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Weight loss and mortality in people living with HIV: Systematic Review Protocol and Meta-analysis

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Abstract:

Introduction: *At the time of the first reported cases of human immunodeficiency virus (HIV) infection, people living with HIV (PLHIV) experienced weight loss. Highly active antiretroviral therapy (HAART) has dramatically changed their weight loss condition to ideal weight, overweight, and even obesity. However, there is a percentage of PLHIV that still presents weight loss, which is an independent predictor of mortality, even on HAART. Therefore, we sought to answer whether the hospitalized PLHIV on HAART, with weight loss, have higher mortality rates compared to hospitalized PLHIV on HAART, without weight loss.*

Method: *This is a systematic review and meta-analysis study protocol for observational studies. A systematic literature search will be performed in the MEDLINE databases via PubMed, Embase, and LILACS, using the descriptors: HIV; highly active antiretroviral therapy; weight loss; hospitalization; malnutrition; thinness; HIV wasting syndrome; body weight and mortality. The detailed study protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO) under the number CRD42020191246. The searching process will be carried out by two reviewers, independently, and segmented into phases: Identification, Screening, Eligibility, and Selection. To analyze the methodological quality and risk of bias, the Joanna Briggs Institute (JBI) critical assessment tool for cohort studies will be used. Heterogeneity among studies will be evaluated using the Cochran's Q test and Higgins and Thompson I^2 statistics. Egger and Begg tests will be used to assess publication bias. The systematic review will be conducted according to the checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).*

Results: *It is expected to produce consistent results, with a high level of scientific evidence, related to the clinical outcomes of hospitalized PLHIV on HAART with weight loss, contributing to relevant knowledge on the subject.*

Conclusion: *From a public health perspective, the knowledge obtained is essential to plan and implement strategies to reduce mortality in PLHIV/AIDS, especially considering the high cost of treating PLHIV in Brazil and its increase if people are hospitalized. Thus, knowing whether hospitalized PLHIV on HAART, with weight loss, have higher mortality rates than those without weight loss, will contribute to new and relevant knowledge regarding a serious public health problem, and may guide public health care and policies.*

Keywords: *HIV; highly active antiretroviral therapy; Weight loss; Hospitalization; Malnutrition; HIV wasting syndrome; Mortality.*

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Abbreviations:
PLHIV: people living with HIV
HAART: Highly active antiretroviral therapy
AIDS: Acquired Immunodeficiency Syndrome.

INTRODUCTION

The human acquired immunodeficiency virus (HIV) epidemic is a global health problem (Chen et al., 2019). Worldwide, the number of people living with the human immunodeficiency virus (PLHIV) is over 36.9 million (Chen et al., 2019). In Brazil, by the end of 2019, there were approximately 920,000 PLHIV, according to the HIV Clinical Monitoring Report (Pascom et al., 2020). The latest Epidemiological Bulletin of HIV and Acquired Immunodeficiency Syndrome (AIDS) reveals that 41,919 new cases of HIV were reported in the Notifiable Diseases Information System (SINAN) in 2019 (Pereira et al., 2020).

Prior to the appearance of the highly active antiretroviral therapy (HAART), observed mortality rates in adults living with HIV in population studies were 10 to 15 times higher than in HIV-negative adults, and life expectancy was low. However, the introduction of HAART changed the epidemiological profile (Falutz et al., 2019; Slaymaker et al., 2014; Trickey et al., 2017; Verheij et al., 2020). Currently, the life expectancy of treated PLHIV resembles that of the general population (Falutz et al., 2019). According to data from the Brazilian Institute of Geography and Statistics, life expectancy for Brazilians at birth was 76.3 years in 2018 (Moutinho, 2019). In Europe and North America, the life expectancy of PLHIV who started treatment after the year 2008 is 78 years of age (Trickey et al., 2017).

Introduction of HAART and more effective treatments caused a dramatic turn, from the weight loss and wasting syndrome associated with HIV, that characterized the early history of the infection (and still occurs in countries where HAART is not readily available or is started late), changing to PLHIV with normal weight, overweight and obesity at rates similar to those found in the general population (Kumar & Samaras, 2018). This tendency is attributable to several factors, including the "return to health" weight gain that comes with the reversal of the catabolic effects of HIV infection after treatment, strategies for early initiation of HAART in the course of HIV infection, and exposure to the modern obesogenic environment (Kumar & Samaras, 2018). However, there is a percentage of PLHIV that even on HAART have weight loss and wasting syndrome associated with HIV, which is a difficult problem to treat.

In the HIV-infected population, weight loss has been associated with a lower CD4+ cell count and is an independent predictor of mortality. In PLHIV, an association between weight loss and mortality has been demonstrated (Mangili et al., 2006). Evidence has also shown an increase in PLHIV hospitalization due to weight loss (Allavena et al., 2018; Navon, 2018).

