


BMJ Open Does undernutrition increase the risk of lost to follow-up in adults living with HIV in sub-Saharan Africa? Protocol for a systematic review and meta-analysis

Animut Alebel ^{1,2}, Daniel Demant,^{2,3} Pammla Petrucka,^{4,5} David Sibbritt²

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¹College of Health Science, Debre Markos University, Debre Markos, Ethiopia

²School of Public Health, Faculty of Health, University of Technology Sydney, Ultimo, New South Wales, Australia

³School of Public Health and Social Work, Faculty of Health, Queensland University of Technology, Kelvin Grove, QLD, Australia

⁴University of Saskatchewan, Saskatoon, Saskatchewan, Canada

⁵Nelson Mandela African Institute of Science and Technology, Arusha, Tanzania

Correspondence to

Animut Alebel;
animut.a23@gmail.com

ABSTRACT

Introduction Undernutrition is considered a marker for poor prognosis among people living with HIV (PLHIV), particularly in sub-Saharan Africa (SSA), where undernutrition and HIV are both highly prevalent. Evidence suggests that undernutrition (body mass index <18.5 kg/m²) is one of the main factors that significantly increases the risk of lost to follow-up (LTFU) in PLHIV. However, primary studies in SSA have reported inconsistent findings on the relationship between undernutrition and LTFU among adults living with HIV. To the best of our knowledge, no systematic review which aimed to summarise the available evidence. Hence, this review aims to determine the pooled effect of undernutrition on LTFU among adults living with HIV in SSA.

Methods and analysis PubMed, EMBASE, Web of Science, Scopus, and, for grey literature, Google Scholar will be systematically searched to include relevant articles published since 2005. Studies reporting the effect of undernutrition on LTFU in adults living with HIV in SSA will be included. The Newcastle-Ottawa Scale will be used for quality assessment. Data from eligible studies will be extracted using a standardised data extraction tool. Heterogeneity between included studies will be assessed using Cochrane Q-test and I² statistics. The Egger's and Begg's tests at a 5% significance level will be used to evaluate publication bias. As heterogeneity is anticipated, the pooled effect size will be estimated using a random-effects model. The final effect size will be reported using the adjusted HR with a 95% CI.

Ethics and dissemination Ethical approval is not required for a protocol for a systematic review. The results of this systematic review will be published in a peer-reviewed journal and will be publicly available.

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INTRODUCTION

HIV remains a global public health challenge. Of the 38 million worldwide HIV cases at the end of 2019, more than two-thirds (25.7 million) were living in sub-Saharan Africa (SSA).¹ Though there is no cure for HIV, antiretroviral (ARV) drugs can suppress viral replication and reduce or eliminate HIV transmission risk.² ARV also assists people

Strengths and limitations of this study

- To the best of our knowledge, this is the first systematic review and meta-analysis protocol designed to examine the effect of undernutrition on lost to follow-up among adults living with HIV in sub-Saharan Africa.
- The protocol included a comprehensive (detailed) searching strategy plans to include all eligible studies as much as possible.
- This protocol planned to quantify the final pooled effect size using adjusted HR to control for potential confounding factors.
- The protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol checklist to ensure quality.
- As different study designs and clinically heterogeneous participants are eligible for this protocol, these may be the possible sources of heterogeneity.

living with HIV (PLHIV) to live comparably healthy.³ The rapid scale-up of antiretroviral therapy (ART), especially in resource-limited settings, is one of the most remarkable achievements in the global efforts against HIV.⁴ Globally, access to ART has increased dramatically from 7% in 2005 to 67% in 2019.¹⁵

