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Effects of undernutrition on treatment outcomes among adults living with HIV in Northwest Ethiopia: A longitudinal study

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Certificate of original authorship

I, Animut Alebel Ayalew, declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy in Public Health in the School of Public Health, Faculty of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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Signature:

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List of abbreviations and acronyms

Abbreviation/acronym	Meaning
AHR	Adjusted Hazard Ratio
AIDS	Acquired Immunodeficiency Syndrome
ALHIV	Adults Living with Human Immunodeficiency Virus
ART	Antiretroviral Therapy
ATE	Average Treatment Effects
BMI	Body Mass Index
CI	Confidence Interval
CPT	Cotrimoxazole Preventive Therapy
DGT	Dolutegravir
DMCSH	Debre Markos Comprehensive Specialized Hospital
EDHS	Ethiopian Demographic and Health Survey
HAART	Highly Active Antiretroviral Treatment
Hgb	Haemoglobin
HIV	Human Immunodeficiency Virus
IPT	Isoniazid Preventive Therapy
LMICs	Low and Middle-income Countries
LTFU	Loss to Follow-Up
Ois	Opportunistic Infections
PLHIV	People Living with Human Immunodeficiency Virus
SSA	Sub-Saharan Africa
TB	Tuberculosis
WHO	World Health Organization

Glossary

Term	Definition
Acquired Immune Deficiency Syndrome (AIDS)	A disease caused by the HIV virus called AIDS.
Antiretroviral therapy	The treatment for HIV is called antiretroviral therapy.
Comprehensive Specialized Hospital	A health facility in the Ethiopian health care system providing curative and rehabilitative services at the tertiary level with a minimum capacity of 110 beds. It should provide a minimum of gynaecology and obstetrics, paediatrics, internal medicine, surgery, orthopaedics, psychiatry, ophthalmology, ENT, dentistry, dermatology specialty services, and emergency services requiring advanced diagnostic facilities and therapeutic interventions. It shall also have a minimum of two additional sub-specialties. In the case of government-owned comprehensive specialized hospitals, the minimum bed capacity shall be 300 beds with at least four subspecialty services.
HIV-status disclosure	Refers to when someone living with HIV tells (discloses) their HIV status to people.
Human immunodeficiency virus	HIV is a virus that attacks the body's immune system.
Opportunistic infections	Opportunistic infections are illnesses that commonly occur in people with weakened immune systems, such as those infected with HIV.
sub-Saharan Africa	It is the region of the African continent located south of the Sahara Desert.

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Abstract

Background: Undernutrition is one of the most common problems among people living with HIV (PLHIV), particularly in sub-Saharan Africa (SSA), where both undernutrition and HIV are highly prevalent. The relationship between HIV and undernutrition is multifactorial and multidimensional. HIV increases the risk of undernutrition, and at the same time, undernutrition accelerates the disease progression from mild to severe, leading to poorer treatment outcomes, including mortality. In addition, the success of antiretroviral therapy (ART), the drug used to treat HIV, depends on the nutritional status of patients. In Ethiopia, although these interrelated conditions highly affect PLHIV, longitudinal studies evaluating the effects of undernutrition on treatment outcomes of this population are lacking. This thesis was designed to fill this gap and inform evidence-based practice.

Aim: The aim of this study was to assess the effects of undernutrition on the overall treatment outcomes of adults living with HIV (ALHIV) on antiretroviral therapy (ART) in Ethiopia.

Objectives: This thesis has five objectives:

1) To examine the effects of undernutrition on mortality and morbidity among ALHIV in SSA since 2002;
2) To determine the effect of undernutrition on loss to follow-up among ALHIV on ART;
3) To determine the effects of undernutrition on opportunistic infections (OIs) among ALHIV on ART at Debre Markos Comprehensive Specialized Hospital, Ethiopia;
4) To assess weight change during the two years of ART among adults living HIV at Debre Markos Comprehensive Specialized Hospital, Ethiopia; and
5) To examine the association between body mass index variation and early mortality among adults living HIV at Debre Markos Comprehensive Specialized Hospital, Ethiopia.

