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Effectiveness of non-pharmacological interventions to decrease fatigue in people living with HIV/AIDS: a protocol of systematic review and meta-analysis

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Abstract

Introduction: Fatigue is a common symptom among people living with HIV (PLWH). It has a substantial adverse impact on functional status and the ability to conduct activities of daily living. Identifying effective strategies to prevent or reduce fatigue is significant to promote the quality of life of this vulnerable population. The purpose of this review is to synthesize the non-pharmacological evidence and assess the effects of interventions on reducing HIV-related fatigue among PLWH.

Methods and analysis: We will comprehensively search literature available up to June 30, 2020, in the following databases: PubMed, Embase, CINAHL, Cochrane Library, Web of Science, and PsycINFO. The reference list of selected studies and relevant published reviews will also be screened to retrieve potential articles. Two reviewers will identify the eligible articles, extract data, and identify the biases in the selected studies. Any disagreements will be referred to a third reviewer. We will qualitatively synthesize the evidence and pool data according to the heterogeneity of different studies.

Ethics and dissemination: This systematic review will not raise any ethical issues since it is a secondary data collection and analysis. The results will inform effective strategies to reduce fatigue among PLWH. The final report will be published in a peer-reviewed journal and academic conferences.

PROSPERO registration number CRD42020153715

Strengths and limitations of this study

- To our knowledge, this will be the first review to summarize the non-pharmacological interventions to reduce fatigue among PLWH and explore the effectiveness of different

strategies.

- The results will provide medical staff, stakeholders and PLWH with a source of high-quality information about options to address fatigue.
- The protocol follows PRISMA-P guidelines. Transparent and robust methods will be used to conduct the systematic review and meta-analysis.
- Pharmacological interventions will not be included.

Background

Though antiretroviral therapy (ART) has turned HIV into a chronic disease, people living with HIV (PLWH) still suffer from many long-term symptoms. Fatigue is one of the most common, distressing and persistent symptoms that is potentially disabling. It manifests as physical/psychological exhaustion with debilitating effects and causing limitations in one's ability to conduct daily activities[1-3]. The proportion of PLWH with fatigue is estimated to range from 30% to as much as 90%[2 4], which is far more frequent than their HIV negative counterparts[5]. The presence of fatigue in PLWH contributes to lower quality of life and worsened health outcomes[2 6 7].

Interventions to prevent or treat fatigue among PLWH are being investigated. Use of pharmacological treatments, such as testosterone and psychostimulants, have reduced fatigue among PLWH[8 9]. However, pharmacological interventions are not consistently recommended for HIV-related fatigue[2], because the symptom cluster of fatigue is complex [3 8]; and thus a more multifaceted treatment approach is required. The high prevalence of

fatigue in PLWH with corresponding impact on health outcomes prompts an urgent need to develop effective interventions to reduce fatigue in this population.

Description of the condition

Fatigue in PLWH is persistent and not relieved by rest[1 10]. Further, the intensity of fatigue in this population will not remit spontaneously according to a 3-year longitudinal study[4]. The experience of fatigue in PLWH is still not well understood and often not fully acknowledged by health providers. PLWH frequently struggle to implement self-care strategies to manage this distressing symptom[11]. PLWH with fatigue experience physical weakness that can lead to difficulties self-managing life with HIV [12]. Fatigue has been associated with less ART adherence and poor health outcomes [13].

The mechanism of fatigue in PLWH remains elusive. A myriad of physiological, psychological, and behavioral factors may contribute to the presence and persistence of fatigue. The relationship between disease progression (e.g., CD4 level and viral load) and fatigue in this population had inconsistent results [14-17]. Other comorbidities, such as cardiovascular disease and metabolic disorders may also contribute to the fatigue experienced by PLWH[18]. Psychological perspectives, depression, anxiety and stress have also been shown to influence the fatigue experience [8 19 20]. The overlap of these conditions and behaviors manifest in a cluster with fatigue[3]. For example, sleep quality has been associated with fatigue in PLWH [21-23], particularly, sleep quality moderates the relationship between fatigue patterns and psychological factors, including depression and

anxiety[24]. Prior evidence underscores the complex picture of fatigue in PLWH, which has hindered the development of effective interventions.

Description of Intervention

There is considerable research that has attempted to manage fatigue among people with long term physical conditions. Previous systematic reviews indicate that exercise and cognitive behavioral therapy (CBT) are common non-pharmacological interventions with potential efficacy in reducing fatigue [25]. One novel CBT strategy was guided imagery. It has been found to reduce fatigue in people with various clinical conditions, but its effectiveness has been inconsistent [26]. Very few studies have explored fatigue in PLWH, and most of the reviews to date have included multiple physical problems, adding complexity in the interpretation of the results in PLWH. One review focusing on PLWH with advanced illness found that progressive resistive exercise and aerobic exercise were effective but the results cannot be expanded to the general PLWH who are in earlier stages of illness[27]. A narrative review conducted in 2010 focused on HIV related fatigue, but it focused on pharmacological treatment[8]. In recent trials, various forms of physical exercise [28-30] and CBT[31 32] interventions have been examined to explore effect in reducing fatigue in PLWH. One hypothesis that can explain why physical exercise works in reducing fatigue in PLWH is its ability to reserve energy and preserve muscle mass. Similarly, psychological interventions and self-care programs reduce fatigue in PLWH by managing mood and behavior [33].

In summary, fatigue in PLWH is potentially different from that in people with other physical conditions; nevertheless, fatigue induces various limitations [2]. To our best knowledge, no in-depth systematic review has focused on non-pharmacological interventions specific for HIV-related fatigue. Therefore, this detailed systematic review and meta-analysis will explore evidence of non-pharmacological interventions in reducing fatigue in PLWH and verify the effectiveness of each intervention in reducing HIV-related fatigues.

Methods and analysis

Study design

This protocol is registered with the International Prospective Register of Systematic Reviews. It has complied with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols recommendations (PRISMA-P)[34]. The PRISMA-P checklist is shown in the online supplementary materials.

