity of intervention effects. Heterogeneity was assessed using the Cochrane's  $\chi^2$  test (10% significance level) and Higgins  $I^2$  for which values of 25%, 50%, and 75% shows low, medium and high heterogeneity respectively as specified by the guidance in the Cochrane Handbook for Systemic Reviews of Interventions [17].

## **Data analysis**

Studies were narratively described, and meta-analysis were conducted using random-effects model to evaluate the overall effect of aerobic exercise interventions on depression in patients living with HIV infection [17]. Meta-analysis was possible because of the homogenous nature of study design, intervention, comparator(s) and

outcomes of the included studies. A substantial heterogeneity was observed in the two studies that considered hs-CRP as an outcome, therefore, only a narrative synthesis was conducted.

### **Quality of evidence and strength of recommendation.**

Two authors (E.M.A, I.B.N) independently graded the quality of the evidence of the included studies on consistency, design, directness, precision, publication bias and study limitations of the Grading of Recommendations Assessment Development and Evaluation (GRADE) [24]. The included studies were graded as high risk of bias or low risk of bias with evidence statement graded from 'High Quality' to 'Very Low Quality' according to the criteria (Appendix V)

## **Results**

### **Study inclusion**

From the database searches, 429 citations were retrieved. After duplicate were removed, 333 underwent title and abstract screening, of which 321 were excluded. The remaining 12 studies underwent full text screening, and 6 studies providing data on 287 participants were included in the final analysis (Figure 1).

### **Characteristics of Included Studies**

#### **Study design and participants**

Four of the included studies were randomized controlled trials (RCTs) [25, 26, 27, 28]. Two studies design were pre-post, with the participants in a control group receiving strengthening exercise [29], or different levels of aerobic exercises including low, moderate and high intensity of aerobic exercises [30]. The number of participants in each study ranged from 21 [30] and 84 [28] of adults ( $\geq 18$  years) diagnosed with HIV infection (See Table 1).

#### **Quality appraisal and risk of bias assessment**

Results of the quality assessment and risk of bias of the 6 included studies are presented in table 2, and 2 studies were rated as high quality [25, 28], while the remaining 4 were rated as low quality [29, 26, 27, 30]. Source of bias were random sequence generation (n=2 [29, 30], allocation concealment (n=5 [25, 26, 27, 29, 30]), blinding of outcome assessment (n= 5 [25, 26, 27, 29, 30], attrition bias, (n= 3 [26, 27, 30], selective reporting (n= 1 [29]).

#### **Outcomes reported in included studies**

Two studies [28, 29] reported high-sensitivity CRP, and four studies reported depression [25, 26, 27, 30]. Depression outcome measurement instruments included Becks Depression Inventory (BDI) score, Centre for Epidemiological Studies Depression score and Montgomery-Asberg Depression score and Positive and Negative Affect Schedule (PANAS). The outcome measure of four of the included articles [26, 27, 29, 30] were measured twice, baseline and 12 weeks post intervention. Also, one study [25] measured at two time points:

baseline and 6 weeks post intervention, while one study [28] measured at three different time points: baseline, 6 months and 12 months post intervention. The clinical characteristics between the intervention and control groups were similar at baseline for all studies included (see Table 3).

### **Aerobic exercise interventions**

The included studies had a wide variation in the types of aerobic exercise intervention used (Table 2). All the included studies reported all the intervention parameters, FITT- frequency, intensity, time, type of aerobic exercise and duration [31]. Walking was the most common type of aerobic exercise used as an intervention in the included studies [27, 28, 29, 30]. Other type of aerobic exercise used as an intervention was stationary bicycle ergometer [25, 26].

### **Effects of intervention**

Except where otherwise stated, the effects of an intervention are reported as comparison of the intervention versus the control group.

### **High-sensitivity C-reactive protein (hs-CRP)**

Two studies provided data on hs-CRP [28, 29]. One high-quality trial [28] reported no statistically significant difference in mean hs-CRP between groups. Also, a low-quality trial [29] reported no statistically significant difference in mean hs-CRP between groups (Table 3).