Methods: Different quantitative research methods and analytical approaches were employed to address the objectives of this research**.** The first objective was addressed using a systematic review and meta-analysis. The systematic review included all observational studies reporting the effects of undernutrition on mortality and morbidity among ALHIV in SSA. The pooled effects of undernutrition on mortality and morbidity were estimated using a random-effects meta-analysis model. The remaining four objectives were addressed through a retrospective longitudinal study. Data for this study were obtained from the medical records of ALHIV, who

received ART at Debre Markos Comprehensive Specialized Hospital, Ethiopia, between June 2014 and June 2020. Data from patients' medical records were extracted manually using a standardized data extraction format. Specifically, the second objective examined the impact of undernutrition on loss to follow-up (LTFU) among 844 ALHIV receiving ART using proportional hazards regression model. The third objective examined the effects of undernutrition on time to develop OIs in 841 participants using inverse-probability weighting. The fourth objective explored weight change during the first two years of ART among 848 ALHIV using a linear mixed-effects model. The last objective examined the association between body mass index (BMI) variation and early mortality in 834 participants using a joint modelling approach (longitudinal and time-to-event data).

Results: Manuscript I found that undernutrition significantly (AHR [adjusted hazard ratio]: 2.1, 95% CI: 1.8, 2.4) increased the risk of mortality in ALHIV, while severely undernourished ALHIV were at higher risk of death (AHR: 2.3, 95% CI: 1.9, 2.8) compared to mildly undernourished ALHIV. This review also showed that undernutrition significantly increased the risk of developing tuberculosis (AHR: 2.1, 95% CI: 1.6, 2.7) among ALHIV.

Findings from Manuscript III (Manuscript II is a protocol) suggested that the incidence of LTFU was higher in undernourished participants (8.2 per 100 person-years) compared to well-nourished participants (4.3 per 100 person-years). After adjusting for potential confounders, the adjusted risk of LTFU among undernourished participants was two times higher than in their well-nourished counterparts (AHR: 2.1, 95% CI: 1.4, 3.2). This study found that undernutrition significantly increased the risk of LTFU among adults living with HIV on ART.

Manuscript IV showed that the incidence of OIs in undernourished ALHIV on ART (21.0 per 100 person-years: 95% CI: 17.8, 27.4) was higher than well-nourished ALHIV on ART (15.0 per 100 person-years: 95% CI: 12.9, 17.4). When everyone in the population of interest is well nourished, the average time to develop OIs is estimated to be 26.5 (95% CI: 20.6, 32.4) months. When everyone is undernourished, the average time to develop OIs decreases by 8.8 (95% CI: -16.6, -1.0) months.

Manuscript V also found that the mean weight of participants increased from 54.2 kg (SD± 9.6 kg) at baseline to 59.5 kg (SD± 10.7 kg) at the end of follow-up. The duration of time on ART, sex, World Health Organization (WHO) clinical disease stage, functional status, nutritional status, and presence of OIs were significant predictors of weight change at ART initiation.

Significant interaction effects were observed between time and sex, WHO clinical disease stage, functional status, isoniazid preventive therapy, and nutritional status.

Finally, findings from Manuscript VI showed that a unit increase in BMI after ART initiation corresponded to an 18% reduction in mortality risk. Patients taking tuberculosis preventive therapy (TPT), those with mild clinical disease stage, and those changing ART regimens were at lower risk of death. However, patients with ambulatory/bedridden functional status were at higher risk of death. Regarding BMI variation over time, patients presenting with OIs, underweight patients, patients who started a Dolutegravir (DGT)-based ART regimen and those with severe immunodeficiency had a higher BMI increase over time. However, patients from rural areas and overweight/obese patients experienced a lower BMI increase over time.