Eligibility criteria for selecting studies

Types of studies

This review will include randomized controlled trials, quasi-randomized controlled trials, and controlled before-and-after studies, as defined by the Cochrane Handbook for Systematic Reviews of Interventions[35]. The randomized and quasi-randomized crossover trials will be included and only results of the first period will be considered. Regarding cluster RCTs, the study with the unit of analysis at an individual level will be included. A full publication in English is required. When multiple studies are based on the same sample, only the one with

the most detailed and longest follow-up will be included.

Participants

Participants will be adults (18 years of age or older) with HIV, irrespective of the stage of the HIV-infection.

Types of interventions

We will include trials evaluating non-pharmacological interventions with either the primary or secondary objective to reduce fatigue in PLWH. Studies with interventions combining pharmacological and non-pharmacological components will be included if the data can be extracted separately. We are not limiting related to the setting, provider, timing, frequency, and duration of the interventions.

The potential interventions may include, but are not restricted to:

- cognitive behavioral therapy,
- self-management strategies,
- patient education program,
- physical training (aerobic training, resistance training, yoga and so on).

Controls

Trials will be included if they compared an intervention group with controls, which could be placebo, standard care/usual care or wait-list or have a comparison between different interventions with a control.

Outcomes

The primary outcome of this systematic review will be fatigue of PLWH evaluated as the rate of or the mean severity of fatigue. This could be measured by the following tools, but is not limited to:

- HIV-related Fatigue Scale,
- Global Fatigue Index,
- Piper Fatigue Scale,
- Fatigue Severity Scale,
- Lee Fatigue Scale.

If possible, the secondary outcomes will include but will not be restricted to quality of life, psychological health (such as depression and stress), treatment adherence and immune function.

Search strategies

The literature search will be conducted in the following electronic databases from the inception to June 30, 2020: PubMed, Embase, CINAHL, Cochrane Library, Web of Science, and PsycINFO. Our search strategies were developed by XX (the first author) and an academic librarian. The search strategies will include the population of interest (PLWH), the intervention (any non-pharmacological interventions), and the primary outcome of interest (fatigue). The search terms for PubMed were displayed in the online supplementary appendix to illustrate the logic of the search. Besides the reference list of included studies, relevant

published reviews will be explored to retrieve the eligible articles.

Selection of studies

The identified studies will be imported into the reference management library (Endnote X7). After removing duplications, two reviewers will independently screen the titles and abstracts, and eliminate records that clearly don't meet the inclusion criteria. The full text of potentially related studies will be obtained and scrutinized for inclusion or exclusion. The excluded studies will be verified by a full text read and be shown in a flow diagram with justifications. Any discrepancies during this process will be solved by the discussion of the two reviewers or by a third arbiter, if necessary. A PRISMA flow will be adopted to detail the information of the screening process[34].

Data extraction

A standardized data extraction form will be designed and impeded into Covidence (www.covidence.org). The data extraction will be conducted by two reviewers independently. Any inconsistencies will be referred to a third arbiter and discussed to reach a consensus. We will include information about general study information (first author, corresponding author, and year of publication), study design (setting, sampling, randomization, allocation, and blinding), sample characteristics (inclusion and exclusion criteria, sample size, age, gender, education background, viral load, $CD4^+$ level, HIV diagnosis duration and drop-off), intervention information (type, content, frequency, duration, provider, control group and timing of follow-ups), and primary and secondary outcomes (measuring time points, tools for

assessment, fatigue rate or severity, any abovementioned secondary results). If necessary, we will contact the corresponding author to clarify missing or for more detailed information.

Risk of bias

Two reviewers will independently assess the risk of bias of the included trials and any disagreements will be discussed to reach a consensus with a third researcher. The methodological quality of the RCTs will be evaluated according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB2)[36], which includes five domains, namely risk of bias arising from the randomization process, risk of bias due to deviation from the intended intervention, risk of bias due to deviations from the intended interventions, missing outcome data, risk of bias in measurement of the outcome, risk of bias in selection of the reported result. The risk of bias of non-RCTs will be assessed based on the Risk of Bias in Non-Randomized studies-of Interventions (ROBINS-I)[37]. This tool includes 7 domains: bias due to confounding, bias in selection of participants into study, bias in classification of intervention, bias due to deviation from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results.

Strategy for data analysis

We will summarize the main characteristics of the included studies in text and table. A qualitative and narrative synthesis will be implemented to describe how fatigue was defined and measured, and the existing intervention methods, especially the contents, ways of delivery, and efficacy and feasibility of these interventions. If it is possible for a meta-

analysis after assessing the extracted data, we will use the Cochrane Review Manager software (RevMan) to conduct statistical analysis. Standardized mean differences and relevant 95% confidence interval (CI) will be calculated for continuous outcomes; risk ratios and relevant 95% CI will be computed for dichotomous outcomes. If studies reported the severity and rate of fatigue, we will report and calculate both types of outcomes.

According to the controls, we will perform separate analyses for trials: intervention versus standard care and intervention versus blank control. For trials comparing different dosages of intervention with control, we will combine results of the various arms of interventions; otherwise, we will divide the numbers of control group into several parts according to the number of intervention arms to ensure the participants will not be double counted. For trials comparing different types of interventions with control, we will split the control group into several parts as well, one to go with each intervention arm.

The heterogeneity of studies will be checked by χ^2 test and I^2 test. If the significance of χ^2 is smaller than 0.1 or I^2 is $\geqslant$50%, we will use random-effects models to synthesize the results from different articles. Otherwise, we will not need to be concerned with the heterogeneity. If substantial heterogeneity is present, a qualitative synthesis will be conducted instead.

Subgroup analysis

We will do subgroup analyses if there are enough trials. It will likely be performed based on characteristics of participants (age, gender, or depression status), types of intervention (self-training versus others delivering, or cognitive behavior therapy versus exercise training) outcomes relevant features (measurements of fatigues, or severity versus rate of fatigue), and

effects of interventions (short term versus long term, or pure non-pharmacological intervention versus non-pharmacological combined with pharmacological interventions). The subgroup analysis will not be limited to those as it highly depends on the extracted data.

Grading quality of evidence

The Grading of Recommendation Assessment, Development, and Evaluation system will guide the evaluation of the evidence of the outcomes[38]. This system considers the risk of bias, consistency, directness of evidence, precision of effects estimates and publication bias.