ART is a daily medication,^{6 7} requiring a lifelong commitment to be effective.⁸ Lost to follow-up (LTFU) from ART profoundly affects success rates. LTFU is defined as when patients do not return to the ART clinic within 90 days (60 days after the next appointment) from the last clinic visit.⁹ It has become an emerging problem in many low- and middle-income countries (LMICs), including SSA.^{10 11} A meta-analysis from 42 LMICs found that nearly 35% of all patients initiated on ART either died or were LTFU at 36 months of follow-up.¹⁰ An additional meta-analysis from SSA has shown that up to 40% of patients were LTFU or died.¹² PLHIV lost to ART are at higher risk of treatment failure,



viral rebound, mortality and opportunistic infections (OIs).^{13 14} The common contributing factors for LTFU are low CD4, advanced WHO clinical staging (III and IV), poor ART adherence, low baseline body weight, weight loss >10% and undernutrition (low body mass index (BMI)).^{15–23}

Undernutrition is considered a marker for poor prognosis among PLHIV, particularly in SSA, where both undernutrition and HIV are highly prevalent.²⁴ While both conditions are global problems, they are most prevalent in the world's poorest areas, such as SSA. SSA accounted for 23% of all people suffering from undernutrition and 68% of all PLHIV worldwide.^{25 26} Undernutrition is characterised by a deficit in macronutrients and/or micronutrients, leading to body composition changes and diminished function.^{27 28} HIV and undernutrition are interrelated. HIV reduces food intake, reduces nutrient absorption and increases energy requirements.^{29–31} At the same time, undernutrition hastens disease progression and increases the occurrence and recurrence of OIs.^{30 32} Undernutrition significantly increases the risk of mortality, treatment failure, and LTFU among PLHIV.^{33–41}

Studies have shown that undernutrition (ie, BMI <18.5 kg/m²) is one of the main factors that significantly increases the risk of LTFU among adults living with HIV.^{42–47} This finding may reflect that undernourished patients are more likely to develop OIs and later died but were under-reported to the HIV clinics due to a passive reporting system.⁴⁸ For example, a meta-analysis in SSA conducted by our team found that the risk of developing TB in undernourished adults living with HIV is twice that of well-nourished counterparts.⁴⁹ In addition, undernourished patients may not be able to report to the health facility for ART refills and complete their appointments in the same manner as well-nourished patients.⁵⁰ Additional study from Uganda has reported that overweight (BMI >30 kg/m²) patients living with HIV are at lower risk of LTFU compared with well-nourished patients living with HIV.⁴⁸

There have been extensive primary studies on the relationship between undernutrition and LTFU among adults living with HIV in SSA.^{42 45–48 50–57} However, these individual studies have reported inconsistent findings. Some studies showed that undernutrition significantly increases the risk of LTFU among adults living with HIV.^{42–47} Conversely, a few studies found that undernutrition and LTFU among adults living with HIV have no significant association.⁴⁷ Estimating the pooled effect of undernutrition on LTFU among adults living with HIV is important to provide evidence for healthcare workers and policy-makers in designing specific interventions to minimise undernutrition-related LTFU among adults living with HIV. However, to the best of our knowledge, there is no systematic review and meta-analysis, which summarised available evidence to show the pooled effect of undernutrition on LTFU among adults living with HIV in SSA. Thus, this review protocol has been designed to address this gap. This systematic review protocol is designed to

estimate the pooled effect of undernutrition on LTFU among adults living with HIV in SSA. The authors will follow this protocol during the literature search, data analysis, and reporting of results.

Review question

Does undernutrition increase the risk of LTFU among adults living with HIV in SSA?

The PICO framework

- ▶ Participants/population: adults (aged ≥15 years) living with HIV.
- ▶ Intervention(s)/exposure(s) group: undernourished adults living with HIV.
- ▶ Comparator(s)/control group: well-nourished adults living with HIV.
- ▶ Outcome(s) of interest: LTFU from ART.