Conclusions: The research presented in this thesis found that undernutrition significantly increases the risk of mortality, morbidity, and LTFU. The risk of mortality is more severe among severely undernourished patients. In addition, undernutrition significantly reduced the time to develop OIs in this population. Moreover, a linear weight gain was observed throughout the follow-up, with a higher rate of increase in the first year. Gender, nutritional status, functional status, WHO disease stage, and IPT were significant determinates of weight change. Further, improvement in nutrition (BMI) after ART initiation was strongly associated with lower mortality risk, regardless of BMI category. Lastly, patients taking DGT-based ART regimens and those with poor clinical conditions (i.e., presence of OIs, underweight and severe immunodeficiency) had higher BMI increases over time.

Therefore, regular nutrition education by nurses and physicians at each ART visit should be a high priority. In developing countries such as Ethiopia, CD4 cell count and viral load measurements are expensive or unavailable, so regular weight measurements can be used as clinical indicators to monitor the success of ART. Although short-term weight gain following ART initiation is associated with a lower risk of early mortality in this research, further studies are needed to understand the long-term effects of weight gain in this population. Further, the diagnosis and management of OIS in undernourished ALHIV require a special approach as this population is at greater risk of developing OIS than other HIV-infected individuals.

Chapter 1 │Introduction

1.1. Chapter introduction

This chapter includes the problem statement, rationale, and thesis outline. The first section (section 1.2) describes the burden of human immunodeficiency virus (HIV), the link between HIV and undernutrition, and the overall effects of undernutrition on treatment outcomes (i.e., loss to follow-up, mortality, and opportunistic infections) in adults living with HIV (ALHIV). The second section (section 1.3) describes the rationale for undertaking this study. The final section presents the thesis outline.

1.2. Problem statement

HIV is a retrovirus that attacks the immune system and makes our body vulnerable to other infections (Calles et al., 2010). If HIV is left untreated, it usually leads to acquired immunodeficiency syndrome (AIDS) (World Health Organisation, 2022). While AIDS-related mortality has reduced by 52% since 2010, it continues to be a significant public health problem. In 2021 alone, 650,000 people died from AIDS-related illnesses worldwide (UNAIDS, 2022), and approximately 38.4 million people were living with HIV (PLHIV) worldwide by the end of 2021. Of these, more than two-thirds (25.6 million; 69.3%) were from sub-Saharan African (SSA) (World Health Organisation, 2022), with Ethiopia being one of the SSA countries with the highest prevalence of HIV, with a prevalence of 0.9% (Central Statistical Agency of Ethiopia (CSA), 2016).

Antiretroviral therapy (ART) is a combination of three or more antiretroviral drugs used to treat HIV infection with the aim of maximal viral load suppression to reduce morbidity and mortality. It is a lifelong medication that must be taken continuously and daily (Deeks et al., 2013). Global ART coverage has increased significantly from 7% in 2005 to 75% in 2022 (World Health Organisation, 2022); however, that coverage is accompanied by barriers to ART adherence, such as loss to follow-up (LTFU), particularly in low- and middle-income countries (LMICs) (Bigna et al., 2016; Geng et al., 2015; Walker et al., 2012). LTFU from HIV-care is an emerging problem in LMICs (Fox & Rosen, 2015; Levi et al., 2016), including SSA (Akilimali et al., 2017). A collaborative analysis found that 18.8% of ALHIV in SSA were LTFU for ART, with the highest prevalence in West Africa and the lowest in central Africa (Haas et al., 2018). LTFU among ALHIV in Ethiopia ranged from 13.7% in Addis Ababa and

Southern Nations, Nationalities and People's Region (Teshale et al., 2020) to 31.4% in Gondar (Wubshet et al., 2012). LTFU is associated with various unfavourable treatment outcomes, such as frequent hospitalisations, treatment failure due to poor ART adherence, higher risk of mortality and developing severe opportunistic infections (OIs) (Schaecher, 2013).