Weight loss has long been associated with mortality in general (Alebel et al., 2021). Despite important advances in the HAART and the increased survival of PLHIV, weight loss remains a problem (Allavena et al., 2018; Navon, 2018). The cost of treating PLHIV in Brazil is high and can be even higher if these patients are hospitalized. Therefore, knowing whether hospitalized PLHIV on HAART with weight loss have higher mortality compared to hospitalized PLHIV on HAART without weight loss, will contribute to new and relevant knowledge regarding a serious public health problem, which may guide health care and public policies.

METHOD

Study design

This is a systematic review and meta-analysis study protocol for observational studies.

Ethical considerations

There is no conflict of interest in this study conduction.

Research Question

The acronym PECOT (population, exposure, comparator, outcome, time) (Brasil. Ministério da Saúde, 2014) was used to describe all components related to the identified problem and to structure the research question: hospitalized PLHIV on HAART, with weight loss, have higher mortality in relation to hospitalized PLHIV on HAART, without weight loss? **Table 1** presents the description of the components of the PECOT strategy used to build the research question.

Eligibility Criteria

Inclusion criteria

Prospective cohort studies, published in English, Spanish or Portuguese, from 1996 to 2020, regarding PLHIV/AIDS, adults and elderly, on HAART, hospitalized, whose primary outcome was death and which analyzed the variable weight loss.

Exclusion Criteria

Studies that do not make reference to weight loss in PLHIV/AIDS. Studies that do not report death/mortality in their subjects. Any gray literature, incomplete articles, abstracts, review articles, editorials, books, scholar

Acronym	Definition	Description
P	Population	Hospitalized PLHIV in use of HAART
E	Exposure	Weight loss
C	Comparator	Hospitalized PLHIV in use of HAART without weight loss
O	Outcome	Mortality
T	Time	Hospitalization ≥ 24h

Note. Reference: Ministério da Saúde, 2014, p.21. Adapted by the authors, 2021.

Table 1. Description of the PECOT strategy for research question formulation

papers, dissertations, theses, scientific event proceedings and papers not available online.

Search strategy and information sources

Databases to be searched will be MedLine via PubMed, Embase and LILACS, with search terms found in the Medical Subject Heading (MeSH): HIV; Highly Active Antiretroviral Therapy; Weight loss; Hospitalization; Malnutrition; Thinness; HIV wasting syndrome; Body weight; Mortality; and correlates adapted for the respective databases and combined employing the Boolean operators "AND" and "OR".

The entire search process will be performed in an ultra-sensitive search. Whenever possible, the following filters will be used: subject: HIV and/or AIDS; language: English, Portuguese, and Spanish; publication date: from 1996 to 2020; type of studies: only in humans; age group: adults and elderly; and methodological design: prospective cohort studies.

Detailed search data for the identified studies, as well as the demonstration of information for each phase, will be presented in a flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method (Page et al., 2021), as shown in **Figure 1**.

Studies identification and data extraction

The study selection process will be carried out by two reviewers, independently, and segmented into phases: Identification, Screening, Eligibility and Selection. Phase 1 (Identification) will consist of searching the databases using descriptors and filters. After the identification of the studies, the removal of duplicates will be carried out. Phase 2 (Screening) will consist of the selection of studies after reading the titles and abstracts. Phase 3 (Eligibility) will consist of the selection of studies after the complete reading of the texts, based on the inclusion/exclusion criteria. Excluded articles will be presented together with the reasons for exclusion. Phase 4 (Selection) will consist of the final selection of studies for analysis. If there is disagreement among reviewers as to whether or not to include a research article, a third reviewer will be assigned the judgment.

After selection, data will be extracted by two reviewers independently. The characteristics of the included studies will be discriminated: authors, year, country, sample number, age range, gender, main objective, hospitalization cause, hospitalization time, coinfections, and other variables such as weight loss, mortality outcome, mortality causes, main results; according to the forms for data extraction in the screening phase (titles and abstracts) and eligibility (full text), as well as the studies exclusion criteria. In cases where data are not available in the original publication, the corresponding authors of the studies may be contacted. There will be a third reviewer to check and improve accuracy.

Rayyan software from the Qatar Computing Research Institute (QCRI) will be used to remove duplicates during data analysis (Ouzzani et al., 2016). Also, EndNote® software (Thomson, 2020) will be used for reference management.

