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EVALUATING THE EFFECTIVENESS OF PHYSICAL EXERCISE INTERVENTIONS IN PERSONS LIVING WITH HIV: OVERVIEW OF SYSTEMATIC REVIEWS

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Abstract

Physical exercise (PE) has not been well studied in persons living with HIV (PLHIV). We conducted an overview of systematic reviews to assess the effectiveness of PE and to determine the most appropriate PE regimen for PLHIV. We used the CDC's Prevention Research Synthesis Project's database and manual searches to identify systematic reviews published between 1996 and 2013. We qualitatively synthesized the findings from five reviews to assess the effectiveness of PE and conducted meta-analyses on CD4 counts to identify the best PE regimen. PE is associated with reduced adiposity and depression, but was not associated with a decrease in HIV viral load. CD4 counts were improved by interventions with interval aerobic or 41–50 minutes of exercise three times per week compared with other modes and duration of exercise. PE appears to benefit PLHIV, but more research is needed to help develop appropriate PE strategies specifically for PLHIV.

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The latest U.S. Centers for Disease Control and Prevention (CDC) report showed that more than 1.2 million persons living with human immunodeficiency virus (PL-HIV) live in the United States (CDC, 2015b). Due to the advances in highly active antiretroviral therapy (HAART), HIV infection has become a manageable chronic illness, and the life expectancy of this population has increased (CDC, 2015a). As they live longer, PLHIV experience age-related heath issues or conditions not associated with acquired immune deficiency syndrome (non-AIDS-defining conditions) such as cardiovascular diseases or cancers (CDC, 2015a). Due to the side-effects of HAART and declining CD4 counts caused by HIV (Helleberg et al., 2013), PLHIV experience an accelerated aging process (Rickabaugh et al., 2015; Smith, de Boer, Brul, Budovskaya, & van Spek, 2012) and increased risks of non-AIDS-defining conditions.

Physical exercise (PE), a subset of physical activity that has a final or intermediate objective for the improvement or maintenance of physical fitness (Caspersen, Powell, & Christenson, 1985), has been recognized as an effective strategy to slow the aging process and reduce the risk for chronic illnesses in general population (U.S. Department of Health and Human Services, 2008). Recent systematic reviews have identified the benefits of PE on physiological, psychological, and immunological outcomes (Barry et al., 2016; Tavares, Moraes, Deslandes, & Laks, 2014; Vendramin et al., 2016; Wilson, Ellison, & Cable, 2015). The 2008 Physical Activity Guidelines for Americans recommend that adults should perform at least 150 minutes a week of moderate-intensity or 75 minutes a week of vigorous-intensity aerobic exercise (AE), or an equivalent combination of both, with two or more times of progressive resistance exercise (PRE) per week regardless of age or the presence of chronic illnesses (U.S. Department of Health and Human Services, 2008).

In terms of managing HIV, previous systematic reviews have found that PE improved body composition (Fillipas, Cherry, Cicuttini, Smirneos, & Holland, 2010; O’Brien, Nixon, Tynan, & Glazier, 2010) and relieved depression (O’Brien et al., 2010), but did not significantly reduce viral load (O’Brien et al., 2010; O’Brien, Tynan, Nixon, & Glazier, 2008). Several systematic reviews have been conducted to understand the effectiveness of various types and frequencies of PE interventions. However, to our knowledge, no overview of systematic reviews, which synthesized data from multiple systematic reviews to explore the effectiveness of PE among PL-HIV, has been conducted to assist healthcare providers with making decisions regarding evidenced-based interventions. Overviews of systematic reviews provide a more comprehensive profile of an intervention effect on the topic when comparing with systematic reviews by synthesizing data reported in the systematic reviews (Higgins & Green, 2011). The purposes of this overview of systematic reviews were to (a) understand the effectiveness of PE on physiological health, psychological health, and virological status (viral load) outcomes by synthesizing currently available systematic reviews, and (b) determine the evidence for an appropriate PE regimen to improve health conditions among PLHIV.

METHODS

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist as a guideline to organize this review (Moher, Liberati, Tetzlaff, & Altman, 2009). Methods of the overview of systematic reviews are similar to those for systematic reviews (Higgins & Green, 2011), thus, we applied established techniques used for synthesizing primary studies to locate, assess, and synthesize relevant systematic reviews (Higgins, Lasserson, Chandler, Tovey, & Churchill, 2016).

SEARCH STRATEGY

We implemented a comprehensive systematic literature search to identify systematic reviews on the effectiveness of PE among PLHIV from 1996–2013 using the CDC HIV/AIDS Prevention Research Synthesis (PRS) Project database (Lyles, Crepaz, Herbst, & Kay, 2006). In January 2015, the PRS database accumulated 69,413 records identified from the years 1988–2013 related to HIV, AIDS, or sexually transmitted disease (STD) behavioral intervention literature. These records are collected by comprehensive automated and manual search strategies that were developed by librarians with expertise in building and conducting systematic literature searches (DeLuca et al., 2008). The four comprehensive automated searches for HIV prevention literature (Risk Reduction; Linkage to, Retention in, and Re-engagement in HIV Care; Medication Adherence; and Overview of Reviews) including primary studies and systematic reviews are implemented annually in the following databases: MEDLINE (OVID), EMBASE (OVID), and PsycINFO (OVID), CAB Global Health (OVID), CINAHL (EBSCOhost), and Sociological Abstracts (ProQuest; DeLuca et al., 2008). The full search strategy is available from the authors. The manual search includes a quarterly hand search of 60 journals, publication alerts, and reference harvesting from relevant HIV behavioral prevention research literature (CDC, 2015c).