### **Depression**

Four studies [25, 26, 27, 30] reported outcomes on depression. One high-quality RCT [25], reported a significant improvement (BDI;  $p=0.001$ ) in the study group. One other low-quality RCT [27], reported a significant improvement (CES-D;  $p=0.028$ ) in the study group as compared to controls. One low quality clinical trial [30], reported no significant ( $p>0.05$ ) changes of the Montgomery-Asberg depression scores groups. One study [26] that reported outcome on negative mood/depression demonstrated significantly lower negative mood in the study group than the control group (Table 3).

### **Meta-analyses- Effect of interventions**

Four studies were included in the meta-analysis. A meta-analysis was conducted to evaluate the overall effect of aerobic exercise interventions on depression (4 studies) in patients living with HIV infection.

### **Heterogeneity test**

There was no significant heterogeneity ( $p>0.1$ ) in the meta-analyses of the effects of the intervention on depression outcome. Therefore, a random effects model was used for the meta-analysis. However, a substantial heterogeneity ( $p<0.1$ ) was observed in the meta-analyses of the effects of the intervention on hs-CRP. This could be as a result of variations in sample sizes and duration of the intervention. Therefore, only a narrative synthesis was reported.

### **Results of Meta-analyses**

When the four studies [25, 26, 27, 30] that considered depression as an outcome measure were pooled together, there was an overall statistically significant ( $Z=3.78$ ,  $p<0.0002$ ) change in depression level between the comparison groups. There was a significant trend towards a decrease in the depression scores in subjects in the aerobic exercise (intervention) group as compared with the control group (Figure 2).

## Discussion

Six trials evaluating a range of aerobic exercise interventions targeted at improving hs-CRP levels and depression in PLWH undergoing HAART were included in this systematic review. The included studies were generally of fair methodological quality. The major sources of risks of bias were lack of blinding of outcome assessment, participant and personnel, lack of allocation concealment and attrition bias. The two studies [28, 29] that evaluated the effect of aerobic exercise on hs-CRP level in PLWH reported no significant effect. Evidence from three studies [25, 26, 27] reported a statistically significant decline in the depression scores of the study group as compared to control group. However, a study [30] reported no significant change in depression scores between the groups because participants in each group was subjected to different intensity of aerobic exercises, ranging from low to high.

For the bio-psychosocial outcome (depression), four studies [25, 26, 27, 30] were included in the meta-analyses. The meta-analyses revealed that aerobic exercise interventions had a significant effect on depression scores, causing a decline in the depression scores of the subjects in the intervention group as compared to those in the control group. This evidence is similar to the findings of a current review [32] that investigated the various pharmacological and non-pharmacological interventions that are effective in the management of depressive symptoms in PLWH. The study included only one article on the effect of aerobic exercise interventions and concluded that exercise could be a remedy to depressive symptoms in PLWH undergoing HAART [32].

For the pro-inflammatory outcome (hs-CRP), a narrative synthesis was conducted due to substantial heterogeneity in the two studies [28, 29]. The two studies reported a non-significant effect of aerobic exercise intervention on hs-CRP in PLWH. This is in agreement with a meta-analyses of five articles that reported a non-significant effect of aerobic exercise on hs-CRP among healthy adults [9]. Also, this is similar to a recent systematic review that reported a no significant change in biomarkers of inflammation (IL-6 and IL-1 $\beta$ ) after exercise intervention [33]. However, the results of the narrative synthesis on effects of aerobic exercise on hs-CRP in PLWH should not be concluded as 'no evidence of effect', because the two clinical trials included do not have sufficient power to detect treatment effects. Therefore, more homogenous studies investigating the effect of aerobic exercise intervention on hs-CRP in PLWH are necessary for an effective estimate of effects.

The meta-analysis of the four article (one high quality and three low quality) reported a significant effect of aerobic exercise on depression in PLWH undergoing HAART. The evidence suggests that aerobic exercise intervention could be effective in reducing depression; however, because of the low quality of the included articles, we suggest that exercise could be incorporated as an adjunct therapy in the care of PLWH. The recommended dosage of aerobic exercise that could elicit an intervention effect as recorded in this review considering the Frequency, Intensity, Time and Type (FITT) principle is thus; exercise frequency of 3-5 sessions/week; Intensity: 55-75% of age-predicted maximal heart rate, 60-80% of  $VO_2$  max, 50-80% of heart rate reserve (HR); Time: 24-60 minutes and Type: continuous or interval aerobic exercises involving large muscle

groups. Such exercises could include, walking, cycling with bicycle ergometer, running, treadmill exercise. It is suggested that qualified professionals (e.g. physiotherapist) should administer and monitor the exercise programs. Generally, the results of this review is an addition to the existing body of evidence highlighting the benefits of exercises for PLWH undergoing HAART.