Identification of variables

Weight loss

Weight loss defined as "a decrease in existing bodyweight" will be investigated in the studies (National Library of Medicine., 2021). In PLHIV, weight loss is a manifestation of moderate or advanced immunodeficiency, characterized by clinical stages 3

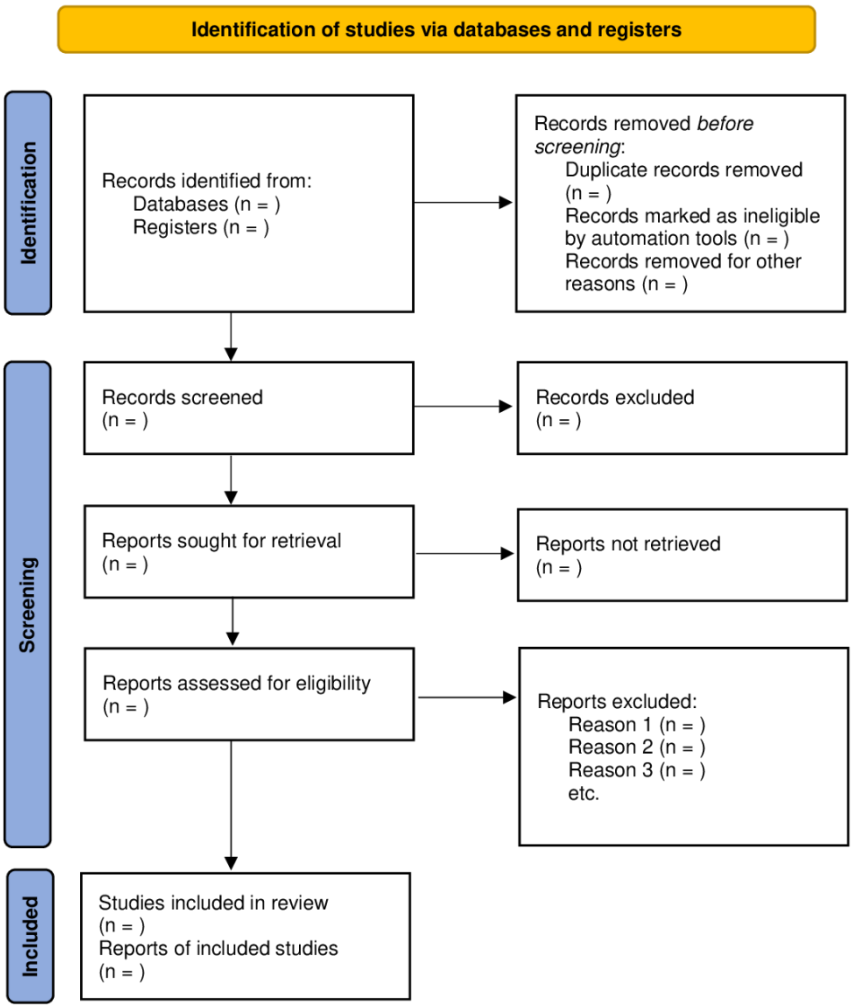


Figure 1. Information flow in the different phases of the systematic review, by Page et al., 2021.

and 4 of the disease by the World Health Organization (WHO) (Benzaken et al., 2018). In stage 4, involuntary weight loss >10% of the usual body weight, accompanied by diarrhea or chronic fatigue, and fever for more than 30 days is called HIV Consumptive Syndrome, which defines AIDS, according to the Center for Diseases Control and Prevention (CDC). Clinical stage 3 of the disease also includes unexplained weight loss >10% with symptoms attributed to HIV or cellular immunodeficiency signs (Benzaken et al., 2018). The study will analyze weight loss >10% in PLHIV.

Mortality

Mortality is the variable that refers to the set of individuals who died in a given period of time. It represents the risk or probability that any person in the population has of dying, or of dying as a result of a certain disease (Pereira, 2004). The study will analyze the number of deaths or mortality outcomes in PLHIV hospitalized for a period ≥ 24h.

Hospitalization

The hospitalization variable will be represented by the definition of the Brazilian Ministry of Health, according to the hospital census nomenclature standardization, which defines hospitalization as the patient admitted to occupy a bed for ≥ 24 hours. (Meinecke et al., 2002). In the study, hospitalization time will be analyzed in days or hours.

Risk of bias and methodological quality analysis

Two reviewers will carry out quality analyses of the selected studies independently. Data for the quality critical analysis will be consolidated in a specific form for evaluation. The Joanna Briggs Institute (JBI) critical assessment tool will be used for cohort studies (Moola

et al., 2020), which aims to assess the studies methodological quality, in addition to determining the risk of bias, conduction and analysis. It is a tool with 11 questions, which can be answered with: Yes, No, It is not clear and Not applicable, as shown in **Figure 2**.