For this overview of systematic reviews, the librarian searched for systematic review citations in the PRS database records using 76 PE search terms identified by a subject matter expert in physical activity. The full search term is available from the authors. Additionally, publications were requested from subject matter experts, and we searched reviews from other sources such as electronic mail lists and conference proceedings. We also conducted hand searches for additional citations in reference lists of identified systematic reviews.

SYSTEMATIC REVIEW SELECTION

All identified citations were exported to the systematic review software, DistillerSR. A two-step approach was used to identify the included studies. First, two reviewers screened the citations by title and abstract to identify the studies that met the following criteria: (a) related to PLHIV but not biomedical interventions treating HIV disease, prevalence, or incidence reports; (b) any type of PE intervention; and (c) published in English. Disagreements were resolved through discussion. If there was a lack of agreement between the two reviewers, discrepancies were resolved by a third reviewer.

Second, two reviewers screened the full text of identified studies that met the subsequent inclusion criteria: (a) report of a systematic review, (b) included interventions conducted with adults who are ≥ 18 years of age or defined by the authors as young adults, (c) included at least one primary study in the U.S., (d) included at least one primary study with a PE only intervention, and (e) reported one or more outcomes of interest (i.e., physical and psychological health and virological status).

QUALITY OF SYSTEMATIC REVIEWS

Three reviewers independently assessed the quality of each identified systematic review with the Assessment of Multiple Systematic Review (AMSTAR) tool. The AMSTAR developed by Shea, Bouter, et al. (2007) contains 11 items (e.g., Was a comprehensive literature search performed? and Was the likelihood of publication bias assessed?) anchored with four multiple choice responses. (No, Yes, Cannot answer, and Not applicable). Total scores were calculated by counting the number of Yes responses to the 11 items. The possible total score ranged from zero to 11. Higher scores indicated better quality of the systematic review. Other researchers have established the AMSTAR score cut points and each systematic review was classified as: high quality (8–11 points), moderate (5–7 points), and low (0–4 points) (Flodgren et al., 2011). The psychometric properties of the AMSTAR published elsewhere (Shea, Grimshaw, et al., 2007) showed good reliability, construct validity, feasibility, and interrater agreement (Shea, Grimshaw, et al., 2007, 2009). For the present study, the discrepancies among the three reviewers on the AMSTAR scores were resolved by discussion.

DATA SYNTHESIS

The PE interventions reported in the systematic reviews were classified into three types for this overview: (a) AE, activities to increase breath and heart rates, and strengthen the heart and lungs (e.g., brisk walking, jogging, rowing, swimming, or cycling); (b) PRE, exercise activities to strengthen muscle (e.g., lifting weights or exercise that uses one's own body weight for resistance); and (c) the combination of AE and PRE at the same exercise session (U.S. Department of Health and Human Services, 2008).

We were unable to conduct a meta-analysis on the systematic reviews due to the nature and variability of the data reported. Consequently, we analyzed the data in two ways—(a) narrative synthesis of systematic reviews and (b) meta-analysis of primary studies from the systematic reviews.

Narrative Synthesis of Systematic Reviews—Because of the nature of included systematic reviews, we synthesized the reported narrative synthesis of findings that were either descriptive or could not be combined with quantitative methods. The findings were categorized into three outcomes according to the fundamentals of health for PLHIV: (a) physiological health, any medical diagnosis (e.g., hypertension, hyperlipidemia, cardiovascular disease, cancer, or osteoporosis) or outcome related to diagnostic procedures or tests associated with the medical diagnosis or physical function (e.g., blood pressure, cholesterol level, bone density); (b) psychological health, including behavior, emotion, social well-being, or overall mental health (e.g., depression, anxiety); and (c) virological status or HIV viral load.

We also reported standardized estimates, e.g., mean difference (MD), standardized mean difference (SMD), or weighted mean difference (WMD) with 95% CI and I^2 (heterogeneity) when authors reported these statistics in the systematic reviews.

Meta-analysis of Primary Studies—We were unable to conduct a meta-analysis of the findings of meta-analytic studies on selected outcomes due to the high number of shared primary studies. Thus, we conducted a meta-analysis of the unique primary studies with stratified analyses to identify the most appropriate PE regimen and to reduce heterogeneity in the overall finding. We stratified by exercise type (AE, PRE, or the combination of AE and PRE), mode (interval or continuous), duration (minutes in one session), frequency (times per week), and length of the intervention (weeks) of PE.