### **Quality of evidence**

Following the specifications in the GRADE ratings for quality of evidence [24], the evidence could be rated as a moderate quality evidence. This is as a result of the identification of specific bias in the included studies. Some studies included in the review demonstrated a high risk of selection bias due to non-utilization of random sequence generation in the recruiting of participants. Some other included studies had detection bias because the assessors were not blinded. Furthermore, some studies had attrition bias due to incomplete outcome reporting and drop-out rate with the failure to conduct an intention-to-treat analysis. Only two out of the six included clinical trials were appraised as high quality, while the others were appraised as low-quality trials. All these culminated to the moderate-GRADE quality of evidence.

## **Conclusions**

### **Implications to Practice**

Incorporating aerobic exercise interventions in the care of PLWH could elicit a decline in depression outcomes in this population. Therefore, PLWH could benefit from patient-specific structured exercise interventions administered by physiotherapists as part of the multidisciplinary health care strategies. However, caution should be applied in using this exercise prescribed above because of the low quality of the studies included that evaluated the effect of aerobic exercise on depression outcomes on PLWH taking HAART. There was no significant effect of the aerobic exercise interventions on hs-CRP. However, the interpretation of this evidence should not be seen as 'no evidence of effect' because the individual clinical trials did not attain sufficient power to detect treatment effects in this population.

### **Implications to research**

The existing pool of RCTs regarding the effects of aerobic exercise on the specified outcomes, especially hs-CRP and depression is insufficient. Among the few articles found, majority of them were of low quality with some methodological issues including small sample size and contains elements of high risk of bias. Therefore, further studies, adequately powered and would demonstrate low risk of bias including blinding of assessors and participants, use of random sequence generation and allocation concealment are necessary. This would strengthen the scientific evidence and inform practice in the management of inflammatory responses and depression in PLWH.

### **Limitations of the study**

While we made considerable effort to ensure the robustness of the search strategy, potentially relevant studies may not have been identified if authors did not use the "MESH" terms we used in our search. Also, it is possible that some studies published in other languages may have been missed since we limited our search to only articles published in English. Funnel plot or sensitivity analysis to determine publication bias (false positives)

was not performed in the meta-analysis, because only 4 studies were included in the meta-analysis, which is less than Cochrane recommended number of ten or more than ten studies needed to perform funnel plot or sensitivity analysis.

## List Of Abbreviations

Human immune deficiency virus		HIV
Highly Active Antiretroviral therapy		HAART
C-reactive protein		CRP
High sensitivity C-reactive protein		Hs-CRP
People living with HIV/AIDS		PLWH
Review Manager		RevMan
Randomized control trials		RCTS
Preferred Reporting Items for Systematic Reviews and Meta-analyses		PRISMA
Physiotherapy Evidence Database		PEDro
Medical subject heading		MeSH
Allied and Complementary Medicine Database Nursing and Allied Health Literature	CINAHL	AMED Cumulative Index to
Excerpta Medica database		EMBASE
Allied and Complementary Medicine Database		AMED
Grading of Recommendations Assessment Development and Evaluation		GRADE
Nigeria Health Research Ethics Committee		NHREC
Becks Depression Inventory		BDI
Positive and Negative Affect Schedule		PANAS

## Declarations

### Ethics approval and consent to participate

This study was approved by the University of Nigeria Health Research Ethics Committee on certificate number - NHREC/05/01/2008B-FWA00002458-1RB00002323. Studies reviewed included only those where the participants gave their written informed consent, prior to participation, and after the purpose of the study was

explained to them. They were informed of their right to withdraw from the study at any time of their choice, and these rights were strictly respected in accordance with the Helsinki declaration.

### **Consent to publish**

Not applicable

### **Availability of data and materials**

The datasets supporting the conclusions of this article are available in the institutional University of Nigeria repository and will be made easily available on request when required.

### **Competing interests**

The Authors declare that they have no competing interests.