OIs are infections most commonly occurring among people with weakened immune systems, such as PLHIV (Centers for Disease Control and Prevention (CDC), 2019). The most common HIV-associated OIs in LMICs are oral candidiasis (19.1%), tuberculosis (TB) (10%), herpes zoster (9.4%), bacterial pneumonia (6.1%), and genital ulcer disease (6.0%) (Low et al., 2016). This is consistent with the commonly reporting OIs in PLHIV in Ethiopia, which are skin diseases (i.e., herpes zoster, impetigo, and cellulitis), diarrhoea, bacterial pneumonia, upper respiratory tract infections, and TB (Weldegebreal et al., 2018). Although the occurrence of OIs in PLHIV has reduced significantly with the introduction of ART, they are still the primary cause of hospitalisation, morbidity, and mortality in this population (Ford et al., 2015; Low et al., 2016; Weissberg et al., 2018). If OIs are not treated promptly, they can reduce quality of life, accelerate disease progression from HIV to AIDS-defining conditions, increase the burden on health care system, and lead to treatment failure (Ghiasvand et al., 2019; Low et al., 2016; Mulisa et al., 2019). Some interventions to reduce OIs in PLHIV are exposure reduction (e.g., personal and environmental hygiene and safe sexual practices), chemoprophylaxis provision (cotrimoxazole preventive therapy (CPT) and isoniazid preventive therapy (IPT)), immunizations, and ART provision (Ministry of Health Ethiopia, 2017).

ART has been effective in reducing mortality and morbidity in PLHIV; however, not all individuals respond to the treatment in the same way (Gupta et al., 2011; Hadgu et al., 2013). These individual differences may be the result of pre-existing or aggravated factors that weaken the immune system and increase early mortality, such as malnutrition (Enwonwu, 2006; França et al., 2009). Malnutrition is a general term for poor nutritional status and refers to undernutrition or overnutrition (World Health Organisation, 2021a). However, because of the high prevalence of the undernutrition form of malnutrition in LMICs, malnutrition is often used to refer to undernutrition and related complications (Saunders & Smith, 2010). In the context of this research, undernutrition is defined as the state of inadequate intake of energy or nutrients to fully support the physiological functions of the human body (Maleta, 2006; World Health Organization, 2009b). Malnutrition and HIV are global challenges; however, SSA is the region most affected by both challenges (Liu et al., 2011). The region is home to 23% the global

population of undernourished people in 2018 (Food and Agriculture Organization of the United Nations, 2019) and 69% of global PLHIV in 2021 (World Health Organisation, 2022).

The relationship between HIV and malnutrition is multifactorial and multidimensional (Lodha & Kabra, 2015). HIV increases patients' vulnerability to malnutrition by three mechanisms. Firstly, it reduces food intake due to oral thrush, oesophageal candidiasis, and ART-induced nausea or loss of appetite (Duggal et al., 2012). Secondly, it decreases nutrient absorption as a result of diarrhoea or infection-related gastrointestinal mucosal damage (Dikman et al., 2015). Lastly, the energy requirements are increased by 10% and 20-30% in asymptomatic and symptomatic HIV-infected adults, respectively (Lisa Kosmiski, 2011). In addition, malnutrition accelerates disease progression from HIV to AIDS, increases occurrence and recurrence of OIs, and increases risk of death (De Pee & Semba, 2010; Duggal et al., 2012).