The overall effectiveness of PE interventions was evaluated by calculating MD estimates using a random effects meta-analysis model. Due to the varied duration of the exercise session in the studies, we categorized the time spent in exercise based on the moderate-intensity aerobic exercise activity from the 2008 Physical Activity Guidelines for Americans which recommends at least 150 minutes of PE per week (U.S. Department of Health and Human Services, 2008). We chose the recommended duration for the moderate-intensity exercise (150 minutes per week) rather than one for vigorous-intensity exercise (75 minutes per week) or strengthening exercise only since most of interventions we identified were considered as moderate-intensity exercise with or without vigorous-intensity exercise or strengthening. As the article review period was from 1995–2013, most of the interventions preceded the release of the 2008 Physical Activity Guidelines; accordingly all interventions used a recommended PE frequency of three times per week. Thus, we chose 50 minutes as a cut-point. To further reduce the heterogeneity in the group of less than or equal to 50, we divided it into two groups: less than or equal to 40 minutes and 41 to 50 minutes.

We conducted step-down analyses of all possible pairwise comparisons as needed when the stratified analysis showed statistically significant differences ($p < .05$). Lastly, we conducted sensitivity analyses to determine if any one study influenced the results and assessed publication bias using the Begg and Mazumdar rank correlation test and Egger’s test of the intercept (Rothstein, Sutton, & Borenstein, 2006).

RESULTS

REVIEW SELECTION

Our systematic search and screening processes are shown in the PRISMA flow-chart in Figure 1. First, the initial search identified 343 citations in the PRS database and no other unique citations through other sources. Of these citations, 26 studies were eliminated due to duplications and 317 studies remained for further screening. Second, we excluded 273 studies based on the title and abstract screening. We screened the remaining 44 studies at full text and further excluded 28 studies. Sixteen potential studies remained for inclusion in the synthesis. In situations of duplicate studies ($n = 5$), the older studies (Nixon, O’Brien, Glazier, & Tynan, 2002, 2005; O’Brien, Nixon, Glazier, & Tynan, 2004; O’Brien, Nixon, Tynan, & Glazier, 2004, 2006) were excluded. An additional six reviews were excluded since all (Baril et al., 2005; Biswas, 2007; Guaraldi, Stentarelli, & Faluz, 2013; London & Manjra, 2011; Young & Busgeeth, 2010) or nearly all primary studies (Keithley & Swanson, 2013) were shared across the systematic reviews. Thus, five systematic reviews (Dudgeon, Phillips, Bopp, & Hand, 2004; Fillipas et al., 2010; Gomes Neto, Ogalha, Andrade, & Brites, 2013; O'Brien et al., 2008, 2010) were included in this overview of systematic reviews (Table 1)

QUALITY OF SYSTEMATIC REVIEWS

The AMSTAR total scores are shown in Table 1. Two systematic reviews were considered as high quality (Fillipas et al., 2010; O'Brien et al., 2010), two were moderate (Gomes Neto et al., 2013; O'Brien et al., 2008), and one was low quality (Dudgeon et al., 2004). Two systematic reviews had the highest score of 9 (Fillipas et al., 2010; O'Brien et al., 2010) and the other three systematic reviews had scores of seven (O'Brien et al., 2008), five (Gomes Neto et al., 2013), and three (Dudgeon et al., 2004).

All systematic reviews (Dudgeon et al., 2004; Fillipas et al., 2010; Gomes Neto et al., 2013; O'Brien et al., 2008, 2010) provided an a priori design and used appropriate methods to synthesize their findings. Four reviews (Fillipas et al., 2010; Gomes Neto et al., 2013; O'Brien et al., 2008, 2010) conducted a comprehensive literature search and reported the screening and data extraction procedures, and the scientific quality of the included studies. Four reviews (Dudgeon et al., 2004; Fillipas et al., 2010; O'Brien et al., 2008, 2010) provided the characteristics of the included studies. No systematic reviews assessed or reported the publication bias or included the conflict of interest statement for the review and primary authors.

DATA SYNTHESIS

Narrative Synthesis of Systematic Reviews—Three (Fillipas et al., 2010; O'Brien et al., 2008, 2010) out of five systematic reviews were meta-analyses (Table 1). The number of primary studies included in each systematic review was between eight (Gomes Neto et al., 2013) and 18 (Dudgeon et al., 2004). The total number of study participants in each systematic review ranged from 332 (O'Brien et al., 2008) to 720 (Dudgeon et al., 2004). The reviews included both male and female participants, but all reviews had predominantly male participants. Interventions include PE only and the combination of PE and pharmacological interventions (e.g., hormone or nutrition supplements; Dudgeon et al., 2004; O'Brien et al., 2008).

All five systematic reviews reported physiological health outcomes while four reviews reported psychological health outcomes (Dudgeon et al., 2004; Gomes Neto et al., 2013; O'Brien et al., 2008, 2010) and two reported virological status outcomes (O'Brien et al., 2008, 2010; Table 2).

Physiological Health: After we examined all identified systematic reviews, we categorized physiological health outcomes into two groups: body composition and cardiopulmonary status.