Sensitivity analysis

We plan to explore the sensitivity of the included articles by excluding trials with a high risk of bias.

Assessment of reporting biases

The funnel plot will be performed to explore the publication biases of the included studies.

Patient and public involvement

We have no patient and public involvement.

Ethics and dissemination

We will not use any identifying information of participants in this systematic review to protect the privacy of patients, so no ethical approval is needed. The results will be

disseminated by social media (such as *WeChat, Twitter, Facebook*), academic meetings and publication in peer-reviewed journals.

Authors' contribution

XX initiated the idea and led the development of the protocol. YL contributed to the methodology development. HW, NR and LS critically reviewed intellectual content and revised successive drafts of the manuscripts. HW and NR provided supervision to XX. All the authors approved the publication of the protocol.

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Competing interest statement

None.

1. USNLo M. Fatigue Secondary Fatigue 2016. https://medlineplus.gov/fatigue.html.
2. Barroso J, Voss JG. Fatigue in HIV and AIDS: an analysis of evidence. The Journal of the Association of Nurses in AIDS Care : JANAC 2013;**24**(1 Suppl):S5-14 doi: 10.1016/j.jana.2012.07.003[published Online First: Epub Date]|.
3. Zhu Z, Zhao R, Hu Y. Symptom Clusters in People Living With HIV: A Systematic Review. Journal of pain and symptom management 2019;**58**(1):115-33 doi: 10.1016/j.jpainsymman.2019.03.018[published Online First: Epub Date]|.
4. Barroso J, Leserman J, Harmon JL, et al. Fatigue in HIV-Infected People: A Three-Year Observational Study. J Pain Symptom Manage 2015;**50**(1):69-79 doi: 10.1016/j.jpainsymman.2015.02.006[published Online First: Epub Date]|.
5. Tran T, Guardigni V, Pencina KM, et al. Atypical Skeletal Muscle Profiles in Human Immunodeficiency Virus-Infected Asymptomatic Middle-Aged Adults. Clin Infect Dis 2018;**66**(12):1918-27 doi: 10.1093/cid/cix1121[published Online First: Epub Date]|.
6. Cook PF, Hartson KR, Schmiege SJ, et al. Bidirectional Relationships Between Fatigue and Everyday Experiences in Persons Living With HIV. Research in nursing & health 2016;**39**(3):154-63 doi: 10.1002/nur.21718[published Online First: Epub Date]|.
7. daCosta DiBonaventura M, Gupta S, Cho M, et al. The association of HIV/AIDS treatment side effects with health status, work productivity, and resource use. AIDS care 2012;**24**(6):744-55 doi: 10.1080/09540121.2011.630363[published Online First: Epub Date]|.
8. Jong E, Oudhoff LA, Epskamp C, et al. Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era. AIDS (London, England) 2010;**24**(10):1387-405 doi: 10.1097/QAD.0b013e328339d004[published Online First: Epub Date]|.
9. Mücke M, Mochamat, Cuhls H, et al. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev 2015(5) doi: 10.1002/14651858.CD006788.pub3[published Online First: Epub Date]|.
10. Loades ME, Kagee A. Exploring our understanding of fatigue among adolescents living with HIV: Highlighting the unknown. Journal of health psychology 2019;**24**(1):125-36 doi: 10.1177/1359105317710320[published Online First: Epub Date]|.
11. Jenkin P, Koch T, Kralik D. The experience of fatigue for adults living with HIV. Journal of clinical nursing 2006;**15**(9):1123-31 doi: 10.1111/j.1365-2702.2006.01343.x[published Online First: Epub Date]|.
12. Kerong W, Wei-Ti C, Lin Z, et al. Facilitators of and barriers to HIV self-management: Perspectives of HIV-positive women in China. Appl Nurs Res 2016;**32**:91-97 doi: 10.1016/j.apnr.2016.06.004[published Online First: Epub Date]|.
13. Al-Dakkak I, Patel S, McCann E, et al. The impact of specific HIV treatment-related adverse events on adherence to antiretroviral therapy: a systematic review and meta-analysis. AIDS care 2013;**25**(4):400-14 doi: 10.1080/09540121.2012.712667[published Online First: Epub Date]|.
14. Safren SA, Hendriksen ES, Smeaton L, et al. Quality of Life Among Individuals with HIV Starting Antiretroviral Therapy in Diverse Resource-Limited Areas of the World. AIDS and behavior 2012;**16**(2):266-77 doi: 10.1007/s10461-011-9947-5[published