Evidence suggests that undernutrition (defined as low body mass index (BMI) or micronutrient deficiency) has been associated with adverse treatment outcomes, including mortality, LTFU, OIs, and treatment failure in PLHIV (Ahoua et al., 2011; Geng et al., 2013; Naidoo et al., 2018; Otwombe et al., 2014; Tchounga et al., 2016; Tesfamariam et al., 2016). These risks appear to be particularly pronounced in individuals with a low BMI at ART initiation (Ahmed et al., 2019; Berhe et al., 2013; Gupta et al., 2011; Silverman et al., 2019; Tesfamariam et al., 2016). Nutritional improvements after ART initiation, such as an increase in weight and BMI, were also reported as a sign of favourable prognosis and associated with lower risk of mortality and treatment failure in underweight and normal-weight patients (Madec et al., 2009; Tsegaye et al., 2016; Yuh et al., 2015). Conversely, weight loss after ART initiation is a strong predictor of mortality (Koethe et al., 2010) with even a comparably minor weight loss of up to 5% significantly increasing the risk of death (Hu et al., 2011).

1.3. Rationale of the study

Although different studies have been conducted to identify the risk factors of mortality (Abebe et al., 2014; Gesesew et al., 2018; Misgina et al., 2019; Tachbele & Ameni, 2016; Tadesse et al., 2014), OIs , and LFTU (Assemie et al., 2018; Jerene et al., 2019; Megerso et al., 2016; Seifu et al., 2018; Wubshet et al., 2012) among ALHIV in Ethiopia, none examined the actual effects of undernutrition on treatment outcomes. In Ethiopia, two previous studies that assessed the association between undernutrition and mortality among ALHIV were identified (Hussen et al., 2016; Tesfamariam et al., 2016). However, these studies failed to control for confounders

to show the actual effects of undernutrition and had insufficient follow-up periods. These studies did not include important confounding variables, such as ART adherence, residence, CPT, IPT, and HIV-status disclosure. Furthermore, these studies were also conducted before the establishment of a new approach called test and treat strategy, which was introduced in Ethiopia in 2016. Lastly, these studies had small sample sizes and focused only on mortality, whereas important issues, such as the effects of undernutrition on LTFU and OIs, were not assessed.

The current ART treatment guidelines used by Ethiopian hospitals recommend that nutritional assessment (weight and BMI measurements) be performed at each ART visit, highlighting the importance of weight control in this population (Ministry of Health Ethiopia, 2017). As per recommendations, clinicians assess patients' nutritional status and provide appropriate dietary advice based on the assessment results at each ART visit. However, longitudinal studies examining weight and BMI variations and their impact on treatment outcomes among this population in Ethiopia are lacking to inform or affirm these guidelines.

In addition, evidence suggests that nutritional improvements, such as weight gain and BMI increase, after initiation of ART, are expected and are associated with a lower risk of mortality in this population (Madec et al., 2009; Sax et al., 2020; Sudfeld et al., 2013; Tang et al., 2011; Weldesenbet et al., 2020; Yuh et al., 2015). However, not all patients gain weight, and improvements vary across individuals. This individual variability of weight gain and its impact on treatment outcomes needs further investigation. Evidence is also lacking as to what constitutes an optimal weight gain after initiation of ART in this population. Furthermore, Ethiopia was one of the 82 LMICs that reported switching to a dolutegravir (DTG)-based HIV regimen in 2019, as per the World Health Organization (WHO) recommendations (World Health Organization, 2019b). However, evidence on the efficacy of this new ART regimen in Ethiopia is lacking, particularly in terms of weight gain. This thesis aims to address the above discussed shortcomings by adding to the body of evidence on the effects of undernutrition on the overall treatment outcome in ALHIV in developing countries.

1.4. Outline of the thesis

This thesis consists of nine chapters. The first chapter contains a general introduction to the research, focussing on the public health importance of HIV and undernutrition in the context of SSA, particularly in Ethiopia. The chapter also discusses why this research was conducted (the rationale) and outlines the thesis structure.

The second chapter provides a general literature review, highlighting the existing body of knowledge in the field. The third chapter provides an overview of the project aim, objectives, study designs and a concise description of methods employed by the included studies.