The impact of exercise on body composition was assessed by four systematic reviews (Dudgeon et al., 2004; Fillipas et al., 2010; O'Brien et al., 2008, 2010). These reviews showed that all types of exercise (AE, PRE, and the combination) can improve particular body composition outcomes. AE reduced abdominal girth, body fat mass (SMD = −0.37, 95% CI [−0.74, −0.01], n = 118, I^2 = 78%), body mass index (MD = −1.31 kg/cm^2, 95% CI

[−2.59, −0.03], n = 186, I^2 = 0%), fat mass (MD = −1.12 %, 95% CI [−2.18, −0.07], n = 119, I^2 = 8%), triceps skinfold thickness of subcutaneous fat (MD = −1.83 mm, 95% CI [−2.36, −1.30], n = 144, I^2 = 92%), waist circumference (SMD = −0.74, 95% CI [−1.08, −0.39], n = 142, I^2 = 21%), and waist-to-hip ratio (SMD = −0.94, 95% CI [−1.30, −0.58], n = 142, I^2 = 90%) for persons who were on HAART and had adiposity or were overweight (Dudgeon et al., 2004; Fillipas et al., 2010; O'Brien et al., 2010). Meanwhile, PRE can increase body weight (MD = 5.02 kg, 95% CI [3.54, 6.49], n = 46, I^2 = 75%), lean body mass, muscle mass, peripheral girth (SMD = 1.08, 95% CI [0.35, 1.82], n = 46, I^2 = 95%), physical functioning, and strength among PLHIV with peripheral fat wasting (Dudgeon et al., 2004; Fillipas et al., 2010; O'Brien et al., 2008). The combination of AE and PRE increased leg muscle area (MD = 4.79 cm^2, 95% CI [2.04, 7.54], n = 60, I^2 = 11%), and muscle mass (Dudgeon et al., 2004; O'Brien et al., 2010). PRE or the combination of AE and PRE increased mean arm and thigh girth (WMD = 7.91 cm, 95% CI [2.18, 13.65], n = 46, I^2 = 67.4%; O'Brien et al., 2008).

Two meta-analyses and one systematic review evaluated the impact on cardio-pulmonary status. These reviews found that all types of exercise can affect selected outcomes of cardiopulmonary status (Gomes Neto et al., 2013; O'Brien et al., 2008, 2010). AE with or without PRE can improve aerobic capacity including VO_2max (Gomes Neto et al., 2013; O'Brien et al., 2010). O'Brien (2008) found that PRE with or without AE can impact submaximum heart rate (MD = 81.99 mL/kg/min, 95% CI [−155.34, 319.33], n = 60, I^2 = 58.6%) and exercise time (MD = 3.92 min, 95% CI [−0.63, 8.47], n = 62, I^2 = 98.4%), but these findings were not statistically significant.

Psychological Health: Four systematic reviews (Dudgeon et al., 2004; Gomes Neto et al., 2013; O'Brien et al., 2008, 2010) reported the effectiveness of PE on psychological outcomes. These outcomes included depression (Dudgeon et al., 2004; O'Brien et al., 2010), mood (O'Brien et al., 2008), and health-related quality of life (Gomes Neto et al., 2013). AE can improve the quality of life, hope, desire to continue living, and depression (Dudgeon et al., 2004; O'Brien et al., 2010). The meta-analysis study found a significant improvement on the Profile on Mood States Depression-Dejection subscale with AE (MD = −7.68 points, 95% CI [−13.47, −1.90], n = 65, I^2 = 94%; O'Brien et al., 2010). A systematic review by Gomes Neto et al. (2013) indicates that the combination of AE and PRE can improve health-related quality of life.

Virological Status: Two (O'Brien et al., 2008, 2010) of the five systematic reviews assessed viral load as an outcome. Interventions included all types of exercise (AE, PRE, and the combination). However, neither review found any significant changes and reported no impact of exercise on viral load as well as no adverse effects.

Meta-analysis of Primary Studies

We conducted a meta-analysis on the CD4 count outcome that was evaluated by the same instruments across systematic reviews. Of the five identified systematic reviews, we found three systematic reviews that reported CD4 counts outcomes (Figure 2; Dudgeon et al., 2004; O'Brien et al., 2008, 2010). We identified 23 primary studies from these systematic reviews that reported the CD4 counts outcome. We excluded 13 primary studies that were duplications and identified 10 unique primary studies (Baigis et al., 2002; Dolan et al., 2006; Grinspoon et al., 2000; LaPerriere et al., 1990; Lox, McAuley, & Tucker, 1995; Mutimura, Stewart, Crowther, Yarasheski, & Cade, 2008; Perna et al., 1999; Rigsby, Dishman, Jackson, Maclean, & Raven, 1992; Smith et al., 2001; Stringer, Berezovskaya, O'Brien, Beck, & Casaburi, 1998) that conducted a PE-only intervention versus a non-exercise control group.

Summary Across Primary Studies—Nine out of ten primary studies were conducted in the U.S. and one was conducted in Rwanda (Table 3). The number of study participants in each study ranged from 17 to 123 individuals. Five (Grinspoon et al., 2000; LaPerriere et al., 1990; Lox et al., 1995; Rigsby et al., 1992; Stringer et al., 1998) studies included only male participants while one (Dolan et al., 2006) included females and four (Baigis et al., 2002; Mutimura et al., 2008; Perna et al., 1999; Smith et al., 2001) included both females and males. Several primary studies had specific inclusion criteria on body composition (e.g., with AIDS-related wasting or severe body fat distribution; Dolan et al., 2006; Grinspoon et al., 2000; Mutimura et al., 2008; Smith et al., 2001) or immunological status (Baigis et al., 2002; Stringer et al., 1998).