Online First: Epub Date]|.
15. Voss JG. Predictors and Correlates of Fatigue in HIV/AIDS. Journal of pain and symptom management 2005;**29**(2):173-84 doi: 10.1016/j.jpainsymman.2004.05.006[published Online First: Epub Date]|.
16. Henderson M, Safa F, Easterbrook P, et al. Fatigue among HIV-infected patients in the era of highly active antiretroviral therapy. Hiv Med 2005;**6**(5):347-52 doi: DOI 10.1111/j.1468-1293.2005.00319.x[published Online First: Epub Date]|.
17. Lee KA, Portillo CJ, Miramontes H. The fatigue experience for women with human immunodeficiency virus. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN 1999;**28**(2):193-200 doi: 10.1111/j.1552-6909.1999.tb01984.x[published Online First: Epub Date]|.
18. Battegay M, Elzi L. Morbidity and mortality in HIV-infected individuals - a shift towards comorbidities. Swiss medical weekly 2009;**139**(39-40):564-70 doi: smw-12662[published Online First: Epub Date]|.
19. Schifitto G, Deng L, Yeh TM, et al. Clinical, laboratory, and neuroimaging characteristics of fatigue in HIV-infected individuals. Journal of neurovirology 2011;**17**(1):17-25 doi: 10.1007/s13365-010-0010-5[published Online First: Epub Date]|.
20. Chen WT, Shiu CS, Yang JP, et al. Fatigue and Sleep Disturbance Related to Perceived Stress in Chinese HIV-Positive Individuals: A Mixed Methods Study. Journal of AIDS & clinical research 2013;**4**(6) doi: 10.4172/2155-6113.1000214[published Online First: Epub Date]|.
21. Barroso J, Voss JG. Fatigue in HIV and AIDS: An Analysis of Evidence. J Assoc Nurses Aids Care 2013;**24**(1):S5-S14 doi: 10.1016/j.jana.2012.07.003[published Online First: Epub Date]|.
22. Salahuddin N, Barroso J, Leserman J, et al. Daytime Sleepiness, Nighttime Sleep Quality, Stressful Life Events, and HIV-Related Fatigue. J Assoc Nurses Aids Care 2009;**20**(1):6-13 doi: 10.1016/j.jana.2008.05.007[published Online First: Epub Date]|.
23. Perazzo JD, Webel AR. Barriers to health-promoting behaviour in people living with HIV: Implications for comorbidity development. Antiviral therapy 2018;**23**:A35
24. Lerdal A, Gay CL, Aouizerat BE, et al. Patterns of morning and evening fatigue among adults with HIV/AIDS. J Clin Nurs 2011;**20**(15-16):2204-16 doi: 10.1111/j.1365-2702.2011.03751.x[published Online First: Epub Date]|.
25. Hulme K, Safari R, Thomas S, et al. Fatigue interventions in long term, physical health conditions: A scoping review of systematic reviews. PloS one 2018;**13**(10) doi: 10.1371/journal.pone.0203367[published Online First: Epub Date]|.
26. Menzies V, Jallo N. Guided Imagery as a Treatment Option for Fatigue A Literature Review. J Holist Nurs 2011;**29**(4):279-86 doi: 10.1177/0898010111412187[published Online First: Epub Date]|.
27. Payne C, Wiffen PJ, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database Syst Rev 2017;**2017**(4) doi: 10.1002/14651858.CD008427.pub3[published Online First: Epub Date]|.
28. Nosrat S, Whitworth JW, Dunsiger SI, et al. Acute effects of resistance exercise in a depressed HIV sample: the exercise for people who are immunocompromised (EPIC) study. Ment Health Phys Act 2017;**12**:2–9 doi:

10.1016/j.mhpa.2016.12.002[published Online First: Epub Date]|.
29. Nosrat S. Acute effects of resistance exercise intensity in a depressed HIV sample: The exercise for people who are immunocompromised (EPIC) study. ProQuest Information & Learning, 2018.
30. Jaggers JR, Hand GA, Dudgeon WD, et al. Aerobic and resistance training improves mood state among adults living with HIV. International journal of sports medicine 2015;**36**(2):175-81 doi: 10.1055/s-0034-1385878[published Online First: Epub Date]|.
31. Doerfler RE, Goodfellow L. Brief Exposure to Cognitive Behavioral Therapy Reduces Side-Effect Symptoms in Patients on Antiretroviral Therapy. The Journal of the Association of Nurses in AIDS Care : JANAC 2016;**27**(4):455-67 doi: 10.1016/j.jana.2016.02.010[published Online First: Epub Date]|.
32. Doerfler RE. Clinical trial of cognitive-behavioral therapy to reduce antiretroviral effects in HIV patients. ProQuest Information & Learning, 2011.
33. Modeste RRM, Majeke SJ. Self-care symptom-management strategies amongst women living with hiv/aids in an urban area in kwazulu-natal. Health SA Gesondheid 2010;**15**(1):162-69 doi: 10.4102/hsag.v15i1.509[published Online First: Epub Date]|.
34. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews 2015;**4**:1 doi: 10.1186/2046-4053-4-1[published Online First: Epub Date]|.
35. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane database of systematic reviews 2019;**10**:ED000142 doi: 10.1002/14651858.ED000142[published Online First: Epub Date]|.
36. Julian PT Higgins, Jelena Savović, Matthew J Page, et al. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Secondary Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) August 22, 2019 2019. https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2.
37. Sterne JAC, Hernán MA, Reeves BC SJ, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ (Clinical research ed) 2016;**355**:i4919
38. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed) 2008;**336**(7650):924-6 doi: 10.1136/bmj.39489.470347.AD[published Online First: Epub Date]|.

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(("Exercise"[Mesh] OR "Yoga"[Mesh] OR "Resistance Training"[Mesh] OR "Exercise Therapy"[Mesh] OR "Mindfulness"[Mesh] OR "Cognitive Behavioral Therapy"[Mesh] OR "Relaxation Therapy"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR "Psychotherapy"[Mesh] OR "Complementary Therapies"[Mesh] OR "Self Care"[Mesh] OR "Social Support"[Mesh] OR "Religion"[Mesh] OR Exercis* [tw] OR yoga [tiab] OR “resistance training” OR “resistance exercise” OR “physical activity” OR aerobic* [tiab] OR isometric* [tiab] OR “exercise training” OR mindful* [tiab] OR “cognitive behavioral therapy” OR “cognitive behavioral therapies” OR “cognitive behavioural therapy” OR “cognitive behavioural therapies” OR “cognitive therapy” OR “cognitive therapies” OR “cognitive psychotherapy” OR “cognitive psychotherapies” OR “Relaxation Therapy” OR “relaxation therapies” OR “relaxation technique” OR “relaxation techniques” OR “expressive support therapy” OR “stress management” OR physiotherap* [tiab] OR psychotherap* [tiab] OR biofeedback* OR acupuncture* [tiab] OR massag* [tiab] OR “self-care” OR “self-management” OR “social support” OR religion [tiab] OR prayer* [tiab] OR "complementary therapy" OR "alternative therapy" OR "complementary therapies" OR "alternative therapies" OR "alternative medicine" OR "tai chi")) AND ((hiv infections[mh] OR hiv[mh] OR hiv[tw] OR hiv-1[tw] OR hiv-2[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunodeficiency virus[tw] OR human immune-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])))) AND ("Asthenia"[Mesh] OR "Fatigue"[Mesh:noexp] OR "Mental Fatigue"[Mesh] OR asthenia[tiab] OR fatigue*[tiab] OR lassitude[tiab] OR lethargy[tiab] OR weakness[tiab] OR debility[tiab] OR feeble*[tiab] OR exhaust*[tiab]))

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Page number(s)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary material

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10/12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

BMJ Open

Effectiveness of non-pharmacological interventions to decrease fatigue in people living with HIV/AIDS: a protocol of systematic review and meta-analysis

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Effectiveness of non-pharmacological interventions to decrease fatigue in people living with HIV/AIDS: a protocol of systematic review and meta-analysis

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Abstract

Introduction: Fatigue is a common symptom among people living with HIV (PLWH). It has a substantial adverse impact on functional status and the ability to conduct activities of daily living. Identifying effective strategies to prevent or reduce fatigue is significant to promote the quality of life of this vulnerable population. The purpose of this review is to synthesize the non-pharmacological evidence and assess the effects of interventions on reducing HIV-related fatigue among PLWH.