METHODS AND ANALYSIS

Information sources and search strategy

This systematic review protocol is prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA) checklist (online supplemental additional file 1).⁵⁸ The following databases will be searched: PubMed, EMBASE (Elsevier), Web of Science, Scopus, and, for grey literature, Google Scholar (see online supplemental additional file 2 for draft search strategy for PubMed). Additional studies will be identified through a review of reference lists of included studies. An updated search will be undertaken prior to the final manuscript submission in order to retain currency. Search limitation will include English publications, human subjects and a publication date since 2005 aligning with the first year in which payment-free ART was available in most African countries. A line-by-line search will be conducted from each database, and a separate searching strategy will be developed for each database, depending on the functions and search interface of databases. The search findings will be exported and managed through Covidence software.

Study selection and eligibility criteria

The systematic review will consider all studies reporting the association between undernutrition and LTFU among adults (aged ≥15 years) living with HIV in SSA. Studies reported the association between undernutrition and LTFU in relative risk (RR) or HR will be considered for meta-analysis. Studies providing incomplete data, descriptive statistics only, review articles, case reports, editorial comments, non-aligned outcomes of interest, conference papers and qualitative studies will be excluded. Additionally, studies conducted among HIV-infected pregnant women will be excluded as the risk of undernutrition, and nutritional assessment tools used for pregnant women are distinct from non-pregnant individuals.⁵⁹ Articles including only malnourished adults living with HIV will also not be considered for this review due to a lack of controls (ie, well-nourished adults living with HIV).

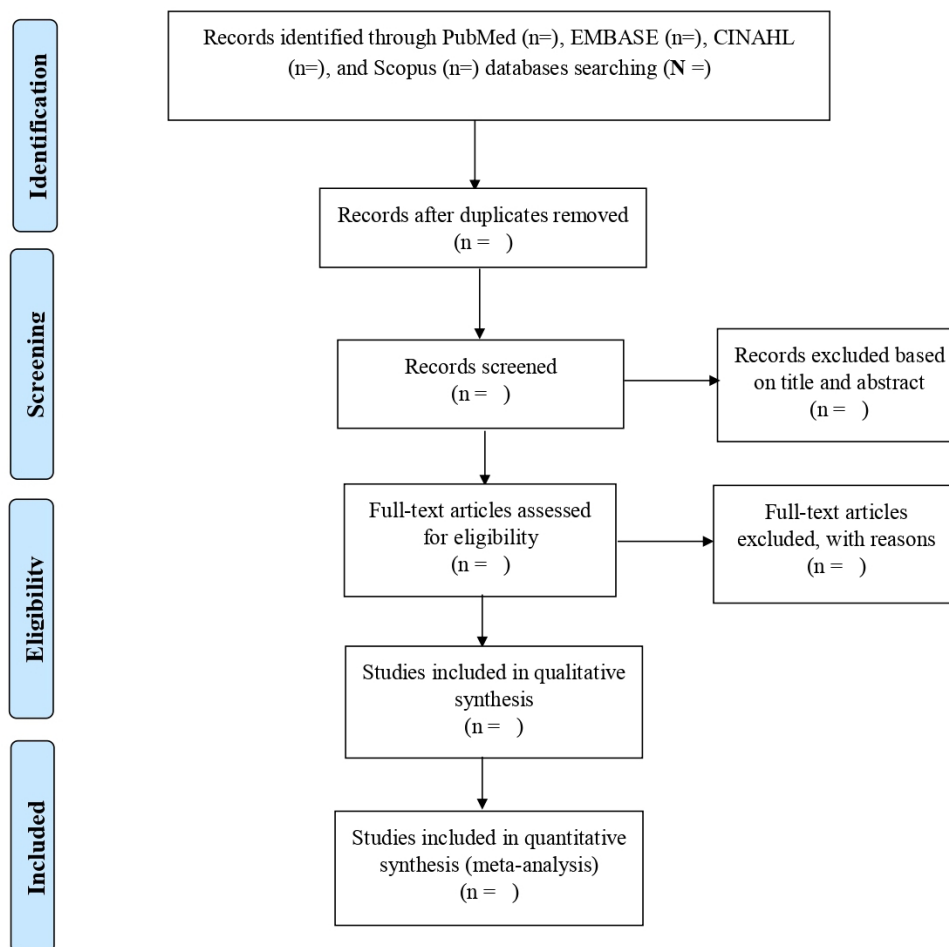


Figure 1 Flow chart of study selection for a systematic review and meta-analysis of the effect of undernutrition on LTFU in adults living with HIV in SSA. LTFU, lost to follow-up; SSA, sub-Saharan Africa.