The types of exercise interventions were AE ($n = 6$; Baigis et al., 2002; LaPerriere et al., 1990; Mutimura et al., 2008; Perna et al., 1999; Smith et al., 2001; Stringer et al., 1998) and combination exercise ($n = 3$; Dolan et al., 2006; Grinspoon et al., 2000; Rigsby et al., 1992). Lox and colleagues (1995) had two intervention groups (AE or PRE) in addition to the control group. This is the only study which had a PRE alone intervention group. Two (LaPerriere et al., 1990; Perna et al., 1999) of the AE interventions were interval exercise, and the others were continuous exercise. The duration of each exercise session ranged from 40 to 120 minutes. All interventions reported a frequency of three times per week. The length of interventions ranged from 5 to 24 weeks and 12 was the most frequent length (Grinspoon et al., 2000; Lox et al., 1995; Perna et al., 1999; Rigsby et al., 1992; Smith et al., 2001) reported.

Meta-analysis—Since Lox and colleagues (1995) had two intervention groups (AE or PRE), we synthesized CD4 count data from 11 exercise interventions within 10 primary studies (Baigis et al., 2002; Dolan et al., 2006; Grinspoon et al., 2000; LaPerriere et al., 1990; Lox et al., 1995; Mutimura et al., 2008; Perna et al., 1999; Rigsby et al., 1992; Smith et al., 2001; Stringer et al., 1998). The meta-analysis showed no impact of exercise on CD4 counts (MD = 22.35, 95% CI [−3.57, 48.27], $n = 412$, $I^2 = 76\%$) using a random effects model (Figure 2). The high heterogeneity implies variation in the study's findings.

Stratified Analysis—We were not able to perform a stratified analysis on the frequency of exercise because all interventions were in the three-times-a-week category. The type, mode, or duration of exercise session for the PRE intervention in the study by Lox et al. (1995) were not applicable or reported; thus, we excluded this primary study from the stratified analysis for these variables.

The stratified analysis showed significant differences in CD4 counts among exercise modes using a random effects model (Q-value = 5.11, $df(Q) = 1$, $p = .02$). An interval exercise mode (Figure 3; MD = 70.17, 95% CI [14.63, 125.71], $n = 45$, $I^2 = 68\%$) demonstrated a statistically significant greater impact on CD4 counts compared to continuous exercise (MD = 0.67, 95% CI [−22.64, 23.98], $n = 345$, $I^2 = 62\%$).

The stratified analysis showed that the duration of exercise session differed in effects on CD4 counts (Q-value = 16.93, $df(Q) = 2$, $p < .005$). Furthermore, in the pairwise comparisons, interventions with 41 to 50 minutes of exercise (Figure 4; MD = 71.62, 95% CI [29.22, 114.01], $n = 66$, $I^2 = 38\%$) had a statistically significant greater impact on CD4 counts compared to those with less than or equal to 40 minutes (MD = 16.51, 95% CI [2.95, 30.07], $n = 91$, $I^2 = 0\%$; Q-value = 5.89, $df(Q) = 1$, $p = .02$) or more than 50 minutes (MD = −16.61 95% CI [−35.10, 1.88], $n = 233$, $I^2 = 11\%$; Q-value = 13.98, $df(Q) = 1$, $p < .005$) using a random effects model. Interventions that were less than or equal to 40 minutes of exercise also had a statistically significant greater impact on CD4 counts compared to those with more than 50 minutes (Q-value = 8.01, $df(Q) = 1$, $p < .005$) using a random effects model. Heterogeneity was reduced in the stratified analysis.

For the length of exercise intervention, 5 out of 10 primary studies were 12 weeks, thus, we divided the length of intervention from the studies into three groups: less than, equal to, or more than 12 weeks. No significant difference was found on CD4 counts among different length of exercise intervention (Q-value = 0.73, $df(Q) = 2$, $p = .69$) as well as exercise type (AE vs PRE; Q-value = 0.010, $df(Q) = 1$, $p = .92$) using a random effects model.

Sensitivity Analysis and Publication Bias—We performed a sensitivity analysis and examined publication bias on the 11 exercise interventions within 10 primary studies. We found no meaningful change on point estimations with one study removed from the analysis. In addition, we found no further potential explanation for the large amount of heterogeneity. Moreover, using visual inspection of a funnel plot and using Begg and Mazumdar rank correlation test ($p = .64$) and Egger's test of the intercept ($p = .13$), we found no statistically significant publication bias.

DISCUSSION

We conducted an overview of systematic reviews on the effectiveness of PE and to determine the most appropriate exercise regimen among PLHIV. To our knowledge, this is the first overview of systematic reviews on this topic. We identified five systematic reviews (Dudgeon et al., 2004; Fillipas et al., 2010; Gomes Neto et al., 2013; O'Brien et al., 2008, 2010), including three meta-analyses with generally moderate to high study quality based on AMSTAR scores.

Using a narrative synthesis, we found that PE appears to be associated with improvements in selected outcomes of physiological and psychological health while it has little to no impact on virological status. Moreover, AE appears to reduce adiposity while PRE increases body weight and muscle mass in PLHIV with wasting syndrome. AE with or without PRE appears to improve anaerobic capacity, depression, and mood.