Methods and analysis: We will comprehensively search literature available up to June 30, 2020, in the following databases: PubMed, Embase, CINAHL, Cochrane Library, Web of Science, and PsycINFO. The reference list of selected studies and relevant published reviews will also be screened to retrieve potential articles. Two reviewers will identify the eligible articles, extract data, and identify the biases in the selected studies. Any disagreements will be referred to a third reviewer. We will qualitatively synthesize the evidence, and pool data with meta-analysis according to the heterogeneity of different studies.

Ethics and dissemination: This systematic review will not raise any ethical issues since it is a secondary data collection and analysis. The results will inform effective strategies to reduce fatigue among PLWH. The final report will be published in a peer-reviewed journal and academic conferences.

PROSPERO registration number CRD42020153715

Strengths and limitations of this study

- To our knowledge, this will be the first review to summarize the non-pharmacological interventions to reduce fatigue among PLWH and explore the effectiveness of different

strategies.

- The results will provide medical staff, stakeholders and PLWH with a source of high-quality information about options to address fatigue.
- The protocol follows PRISMA-P guidelines. Transparent and robust methods will be used to conduct the systematic review and meta-analysis.
- Pharmacological interventions will not be included.

Background

Though antiretroviral therapy (ART) has turned HIV into a chronic disease, people living with HIV (PLWH) still suffer from many long-term symptoms. Fatigue is one of the most common, distressing and persistent symptoms that is potentially disabling. It manifests as physical/psychological exhaustion with debilitating effects and causing limitations in one's ability to conduct daily activities[1-3]. The proportion of PLWH with fatigue is estimated to range from 30% to as much as 90%[2 4], which is far more frequent than their HIV negative counterparts[5]. The presence of fatigue in PLWH contributes to lower quality of life and worsened health outcomes[2 6 7].

Interventions to prevent or treat fatigue among PLWH are being investigated. Use of pharmacological treatments, such as testosterone and psychostimulants, have reduced fatigue among PLWH[8 9]. However, pharmacological interventions are not consistently recommended for HIV-related fatigue[2], because the symptom cluster of fatigue is complex [3 8]; and thus a more multifaceted treatment approach is required. The high prevalence of

fatigue in PLWH with corresponding impact on health outcomes prompts an urgent need to develop effective interventions to reduce fatigue in this population.

Description of the condition

Fatigue in PLWH is persistent and not relieved by rest[1 10]. Further, the intensity of fatigue in this population will not remit spontaneously according to a 3-year longitudinal study[4]. The experience of fatigue in PLWH is still not well understood and often not fully acknowledged by health providers. PLWH frequently struggle to implement self-care strategies to manage this distressing symptom[11]. PLWH with fatigue experience physical weakness that can lead to difficulties self-managing life with HIV [12]. Fatigue has been associated with less ART adherence and poor health outcomes [13].

The mechanism of fatigue in PLWH remains elusive. A myriad of physiological, psychological, and behavioral factors may contribute to the presence and persistence of fatigue. The relationship between disease progression (e.g., CD4 level and viral load) and fatigue in this population had inconsistent results [14-17]. Other comorbidities, such as cardiovascular disease and metabolic disorders may also contribute to the fatigue experienced by PLWH[18]. Psychological perspectives, depression, anxiety and stress have also been shown to influence the fatigue experience [8 19 20]. The overlap of these conditions and behaviors manifest in a cluster with fatigue[3]. For example, sleep quality has been associated with fatigue in PLWH [21-23], particularly, sleep quality moderates the relationship between fatigue patterns and psychological factors, including depression and

anxiety[24]. Prior evidence underscores the complex picture of fatigue in PLWH, which has hindered the development of effective interventions.

Description of Intervention

There is considerable research that has attempted to manage fatigue among people with long term physical conditions. Previous systematic reviews indicate that exercise and cognitive behavioral therapy (CBT) are common non-pharmacological interventions with potential efficacy in reducing fatigue [25]. Very few studies have explored fatigue in PLWH, and most of the reviews to date have included multiple physical problems, adding complexity in the interpretation of the results in PLWH. One review focusing on PLWH with advanced illness found that progressive resistive exercise and aerobic exercise were effective but the results cannot be expanded to the general PLWH who are in earlier stages of illness[26]. A narrative review conducted in 2010 focused on HIV related fatigue, but it focused on pharmacological treatment[8]. In recent trials, various forms of physical exercise [27-29] and CBT[30 31] interventions have been examined to explore effect in reducing fatigue in PLWH. One hypothesis that can explain why physical exercise works in reducing fatigue in PLWH is its ability to reserve energy and preserve muscle mass. Similarly, psychological interventions and self-care programs reduce fatigue in PLWH by managing mood and behavior [32].

In summary, fatigue in PLWH is potentially different from that in people with other physical conditions; nevertheless, fatigue induces various limitations [2]. To our best knowledge, no

in-depth systematic review has focused on non-pharmacological interventions specific for HIV-related fatigue. Therefore, this detailed systematic review and meta-analysis will explore evidence of non-pharmacological interventions in reducing fatigue in PLWH and verify the effectiveness of each intervention in reducing HIV-related fatigues.

Methods and analysis

Study design

This protocol is registered with the International Prospective Register of Systematic Reviews. It has complied with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols recommendations (PRISMA-P)[33]. The PRISMA-P checklist is shown in the online supplementary materials.

Eligibility criteria for selecting studies

Types of studies

This review will include randomized controlled trials, quasi-randomized controlled trials, and controlled before-and-after studies, as defined by the Cochrane Handbook for Systematic Reviews of Interventions[34]. The randomized and quasi-randomized crossover trials will be included and only results of the first period will be considered. Regarding cluster RCTs, the study with the unit of analysis at an individual level will be included. A full publication in English is required. When multiple studies are based on the same sample, we will include all the papers and staple our interested outcomes together.