Statistical analysis

For the meta-analysis, after selecting the studies and identifying the outcome variables, Software Review Manager (RevMan) (Deeks, J., & Higgins, 2020), version 5.4.1, will be used for statistical analysis, with a 95% confidence interval (95% CI), heterogeneity (I2) and total effect size (Z), with a significant p-value <0.05 for total scores mean evaluation.

Association measures, such as the odds ratio (OR), will be used to analyze the probability of hospitalized PLHIV with weight loss evolving to mortality when compared to those without weight loss.

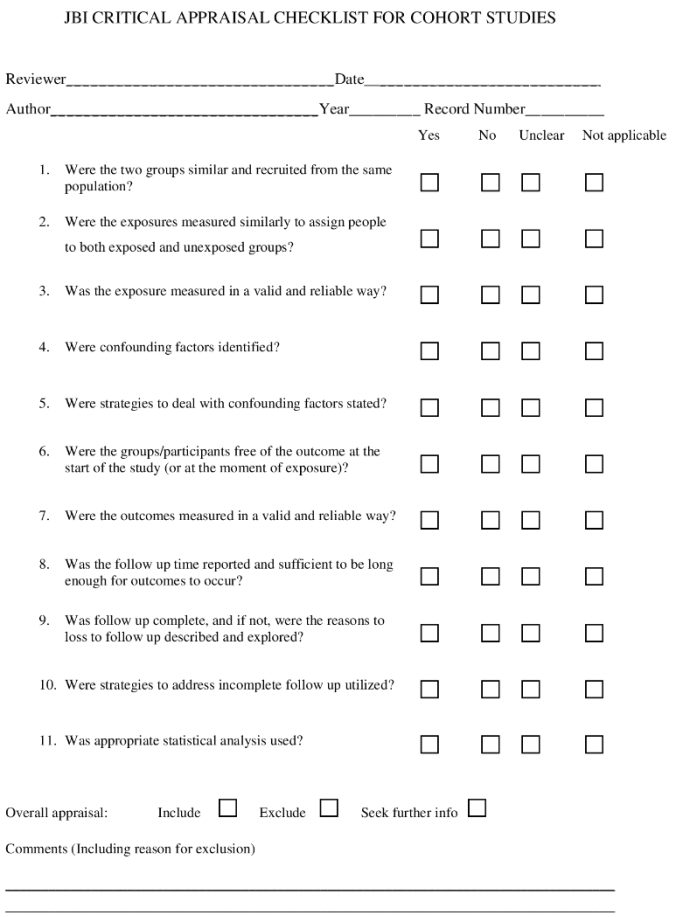
Cochran's Q test and Higgins and Thompson's I^2 statistic will be used to assess heterogeneity. In the presence of heterogeneity, alternative analyzes, such as subgroup meta-analysis, will be considered to explain variability among groups.

Random effect models may be used, depending on the number of selected studies. If the number of studies is too small, impacting on the precision of the estimation of variance among studies, data will be reported separately and not as a summary measure.

To assess publication bias, a funnel plot will be established. Hypothesis tests may also be performed. In the case of normal distribution, Egger's test can be used. If the distribution is asymmetric, the Begg test can be used. Both the visual evaluation of the funnel plot and the statistical hypothesis tests can be used if there is a significant number of studies included in the meta-analysis.

Primary outcome and secondary outcomes

For this systematic review, mortality will be used as the primary outcome. Hospitalization time and clinical complications, such as pneumonia/tuberculosis,



JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____Date_____

Author_____Year_____ Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☐	☐
11. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Figure 2. Critical Assessment Instrument for Joanna Briggs Institute (JBI) Cohort Studies, by Moola et al., 2020.

anemia, hypoalbuminemia, and low CD4+ cell count will be analyzed as secondary outcomes.

Protocol Registration

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), under the number CRD42020191246.

RESULTS

Weight loss can be negatively related to the survival of PLHIV, therefore, eliminating the causes of this loss through nutritional clinical approaches can contribute to the reduction of mortality in this population, since food can improve the effectiveness of antiretroviral therapy, and therefore, help to minimize symptoms such as fatigue, decreased strength, as well as symptoms that hinder food intake, such as oral ulcers, nausea and vomiting that lead to weight loss. Therefore, this study intends to produce consistent results with a high level of scientific evidence related to clinical outcomes of hospitalized PLHIV on HAART, with weight loss, contributing to relevant knowledge on the subject, through clinical questions that can be answered for better clinical practice.

Study limitations

We considered the PLHIV population limited to the studies found in the search results in Pubmed, Embase and LILACS, and therefore not corresponding to a generalizable sample.

CONCLUSION

Knowing whether hospitalized PLHIV on HAART, with weight loss, have a higher risk of mortality than those without weight loss, will contribute to relevant knowledge about a serious public health problem and may guide public health care and policies.

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Conflict of interest

None.

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