The primary author (AA) will assess the titles and abstracts of potentially relevant studies. Then, two reviewers, (AA and DD), will determine the inclusion and exclusion of full-texts based on the predetermined criteria. A third reviewer will be invited in cases of disagreement. The flow chart for this systematic review is described in [figure 1](#).

Data extraction and management

A standardised data extraction tool will be adapted from the Joanna Briggs Institute (JBI).⁶⁰ The following variables will be extracted: primary author name, publication year, study design, country/countries where the study was conducted, study/follow-up period, sample size, sex/gender of the participants, LTFU rate/proportion, adjusted confounders for LTFU (ie, sex, residence, age, distance from health facility, ART regimen, functional status, CD4 cell count, WHO clinical staging, ART adherence, OIs, cotrimoxazole preventive therapy, and isoniazid preventive therapy) and adjusted HR (AHR) for time-to-event analysis/adjusted OR/adjusted risk ratio (ARR) with 95% CIs. Any queries on primary article data collection or critical appraisal will lead to contact with corresponding authors. Failure to make the necessary connection will result in the article being excluded from

our review. The primary author (AA) will extract data from included studies. To assure data quality, extracted data will be double-checked by another author (DD).

Outcomes

The outcome of this review is LTFU among adults living with HIV. LTFU will be identified as events in which patients not returning to the ART clinic within 90 days (60 days after the next appointment) from the last clinic visit.⁹ Undernourished adults living with HIV will be considered as exposed the group to estimate the effect size of undernutrition on LTFU. Undernutrition (underweight) reflects an individual with a BMI of less than 18.5 kg/m². The severity of undernutrition is further classified as severe (BMI <16 kg/m²), moderate (BMI 16–16.99 kg/m²) or mild (BMI 17–18.48 kg/m²).⁶¹

Risk of bias in individual studies

The Newcastle-Ottawa Scale (NOS) quality assessment tool will be used to assess the risk of bias in individual studies.⁶² The NOS is a validated tool with grading from zero to nine for case-control and cohort studies.⁶³ The tool has three components: selection, comparability, and outcome/exposure. The selection part is scored from zero to four stars, and the comparability is scored



from zero to two stars. The outcome/exposure is mainly related to the statistical analysis and confounding handling mechanisms, which is scored from zero to three stars. Furthermore, to minimise the subjective interpretation of bias from scoring the NOS, three reviewers (AA, DD, and DS) will assess the quality of individual studies with consensus being achieved on all instances. Inter-rater reliability will be assessed using Cohen's kappa statistics. Finally, the quality score of each study will be calculated as the sum of scores.

Data synthesis

All statistical analyses will be done using Stata (V.16) statistical software. The effect of undernutrition on LTFU will be estimated using the AHR by considering undernutrition as exposure variable. RRs, rate ratios and incidence density ratios will be directly used as hazard ratios. Adult HIV patients with BMI ≥ 18.5 kg/m² will be considered non-exposed (control group). In order to adjust for primary studies reporting AHRs considering undernourished adults living with HIV as a reference category, new AHRs with their 95% CIs will be estimated by considering the reciprocal of the reported AHRs to ensure consistency and uniformity.⁶⁴ If a study does not report RR/HR but reports the regression coefficient (β), we will undertake conversion into RR/HR by exponentiation of the coefficient (ie, $RR = \exp(\beta)$).⁶⁵ The effect size (pooled AHR) will be estimated based on two nutritional status categories (undernutrition vs well nourished). If reported AHR is based on the severity level of undernutrition (mild, moderate and severe), categories will be considered in the subgroup analyses. Finally, those studies reporting nutritional status (BMI) as a continuous variable and cross-sectional studies reported ORs which are not eligible for meta-analysis will be addressed using a narrative synthesis approach.