Participants

Participants will be adults (18 years of age or older) with HIV, irrespective of the stage of the HIV-infection.

Types of interventions

We will include trials evaluating non-pharmacological interventions with either the primary or secondary objective to reduce fatigue in PLWH. Studies with interventions combining pharmacological and non-pharmacological components will be included if the data can be extracted separately. We are not limiting related to the setting, provider, timing, frequency, and duration of the interventions.

The potential interventions may include, but are not restricted to:

- cognitive behavioral therapy,
- self-management strategies,
- patient education program,
- physical training (aerobic training, resistance training, yoga and so on).

Controls

Trials will be included if they compared an intervention group with controls, which could be placebo, standard care/usual care or wait-list or have a comparison between different interventions with a control.

Outcomes

The primary outcome of this systematic review will be fatigue of PLWH evaluated as the rate of or the mean severity of fatigue. This could be measured by the following tools, but is not limited to:

- HIV-related Fatigue Scale,
- Global Fatigue Index,
- Piper Fatigue Scale,
- Fatigue Severity Scale,
- Lee Fatigue Scale.

If possible, the secondary outcomes will include but will not be restricted to quality of life, psychological health (such as depression and stress), treatment adherence and immune function.

Search strategies

The literature search will be conducted in the following electronic databases from the inception to June 30, 2020: PubMed, Embase, CINAHL, Cochrane Library, Web of Science, and PsycINFO. Our search strategies were developed by XX (the first author) and an academic librarian. The search strategies will include the population of interest (PLWH), the intervention (any non-pharmacological interventions), and the primary outcome of interest (fatigue). The search terms for PubMed were displayed in the online supplementary appendix to illustrate the logic of the search. Besides the reference list of included studies, relevant published reviews will be explored to retrieve the eligible articles.

Selection of studies

The identified studies will be imported into COVIDENCE. After removing duplications, two reviewers will independently screen the titles and abstracts, and eliminate records that clearly don't meet the inclusion criteria. The full text of potentially related studies will be obtained and scrutinized for inclusion or exclusion. The excluded studies will be verified by a full text read and be shown in a flow diagram with justifications. Any discrepancies during this process will be solved by the discussion of the two reviewers or by a third arbiter, if necessary. A PRISMA flow will be adopted to detail the information of the screening process[33].

Data extraction

A standardized data extraction form has been designed (online supplementary materials). After piloted and further revised by our team members, this form will be impeded into COVIDENCE (www.covidence.org). The data extraction will be conducted by two reviewers independently. Any inconsistencies will be referred to a third arbiter and discussed to reach a consensus. We will include information about general study information (first author, corresponding author, and year of publication), study design (setting, sampling, randomization, allocation, and blinding), sample characteristics (inclusion and exclusion criteria, sample size, age, gender, education background, viral load, $CD4^+$ level, HIV diagnosis duration and drop-off), intervention information (type, content, frequency, duration, provider, control group and timing of follow-ups), and primary and secondary outcomes (measuring time points, tools for assessment, fatigue rate or severity, any abovementioned

secondary results). If necessary, we will contact the corresponding author to clarify missing or for more detailed information.

Risk of bias

Two reviewers will independently assess the risk of bias of the included trials and any disagreements will be discussed to reach a consensus with a third researcher. The methodological quality of the RCTs will be evaluated according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB2)[35], which includes five domains, namely risk of bias arising from the randomization process, risk of bias due to deviation from the intended intervention, risk of bias due to deviations from the intended interventions, missing outcome data, risk of bias in measurement of the outcome, risk of bias in selection of the reported result. The risk of bias of non-RCTs will be assessed based on the Risk of Bias in Non-Randomized studies-of Interventions (ROBINS-I)[36]. This tool includes 7 domains: bias due to confounding, bias in selection of participants into study, bias in classification of intervention, bias due to deviation from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results.

Strategy for data analysis

We will summarize the main characteristics of the included studies in text and table. A qualitative and narrative synthesis will be implemented to describe how fatigue was defined and measured, and the existing intervention methods, especially the contents, ways of delivery, and efficacy and feasibility of these interventions. If it is possible for a meta-

analysis after assessing the extracted data, we will use the Cochrane Review Manager software (RevMan) to conduct statistical analysis. Standardized mean differences and relevant 95% confidence interval (CI) will be calculated for continuous outcomes; risk ratios and relevant 95% CI will be computed for dichotomous outcomes. If studies reported the severity and rate of fatigue, we will report and calculate both types of outcomes.

According to the controls, we will perform separate analyses for trials: intervention versus standard care and intervention versus blank control. For trials comparing different dosages of intervention with control, we will combine results of the various arms of interventions; otherwise, we will divide the numbers of control group into several parts according to the number of intervention arms to ensure the participants will not be double counted. For trials comparing different types of interventions with control, we will split the control group into several parts as well, one to go with each intervention arm.

The heterogeneity of studies will be checked by χ^2 test and I^2 test. If the significance of χ^2 is smaller than 0.1 or I^2 is $\geqslant$50%, we will use random-effects models to synthesize the results from different articles. Otherwise, we will not need to be concerned with the heterogeneity. If substantial heterogeneity is present, a qualitative synthesis will be conducted instead.

Subgroup analysis

We will do subgroup analyses if there are enough trials. It will likely be performed based on characteristics of participants (age, gender, or depression status), types of intervention (self-training versus others delivering, or cognitive behavior therapy versus exercise training) outcomes relevant features (measurements of fatigues, or severity versus rate of fatigue), and

effects of interventions (short term versus long term, or pure non-pharmacological intervention versus non-pharmacological combined with pharmacological interventions). The subgroup analysis will not be limited to those as it highly depends on the extracted data.

Grading quality of evidence

The Grading of Recommendation Assessment, Development, and Evaluation system will guide the evaluation of the evidence of the outcomes[37]. This system considers the risk of bias, consistency, directness of evidence, precision of effects estimates and publication bias.

Sensitivity analysis

We plan to explore the sensitivity of the included articles by excluding trials with a high risk of bias.

Assessment of reporting biases

The funnel plot will be performed to explore the publication biases of the included studies.