This overview also found that PE appears to improve HIV-associated lipodystrophy, i.e., AE decreased body fat mass for adiposity and PRE increased muscle mass for peripheral fat wasting. A recent study of PLHIV showed that more than half of the study sample suffered from HIV-associated lipodystrophy, which was the main body image concern (Alexias, Savvakis, & Stratopoulou, 2015; Gomes Neto, Conceição, Ogalha, & Brites, 2016). Other systematic reviews also reported similar findings for persons not infected with HIV in that AE decreases body fat in overweight or obese persons (Shaw, Gennat, O'Rourke, & Del Mar, 2006) while PRE increases body fat mass in post-treatment cancer patients who lost lean body mass (Lonbro, 2014). Appropriate PE appears to have physiological health benefits, especially on managing lipodystrophy among PLHIV.

Physical exercise also has a positive impact on depression, which is the most common psychological disorder other than substance use among PLHIV (Rabkin, 2008). A recent systematic review and meta-analysis in the general population also found that AE can decrease depression symptoms (Silveira et al., 2013). AE might be a good strategy to manage depressive symptoms among PLHIV.

In the meta-analysis of primary studies, AE, especially 41 to 50 minutes of interval exercise three times a week, shows improvement in CD4 counts. The improvement can be clinically meaningful for PLHIV, but it depends upon their CD4 count at baseline. Our findings should be interpreted cautiously since the number of primary studies is small. Even though heterogeneity was reduced by stratification on the duration of exercise sessions, heterogeneity for exercise mode remained high. More systematic reviews and evidence are needed to confirm our findings.

Results of our meta-analyses with primary studies showed no significant changes in CD4 counts between exercise groups and non-exercise groups. Even though the sensitivity analysis showed that removal of any one study would not change the point estimate, there is heterogeneity among the primary studies. One of the reasons for heterogeneity might be due to the number or types of antiretroviral treatment (ART) drugs that study participants were on. In the study by Smith and colleagues (2001), which reported CD4 counts increased among the non-exercise group compared to the exercise group, study participants were on a simple ART regimen. Other studies found a significant improvement in CD4 counts in the exercise group that were on HAART or a more complex regimen (LaPerriere et al., 1991; Rigsby et al., 1992). The different combinations of ART might change the impact of PE. PLHIV on HAART may be able to get a greater impact on their CD4 counts with appropriate PE compared to PLHIV who are not taking HAART.

Despite the heterogeneity of the studies and small mean difference on outcome (up to 72 cell/mm^3), we found that 41 to 50 minutes of interval AE three times per a week does not appear to be harmful (i.e., no decline in CD4 counts) and possibly maximizes the clinical benefits on CD4 counts compared with other durations of session or modes of PE among PLHIV. This finding extends the findings from O'Brien and colleagues (O'Brien et al., 2010) who recommend continuous or interval AE, or the combination of continuous AE and PRE for at least 20 minutes for a minimum of three times per week. In addition, our meta-analyses did not find a statistically significant effect on CD4 counts for the more than 50 minutes exercise group while both the less than or equal to 40 minutes and the 41 to 50 minutes intervention groups had statistically significant positive effects. In spite of exercising less than the 2008 Physical Activity Guidelines for Americans recommendation, PLHIV can experience the positive benefits of being physically active. Future studies that assess more than 150 minutes of weekly exercise are necessary to confirm this finding.

In terms of mode of exercise, recent studies found that interval training, such as high intensity interval training (exercising at a high intensity for 30 seconds to several minutes followed by low intensity or no exercise for one to 5 minutes), can have benefits on metabolic outcomes and high compliance (Shiraev & Barclay, 2012). Again, future research studies, especially those focusing on physical interventions with a variety of activity regimens (e.g., mode and dose) and different subgroups of PLHIV (e.g., type of ART regimen and baseline CD4 counts), are necessary.

LIMITATIONS

This overview of systematic reviews has several limitations. First, the number of systematic reviews included in this overview was small ($n = 5$). Moreover, the frequencies of PE interventions reported in identified primary studies were all three times per week, thus, the ideal dose of PE for this population was not possible to identify and remains unclear.

Our review may also be prone to biases subject to an overview of reviews approach and from the included systematic reviews. As an example, the narrative findings might not be a result of an exercise intervention alone since some systematic reviews include the combination of PE and pharmacological interventions. Another example for the narrative synthesis is that positive results were often highlighted in the conclusions of the included systematic reviews, while negative results might be excluded from the conclusions by the review authors. Another limitation of conducting an overview is that identified reviews might not represent the latest knowledge about a topic due to the lengthy duration of conducting systematic reviews and publication.

We also cannot ignore that heterogeneity reported in the identified meta-analyses was high, thus findings should be interpreted cautiously. For the meta-analysis of primary studies, the fact that we included only primary studies from identified systematic reviews might be a limitation. We might have also missed some primary studies that have CD4 counts outcomes with exercise interventions. Some primary studies were also in more than one systematic review, but this issue was minimized when we conducted the meta-analyses of the unique primary studies. Finally, we may have missed recent published primary studies due to the search time frame.