Heterogeneity between included studies will be assessed using Cochrane Q-test and I² statistics. The I² value will be interpreted as: 0% to 40% (might not be important); 30% to 60% (may represent moderate heterogeneity); 50%–90% (may represent substantial heterogeneity); and 75%–100% (considerable heterogeneity).⁶⁶ As heterogeneity is anticipated, the pooled effect size and 95% CI will be estimated using a random-effects model with logit transformation and back transformation. Finally, all relevant findings will be presented using text, tables, and forest plots.

Subgroup and sensitivity analyses

When considerable heterogeneity (I² $\geq 75\%$) is detected, potential sources of heterogeneity will be investigated using subgroup and meta-regression analyses. If appropriate, sub-group analyses will be conducted using different variables based on country, design, degree of undernutrition, sample size, and publication year. Furthermore, sensitivity analysis will be done by sequential removal of individual studies from the analysis.

Meta-bias

If more than eight individual studies are included in a meta-analysis, funnel plots will be used to assess publication bias graphically.⁶⁷ The Egger's and Begg's tests at a 5% significance level will be used to confirm publication bias.⁶⁸ In the presence of significant publication bias, trim and fill analyses will be done, and adjusted effect sizes will be reported.

Patient and public involvement statement

No involvement of patients or the public occurred during design, conduct, reporting or dissemination plans in this research.

DISCUSSION

LTFU from ART became a significant public health problem as ART was rapidly scaled up.^{4 10 11} Evidence shows that undernutrition significantly increases the risk of LTUF among adults living with HIV.^{42–47} Therefore, understanding the impact of undernutrition on LTFU is essential in designing appropriate interventions. However, there is no systematic review and meta-analysis summarising available evidence about the pooled effect of undernutrition on LTFU among adults living with HIV in SSA. Thus, we propose this systematic review and meta-analysis protocol which is feasible, attainable, and timely. This review is the first systematic review examining the effect of undernutrition on LTFU among adults living with HIV in SSA to the best of our knowledge.

This review will synthesise all the available studies reporting the effect of undernutrition on LTFU among adults living with HIV in SSA. Findings will be presented at conferences in poster or oral presentations. In addition, the final manuscript will be published in a peer-reviewed journal for broader dissemination. Furthermore, the final manuscript will report any reason for significant changes to the protocol following publication.

This review has a number of strengths and limitations. The final manuscript of this review will be reported in line with the PRISMA guidelines.⁶⁹ This review will pursue a comprehensive search strategy to include all eligible studies. Predefined eligibility criteria concerning population, exposure, control and outcomes will be applied. The final pooled effect size will be reported using AHR to control potential confounders. Despite these strengths, it is essential to acknowledge the possible anticipated limitations. By limiting our search to studies published in the English language, we are potentially missing a few important non-English studies. Varying definitions of LTFU and follow-up duration of the included studies may limit the comparability of data. All studies included in our systematic review might not be included in our meta-analysis as studies might report BMI in different categories.

ETHICS AND DISSEMINATION

Ethical approval is not required for a protocol for a systematic review. The results of this systematic review will be published in a peer-reviewed journal and will be publicly available.

Contributors AA: conceived the review protocol, designed the study methodology, drafted and revised the protocol, and designed the statistical analyses plan. DD and DS: conceived the review protocol, reviewed and edited the protocol, and reviewed the statistical analyses plan. PMP: critically reviewed the protocol and made revisions. All authors read and approved the final manuscript.

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ORCID iD

Animut Alebel <http://orcid.org/0000-0003-2822-2062>

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