Patient and public involvement

We have no patient and public involvement.

Ethics and dissemination

We will not use any identifying information of participants in this systematic review to protect the privacy of patients, so no ethical approval is needed. The results will be

disseminated by social media (such as *WeChat, Twitter, Facebook*), academic meetings and publication in peer-reviewed journals.

Authors' contribution

XX and MW initiated the idea and led the development of the protocol. YL contributed to the methodology development. HW, NR, MW and LS critically reviewed intellectual content and revised successive drafts of the manuscripts. HW and NR provided supervision to XX. All the authors approved the publication of the protocol.

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Competing interest statement

None.

1. USNLo M. Fatigue Secondary Fatigue 2016. https://medlineplus.gov/fatigue.html.
2. Barroso J, Voss JG. Fatigue in HIV and AIDS: an analysis of evidence. The Journal of the Association of Nurses in AIDS Care : JANAC 2013;**24**(1 Suppl):S5-14 doi: 10.1016/j.jana.2012.07.003[published Online First: Epub Date]|.
3. Zhu Z, Zhao R, Hu Y. Symptom Clusters in People Living With HIV: A Systematic Review. Journal of pain and symptom management 2019;**58**(1):115-33 doi: 10.1016/j.jpainsymman.2019.03.018[published Online First: Epub Date]|.
4. Barroso J, Leserman J, Harmon JL, et al. Fatigue in HIV-Infected People: A Three-Year Observational Study. J Pain Symptom Manage 2015;**50**(1):69-79 doi: 10.1016/j.jpainsymman.2015.02.006[published Online First: Epub Date]|.
5. Tran T, Guardigni V, Pencina KM, et al. Atypical Skeletal Muscle Profiles in Human Immunodeficiency Virus-Infected Asymptomatic Middle-Aged Adults. Clin Infect Dis 2018;**66**(12):1918-27 doi: 10.1093/cid/cix1121[published Online First: Epub Date]|.
6. Cook PF, Hartson KR, Schmiege SJ, et al. Bidirectional Relationships Between Fatigue and Everyday Experiences in Persons Living With HIV. Research in nursing & health 2016;**39**(3):154-63 doi: 10.1002/nur.21718[published Online First: Epub Date]|.
7. daCosta DiBonaventura M, Gupta S, Cho M, et al. The association of HIV/AIDS treatment side effects with health status, work productivity, and resource use. AIDS care 2012;**24**(6):744-55 doi: 10.1080/09540121.2011.630363[published Online First: Epub Date]|.
8. Jong E, Oudhoff LA, Epskamp C, et al. Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era. AIDS (London, England) 2010;**24**(10):1387-405 doi: 10.1097/QAD.0b013e328339d004[published Online First: Epub Date]|.
9. Mücke M, Mochamat, Cuhls H, et al. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev 2015(5) doi: 10.1002/14651858.CD006788.pub3[published Online First: Epub Date]|.
10. Loades ME, Kagee A. Exploring our understanding of fatigue among adolescents living with HIV: Highlighting the unknown. Journal of health psychology 2019;**24**(1):125-36 doi: 10.1177/1359105317710320[published Online First: Epub Date]|.
11. Jenkin P, Koch T, Kralik D. The experience of fatigue for adults living with HIV. Journal of clinical nursing 2006;**15**(9):1123-31 doi: 10.1111/j.1365-2702.2006.01343.x[published Online First: Epub Date]|.
12. Kerong W, Wei-Ti C, Lin Z, et al. Facilitators of and barriers to HIV self-management: Perspectives of HIV-positive women in China. Appl Nurs Res 2016;**32**:91-97 doi: 10.1016/j.apnr.2016.06.004[published Online First: Epub Date]|.
13. Al-Dakkak I, Patel S, McCann E, et al. The impact of specific HIV treatment-related adverse events on adherence to antiretroviral therapy: a systematic review and meta-analysis. AIDS care 2013;**25**(4):400-14 doi: 10.1080/09540121.2012.712667[published Online First: Epub Date]|.
14. Safren SA, Hendriksen ES, Smeaton L, et al. Quality of Life Among Individuals with HIV Starting Antiretroviral Therapy in Diverse Resource-Limited Areas of the World. AIDS and behavior 2012;**16**(2):266-77 doi: 10.1007/s10461-011-9947-5[published

Online First: Epub Date]|.
15. Voss JG. Predictors and Correlates of Fatigue in HIV/AIDS. Journal of pain and symptom management 2005;**29**(2):173-84 doi: 10.1016/j.jpainsymman.2004.05.006[published Online First: Epub Date]|.
16. Henderson M, Safa F, Easterbrook P, et al. Fatigue among HIV-infected patients in the era of highly active antiretroviral therapy. Hiv Med 2005;**6**(5):347-52 doi: DOI 10.1111/j.1468-1293.2005.00319.x[published Online First: Epub Date]|.
17. Lee KA, Portillo CJ, Miramontes H. The fatigue experience for women with human immunodeficiency virus. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN 1999;**28**(2):193-200 doi: 10.1111/j.1552-6909.1999.tb01984.x[published Online First: Epub Date]|.
18. Battegay M, Elzi L. Morbidity and mortality in HIV-infected individuals - a shift towards comorbidities. Swiss medical weekly 2009;**139**(39-40):564-70 doi: smw-12662[published Online First: Epub Date]|.
19. Schifitto G, Deng L, Yeh TM, et al. Clinical, laboratory, and neuroimaging characteristics of fatigue in HIV-infected individuals. Journal of neurovirology 2011;**17**(1):17-25 doi: 10.1007/s13365-010-0010-5[published Online First: Epub Date]|.
20. Chen WT, Shiu CS, Yang JP, et al. Fatigue and Sleep Disturbance Related to Perceived Stress in Chinese HIV-Positive Individuals: A Mixed Methods Study. Journal of AIDS & clinical research 2013;**4**(6) doi: 10.4172/2155-6113.1000214[published Online First: Epub Date]|.
21. Barroso J, Voss JG. Fatigue in HIV and AIDS: An Analysis of Evidence. J Assoc Nurses Aids Care 2013;**24**(1):S5-S14 doi: 10.1016/j.jana.2012.07.003[published Online First: Epub Date]|.
22. Salahuddin N, Barroso J, Leserman J, et al. Daytime Sleepiness, Nighttime Sleep Quality, Stressful Life Events, and HIV-Related Fatigue. J Assoc Nurses Aids Care 2009;**20**(1):6-13 doi: 10.1016/j.jana.2008.05.007[published Online First: Epub Date]|.
23. Perazzo JD, Webel AR. Barriers to health-promoting behaviour in people living with HIV: Implications for comorbidity development. Antiviral therapy 2018;**23**:A35
24. Lerdal A, Gay CL, Aouizerat BE, et al. Patterns of morning and evening fatigue among adults with HIV/AIDS. J Clin Nurs 2011;**20**(15-16):2204-16 doi: 10.1111/j.1365-2702.2011.03751.x[published Online First: Epub Date]|.
25. Hulme K, Safari R, Thomas S, et al. Fatigue interventions in long term, physical health conditions: A scoping review of systematic reviews. PloS one 2018;**13**(10) doi: 10.1371/journal.pone.0203367[published Online First: Epub Date]|.
26. Payne C, Wiffen PJ, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database Syst Rev 2017;**2017**(4) doi: 10.1002/14651858.CD008427.pub3[published Online First: Epub Date]|.
27. Nosrat S, Whitworth JW, Dunsiger SI, et al. Acute effects of resistance exercise in a depressed HIV sample: the exercise for people who are immunocompromised (EPIC) study. Ment Health Phys Act 2017;**12**:2–9 doi: 10.1016/j.mhpa.2016.12.002[published Online First: Epub Date]|.
28. Nosrat S. Acute effects of resistance exercise intensity in a depressed HIV sample: The exercise for people who are immunocompromised (EPIC) study. ProQuest

