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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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 synthesise 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 30 June 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 synthesise 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 summarise the non-pharmacological interventions to reduce fatigue among people living with HIV (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 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 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 behavioural factors may contribute to the presence and persistence of fatigue. The relationship between disease progression (eg, 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 behaviours manifests in a cluster with fatigue.[3] For example, sleep quality has been associated with fatigue in PLWH,[2 21 22] particularly, sleep quality moderates the relationship between fatigue patterns and psychological factors, including depression and anxiety.[23] 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 behavioural therapy (CBT) are common non-pharmacological interventions with potential efficacy in reducing fatigue.[24] 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.[25] 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[26–28] and CBT[29 30] 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 programmes reduce fatigue in PLWH by managing mood and behaviour.[31]

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).[32] The PRISMA-P checklist is shown in the online supplemental file 1.

Eligibility criteria for selecting studies
Types of studies

This review will include randomised controlled trials (RCTs), quasi-RCTs and controlled before-and-after studies, as defined by the Cochrane Handbook for Systematic Reviews of Interventions.[33] The randomised and quasi-randomised 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 behavioural therapy.
► Self-management strategies.
► Patient education programme.
► 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 30 June 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 supplemental file 2 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 do not meet the inclusion criteria. The full text of potentially related studies will be obtained and scrutinised 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.[32]

Data extraction

A standardised data extraction form has been designed (online supplemental file 3). 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, randomisation, 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 randomised trials,[34] which includes five domains, namely risk of bias arising from the randomisation 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-randomised Studies of Interventions.[35] This tool includes seven 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 summarise 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 to conduct statistical analysis. Standardised mean differences and relevant 95% 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 ≥50%, we will use random-effects models to synthesise 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 vs others delivering, or CBT vs exercise training), outcomes relevant features (measurements of fatigues, or severity vs rate of fatigue) and effects of interventions (short term vs long term, or pure non-pharmacological intervention vs 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.[36] 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.

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