### **Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

### **Authors' Contributions**

EMA and MEK conceived the study, participated in literature search and review, data extraction, study design and coordination, performed the statistical analysis, and helped draft the manuscript. IBN, OJA and UOA participated in data extraction and helped drafted the manuscript. OAE and UOA participated in literature search and review, data extraction and helped draft the manuscript. OAE, UOA, and IBN participated in the design of the study, coordination, and helped draft the manuscript. All authors read and approved the final manuscript.

### **Acknowledgements**

We wish to acknowledge the library staff of the Department of Medical Rehabilitation and College of Medicine, University of Nigeria, Enugu Campus, for all their support, assistance, and contributions towards the success of this work.

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## Tables

**Table 1: Study characteristics, intervention parameters, outcome and conclusion**

Study, (Country), Design, Attrition	Participant (sample size)	Interventions parameters & description	Outcomes	Conclusion
<b>Aweto et al. [25] (Nigeria), RCT, 17.5%</b>	Individuals with HIV on HAART (n=40)	Description: Aerobic exercise training three times a week for six weeks and counselling.  Control: Only Counselling.	Depression: Becks Depression Inventory (BDI). Outcome assessed at baseline and at 6 weeks.	Aerobic exercise training significantly reduced depressive symptoms in people living with HIV.
<b>Lox et al. [26] (USA), RCT, 2.9%</b>	HIV-I-infected men on HAART (n=22)	Duration= 12 weeks Description Aerobic exercise conducted on a Lifecycle 9500 using the "manual7" option at a constant pedal rate between 76 and 84 revolutions per minute (RPM). Administered by: Physiotherapists  Control: stretching/flexibility control group.	Negative mood: Positive and Negative Affect Schedule (PANAS). Outcome assessed at baseline and at 12 weeks.	Exercise may be one therapeutic modality capable of enhancing components of subjective well-being and should be considered a complimentary therapy for treating the psychological and emotional manifestations associated with a positive HIV- 1 diagnosis.
<b>Neidig et al. [27] (USA), RCT, 20%</b>	HIV-infected adults on HAART (n=60)	Duration= 12 weeks Description: supervised 12-week aerobic exercise training program with either treadmill, stationary biking or walking. Administered by: Nurses, exercise physiologists and physicians  Control: a wait list (maintain usual activity).	Depression: Center for epidemiological studies-depression Scale. Outcome assessed at baseline and at 12 weeks.	As compared to study controls, exercise participants showed reductions in depressive symptoms on all indices, and total depressive symptoms scores were highly correlated.
<b>Ross et al. [28] (South Africa)pilot c, RCT, 39.2%</b>	HIV+ on HAART for ≥6 months. (n=84)	Duration= 12 months Description: education and home-based pedometer walking program to improve participants' activity levels to meet the Public Health physical activity recommendations of 30 minutes of moderate intensity brisk walking. 30 minutes walking programme 3 or 5 times a week over a 12-month period. Administered by: Physiotherapists  Control: continued with standard clinic management.	High Sensitivity CRP. Outcome assessed at baseline and at 12 months.	An education and home-based pedometer walking program improves physical activity levels, and beneficial changes in other IHD risk factors (hs-CRP) were noted.
<b>Terry et al. [30]</b>	Carriers of	Intensity= 55-60% of maximal heart rate	Depression: Montgomery-	HIV seropositive

<b>(Brazil),Pre-test-post-test design,32.3%</b>	the HIV-1 virus on HAART (n=22)	Duration= 12 weeks Description: 12 week aerobic exercise training program (36 sessions of 30 minutes, 3 times per week), in a moderate intensity group (60±4% of maximal heart rate).  Control: Pre-test-post-test design (Self-controlled)	Asberg Depression Scores. Outcome assessed at baseline and at 12 weeks.	individuals that participate in moderate and high intensity exercise programs are able to increase their functional capacity without any detectable changes in immunologic variables, anthropometric measurements or depression scores.
<b>Bonato et al. [29] (Italy), Pilot clinical trial, 28.6%</b>	cART-treated, sedentary adults living with HIV (n=35)	Intensity= 65-75% of maximal heart rate Duration= 12 weeks Description: 12-week protocol, consisting of three sessions per week of 30 min circuit-training walk group  Control: Pre-test- post-test design (Self-controlled)	High-sensitivity CRP Outcome assessed at baseline and at 12 weeks.	Brisk walking could improve lipid profile and inflammatory Markers (hs-CRP) in chronic HIV infection.