Information & Learning, 2018.
29. Jaggers JR, Hand GA, Dudgeon WD, et al. Aerobic and resistance training improves mood state among adults living with HIV. International journal of sports medicine 2015;**36**(2):175-81 doi: 10.1055/s-0034-1385878[published Online First: Epub Date]|.
30. Doerfler RE, Goodfellow L. Brief Exposure to Cognitive Behavioral Therapy Reduces Side-Effect Symptoms in Patients on Antiretroviral Therapy. The Journal of the Association of Nurses in AIDS Care : JANAC 2016;**27**(4):455-67 doi: 10.1016/j.jana.2016.02.010[published Online First: Epub Date]|.
31. Doerfler RE. Clinical trial of cognitive-behavioral therapy to reduce antiretroviral effects in HIV patients. ProQuest Information & Learning, 2011.
32. Modeste RRM, Majeke SJ. Self-care symptom-management strategies amongst women living with hiv/aids in an urban area in kwazulu-natal. Health SA Gesondheid 2010;**15**(1):162-69 doi: 10.4102/hsag.v15i1.509[published Online First: Epub Date]|.
33. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews 2015;**4**:1 doi: 10.1186/2046-4053-4-1[published Online First: Epub Date]|.
34. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane database of systematic reviews 2019;**10**:ED000142 doi: 10.1002/14651858.ED000142[published Online First: Epub Date]|.
35. Julian PT Higgins, Jelena Savović, Matthew J Page, et al. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Secondary Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) August 22, 2019 2019. https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2.
36. Sterne JAC, Hernán MA, Reeves BC SJ, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ (Clinical research ed) 2016;**355**:i4919
37. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed) 2008;**336**(7650):924-6 doi: 10.1136/bmj.39489.470347.AD[published Online First: Epub Date]|.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Page number(s)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary material

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10/12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

Database: PubMed

(("Exercise"[Mesh] OR "Yoga"[Mesh] OR "Resistance Training"[Mesh] OR "Exercise Therapy"[Mesh] OR "Mindfulness"[Mesh] OR "Cognitive Behavioral Therapy"[Mesh] OR "Relaxation Therapy"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR "Psychotherapy"[Mesh] OR "Complementary Therapies"[Mesh] OR "Self Care"[Mesh] OR "Social Support"[Mesh] OR "Religion"[Mesh] OR Exercis* [tw] OR yoga [tiab] OR “resistance training” OR “resistance exercise” OR “physical activity” OR aerobic* [tiab] OR isometric* [tiab] OR “exercise training” OR mindful* [tiab] OR “cognitive behavioral therapy” OR “cognitive behavioral therapies” OR “cognitive behavioural therapy” OR “cognitive behavioural therapies” OR “cognitive therapy” OR “cognitive therapies” OR “cognitive psychotherapy” OR “cognitive psychotherapies” OR “Relaxation Therapy” OR “relaxation therapies” OR “relaxation technique” OR “relaxation techniques” OR “expressive support therapy” OR “stress management” OR physiotherap* [tiab] OR psychotherap* [tiab] OR biofeedback* OR acupuncture* [tiab] OR massag* [tiab] OR “self-care” OR “self-management” OR “social support” OR religion [tiab] OR prayer* [tiab] OR "complementary therapy" OR "alternative therapy" OR "complementary therapies" OR "alternative therapies" OR "alternative medicine" OR "tai chi")) AND ((hiv infections[mh] OR hiv[mh] OR hiv[tw] OR hiv-1[tw] OR hiv-2[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunodeficiency virus[tw] OR human immune-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])))) AND ("Asthenia"[Mesh] OR "Fatigue"[Mesh:noexp] OR "Mental Fatigue"[Mesh] OR asthenia[tiab] OR fatigue*[tiab] OR lassitude[tiab] OR lethargy[tiab] OR weakness[tiab] OR debility[tiab] OR feeble*[tiab] OR exhaust*[tiab]))

Data extraction form

General information	
First author	
Year of publication	
Corresponding author and email address	
Study design	
Study setting	
Sampling method	
Randomization method	
Allocation method	
Blinding	
Sample characteristics	
Inclusion and exclusion criteria	
Sample size	
Characteristics of sample in the baseline	
Tool used to measure fatigue	
Intervention	
Description of intervention	
Number of participants in intervention group	
Primary outcome: fatigue	
Secondary outcome	
Notes	
Control	
Description of control	
Number of participants in intervention group	
Primary outcome: fatigue	
Secondary outcome	
Notes	
Risk of bias	