CONCLUSION

Our results suggest that an appropriate amount of PE among PLHIV appears to improve selected outcomes of physiological and psychological health and causes no harmful effects on virological or immunological outcomes. Interval aerobic exercise, up to 50 minutes, three times per week, appears to positively affect CD4 counts among PLHIV. Physical exercise appears to be a good strategy to prevent non-AIDS defining conditions, but people with chronic conditions should be monitored regularly by their primary healthcare providers per the guideline (U.S. Department of Health and Human Services, 2008). Finally, more research is needed to develop a clinical pathway that integrates evidence-informed practice into healthcare providers' decision making process for HIV patient care.

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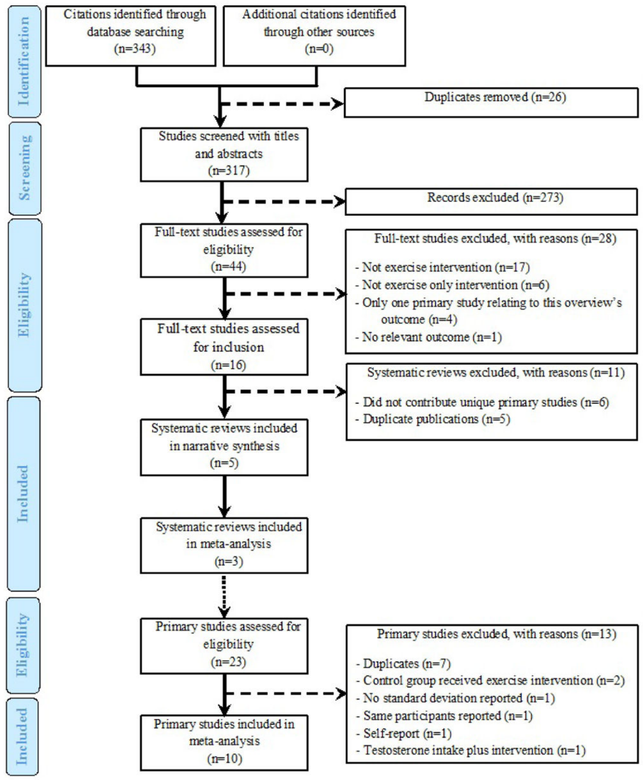

FIGURE 1.

PRISMA flowchart for screening: Systematic reviews.

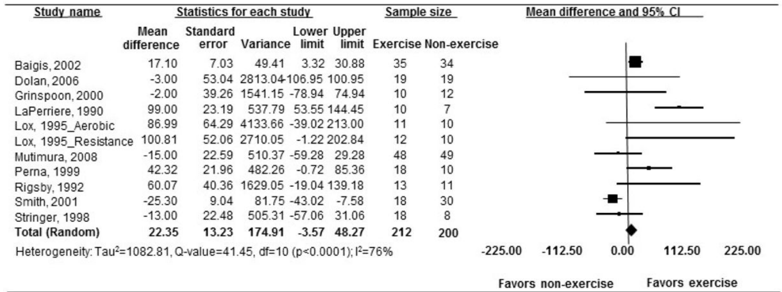

FIGURE 2.

Forest plot for CD4 counts (cell/mm3) changes in exercise intervention group compared to non-exercise control group (k = 11).

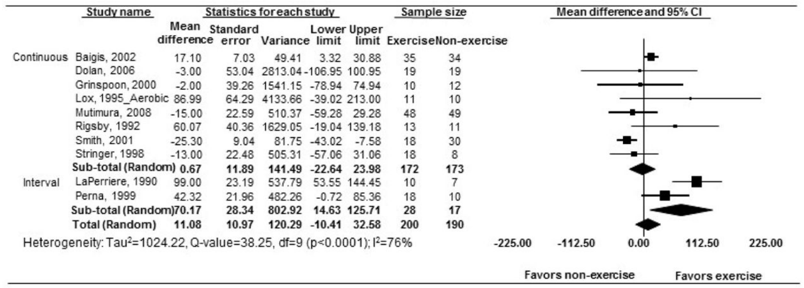

FIGURE 3.

Forest plot for CD4 counts (cell/mm3) changes by mode of exercise ($k = 10$).

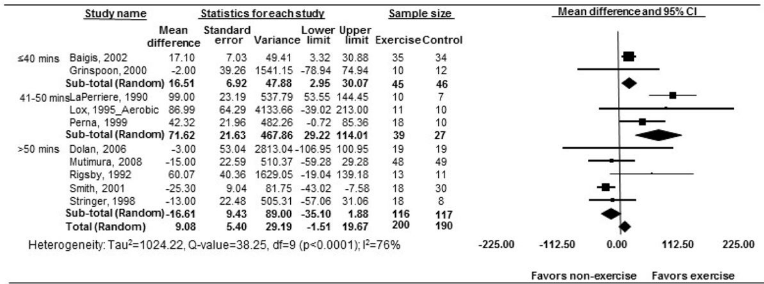

FIGURE 4.

Forest plot for CD4 counts (cell/mm3) changes by duration of exercise session ($k = 10$).