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**Table 2: Risk of bias in individual studies**

Study	Sources/Potential sources of bias <sup>a</sup>							Summary of bias <sup>a</sup>	Quality index <sup>b</sup>
	Selection bias		Performance bias	Detection bias	Bias due to attrition	Reporting bias	Other bias		
	Random sequence generation	Allocation concealment	Participants and personnel blinding	Blinding of outcome assessment	Incomplete data	Selective reporting			
<b>Aweto et al. [25]</b>	No	Yes	No	Yes	No	No	No	Low	High
<b>Lox et al. [26]</b>	No	Yes	No	Yes	Yes	No	No	High	Low
<b>Neidig et al. [27]</b>	No	Yes	No	Yes	Yes	No	No	High	Low
<b>Ross et al. [28]</b>	No	No	No	No	No	No	No	Low	High
<b>Terry et al. [30]</b>	Yes	Yes	No	Yes	Yes	No	No	High	Low
<b>Bonato et al. [29]</b>	Yes	Yes	No	Yes	No	Yes	No	High	Low

The Cochrane's tool was used to determine and summarize possible sources of risk of bias in the included studies [17] (Yes indicates the presence of or potential presence of a source of bias).

<sup>a</sup> summary risk of bias in included studies was presented.

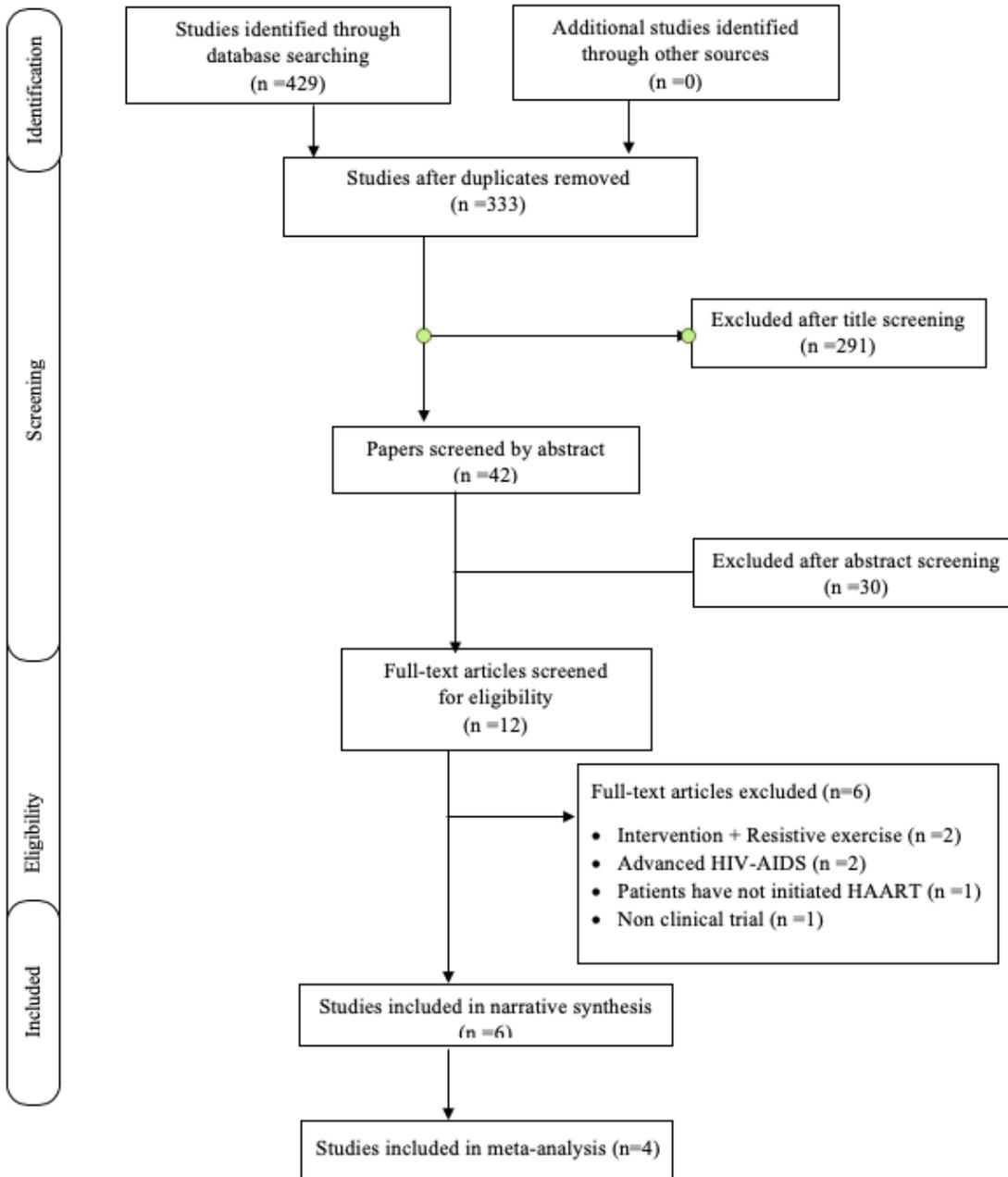
<sup>b</sup> studies were subsequently rated as low quality trials (i.e. having high risk of bias) or high quality trials (i.e. having low to moderate risk of bias if there was  $\geq 3$  or  $< 3$  identifiable sources of bias respectively [23]).