TABLE 1

Descriptions of Included Systematic Reviews in the Overview of Systematic Reviews ($n = 5$)

First Author, Year	SR/MA	Search Years	n^a	Type of Exercise	Total Number and Characteristics of Participants	AMSTAR Total Score[b]
Dudgeon, 2004	SR	NR	18	AE or/and PRE	$n = 720$ (3% female)	3
Fillipas, 2010	MA	1980–2009	9	AE or/and PRE	$n = 494$ (41% female)	9
Gomes Neto, 2013	SR	1950–2012	8	AE and PRE	$n = 334$ (37% female), adults aged 18–60	5
O’Brien, 2010	MA	1980–2009	14	AE (includes combination of AE/PRE)	$n = 454$ (about 30% female), adults aged 18–58	9
O’Brien, 2008	MA	1980–2006	10	PRE (includes combination of AE/PRE)	$n = 332$ (26% female), adults aged 18–66	7

Note. SR: systematic review, MA: meta-analysis; NR: not reported; AE: aerobic exercise; PRE: progressive resistance exercise.

[a]Number of primary studies.

[b]AMSTAR: A Measurement Tool to Assess Systematic Reviews (high quality, 8–11 points; moderate, 5–7 points; and low, 0–4 points).

TABLE 2

Main Outcomes of Included Systematic Reviews (*n* = 5)

Review	Physiological Health		Psychological Health	Virological Status
First Author, Year	Body Composition	Cardiopulmonary Status		
Dudgeon, 2004	AE: Reduced abdominal girth, BMI, and SFT[a]	NR	AE: Improved quality of life, hope, desire to continue living, depression, and depression/dejection	NR
	PRE: Reduced fat massa and increased lean body mass, physical functioning, and strength			
	Combo: Increased muscle mass			
Fillipas, 2010	AE: Reduced BMI, body fat mass, triceps SFT, waist circumference, and WHR[a]	NR	NR	NR
	PRE: Increased body weight and peripheral girths[b]			
Gomes Neto, 2013	NR	Combo: Improved VO_2max	Combo: Improved HRQOL	NR
O'Brien, 2010	AE: Reduced fat mass[a]	AE: Improved VO_2max	AE: Improved depression/dejection	AE: No significant differences were found in all but trend toward improvements
	Combo: Increased leg muscle area			
O'Brien, 2008	PRE: Increased body weight[b]		PRE: Improved mood	No difference or change in viral load
	PRE with/out AE: Increased peripheral girths (arm and thigh)[b]	PRE with/out AE: No significant but trend toward improvements in submaximum heart rate and exercise time		

Note. All listed outcomes are improvements. AE: aerobic exercise; BMI: body mass index; Combo: the combination of aerobic exercise and progressive resistance exercise; HAART: highly active antiretroviral therapy; HRQOL: health-related quality of life; NR: not reported; PRE: progressive resistance exercise; SFT: skinfold thickness of subcutaneous fat; WHR: waist to hip ratio.

[a]Study targets included overweight/persons with central adiposity.

[b]Study targets included persons with HIV wasting syndrome.

TABLE 3

Study Characteristics for Primary Studies Included in the Meta-Analysis (*n* = 10)

First Author, Year	Sample Size	Participants' Characteristics[a]	Type of Exercise (Duration, Length)[b]
Baigis, 2002	*n* = 123, I = 68, C = 55	CD4: 200–500	Continuous AE (40 min, 15 weeks)
Dolan, 2006	*n* = 40, I = 20, C = 20	Females only; waist-to-hip ratio of > 0.85	Continuous Combo (120 min, 16 weeks)
Grinspoon, 2000	*n* = 26, I = 13, C = 13	Males only; AIDS-related wasting; normal serum level of free testosterone	Continuous Combo (20 min+, 12 weeks)
LaPerriere, 1990	*n* = 17, I = 10, C = 7	Gay males only; asymptomatic and relatively healthy	Interval AE (45 min, 5 weeks)
Lox, 1995	*n* = 34, I = 24 (12Aerobic, 12PRE), C = 10	Males only; asymptomatic; on ARV	Continuous AE or PRE (45 min for AE; NR for PRE, 12 weeks)
Mutimura, 2008[c]	*n* = 100, I = 50, C = 50	Mod to severe body fat redistribution; HAART for 6 months	Continuous AE (90 min, 24 weeks)
Perna, 1999	*n* = 43, I = 18, C = 10	Symptomatic mildly progressed HIV infection (but not AIDS); > 6 months of HIV	Interval AE (45 min, 12 weeks)
Rigsby, 1992	*n* = 37, I = 19, C = 18	Males only	Continuous Combo (60 min, 12 weeks)
Smith, 2001	*n* = 60, I = 30, C = 30	On stable ARV; no AIDS, fever, active wasting or < 85% of their ideal body weight.	Continuous AE (60 min, 12 weeks)
Stringer, 1998	*n* = 34, Moderate = 12, Heavy = 11, C = 11	Males only; CD4: 100–500 cells/mm^3; no signs of opportunistic infection	Continuous AE (60 min, 6 weeks)

Note. AE: aerobic exercise; ARV: antiretroviral; C: control; HAART: highly active antiretroviral therapy; Combo: the combination of aerobic exercise and progressive resistance exercise; I: intervention; NR: not reported; PRE: progressive resistance exercise.

[a]All female and male adults with any type of body or HIV/AIDS condition unless otherwise specified.

[b]Duration for each exercise session in minutes and length of intervention in weeks. All interventions were three times per week.

[c]The study was performed in Rwanda and all others were done in the US.