**Table 3: Data extraction of findings (except where specified, results are presented as Intervention vs Control)**

Study/year	Outcome	Baseline (Mean ± SD)		P value	Post intervention (Mean ± SD)		P value
		Intervention	Control		Intervention	Control	
Aweto et al. [25]	Depression Becks Depression Inventory	10.33 ± 6.48	10.06 ± 5.96	p ≥ 0.05	3.50 ± 1.27	8.33 ± 5.80	*p = 0.001
Lox et al. [26]	Depression Positive and negative affect schedule	25.64 ± 8.67	23.40 ± 8.58	p ≥ 0.05	20.18 ± 8.48	25.40 ± 8.51	p < 0.05
Neidig et al. [27]	Depression Centre for Epidemiological studies- Depression scale	12.3 ± 11.8	14.1 ± 10.7	p ≥ 0.05	7.2 ± 7.1	14.1 ± 11.3	*p = 0.028
Terry et al. [30]	Depression Montgomery-Asberg Depression Scores	3.6 ± 4.4	4.1 ± 6.2	p > 0.05	3.0 ± 4.1	3.7 ± 6.3	p > 0.05
Bonato et al. [29]	hs-CRP	2.0 ± NS	3.1 ± NS	NS	0.9 ± NS	1.8 ± NS	p > 0.05
Ross et al. [28]	hs-CRP	8.58 ± 1.29	5.45 ± 1.02	p ≥ 0.05	0.31 ± 1.29 (At 12 months)	0.21 ± 0.59 (At 12 months)	p = 0.59

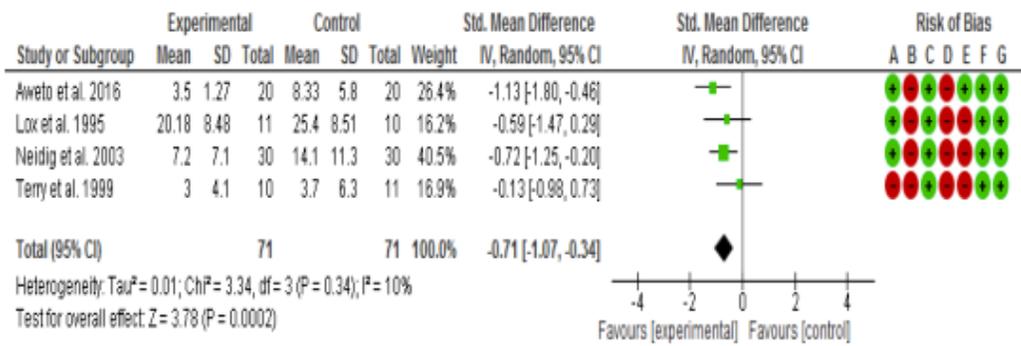
**Note:** \*p<0.05 is statistically significant; NS= not stated; Int.= intervention; Cont.= control. Confidence interval was reported in figure 2

## Figures



**Figure 1**

Aerobic exercise interventions review PRISMA flow diagram



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**Figure 2**

Meta-analysis of effects of aerobic exercise intervention on depression in PLWH

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SRAppendixBMCSUBmit.docx](#)