The thesis results are presented in chapters four through eight based on published manuscripts. Chapter four describes the results of a published systematic review and meta-analysis that examined the effects of undernutrition on mortality and morbidity among ALHIV in SSA. The fifth chapter consists of a published manuscript that examined the association between undernutrition and LTFU among ALHIV on ART in Ethiopia. This chapter also includes a published protocol as a supportive article. Chapter six includes results from a published manuscript focused on the effects of undernutrition on OIs in ALHIV on ART. The seventh chapter reports findings from a published longitudinal study on weight change after ART initiation. The eighth chapter contains a published manuscript that examined the association between BMI variation and early mortality in ALHIV on ART.

The last chapter of this thesis includes the overall discussion of the key findings, including strengths and limitations as well as implications for future research and practice.

1.5. Chapter summary

This chapter discussed the public health importance of HIV and undernutrition in the context of SSA, including Ethiopia and highlighted the complex relationship between HIV and undernutrition. It further described the impacts of undernutrition on the overall treatment outcomes (i.e., mortality, LTFU, and OIs) of PLHIV. Finally, this chapter explained why this study was needed in the context of Ethiopia. The following chapter provides an overview of existing literature in the field, and the chapter is organised based on the thesis objectives.

Chapter 2 | Literature Review

2.1. Chapter introduction

This chapter provides a comprehensive literature review on the factors affecting the treatment outcomes (i.e., mortality, LTFU, and OIs) of ALHIV. The chapter is organised into eight sections. The first section highlights the burden of HIV and access to ART in the Ethiopian context, followed by a brief overview of malnutrition in Ethiopia in section two. Factors associated with mortality in ALHIV are presented in section three followed by factors associated with LTFU in ALHIV in section four. In section five, the current body of literature on the predictors of OIs are discussed. Section six focuses on weight change after ART initiation in ALHIV. Section seven discusses the association between BMI variation and early mortality. Finally, gaps identified in the existing literature and how the current study address these gaps are elaborated in section eight.

2.2. HIV burden and access to ART in Ethiopia

The first confirmed HIV case and the first hospitalised AIDS patient in Ethiopia were reported in 1984 and 1986, respectively (Hladik et al., 2006). According to the 2016 Ethiopia Demographic and Health Survey (EDHS) report, the prevalence of HIV in Ethiopia was estimated to be 0.9%, with a higher prevalence in women (1.2%) than men (0.6%) (Central Statistical Agency of Ethiopia (CSA), 2016). A higher prevalence of HIV was also seen in urban areas compared to rural areas (2.9% versus 0.4%), which might be associated with a higher concentration of commercial sex workers in urban areas in Ethiopia, a sub-population with one of the highest prevalence rates of HIV in the region (Family Health International (FHI)-Ethiopia, 2002). Findings from the global burden of disease study showed that the prevalence of HIV in Ethiopia peaked at 2% in 2000, declined to 1% in 2010, and has since remained relatively stable around 1%. This study also reported that AIDS-related mortality in Ethiopia peaked in 2005 with 150 cases per 100,000 (Deribew et al., 2019). According to the Ethiopian Public Health Institute report, 612,925 people were living with HIV in Ethiopia by 2021. In the same year, 11,627 people died from AIDS-related illnesses (Ethiopian Public Health Institute (EPHI), 2022).

Ethiopia introduced fee-based and free ART in 2003 and 2005, respectively, (Assefa et al., 2011) and achieved remarkable success in terms of HIV service expansion and uptake,

resulting in a decline of new HIV infections by 95% between 1994 and 2012, and a decline of AIDS-related deaths by 73% between 2006 and 2016 (Ministry of Health Ethiopia, 2017). Despite the number of PLHIV on ART dramatically increasing from 110,000 in 2007 to 356,000 in 2016, the overall ART coverage remains below the 90-90-90 joint United Nations Program on HIV/AIDS (UNAIDS) targets (i.e., diagnose 90% of all HIV-positive persons, provide ART for 90% of those diagnosed, and achieve viral suppression for 90% of those treated) (Getaneh et al., 2020), with only 71% of eligible PLHIV in Ethiopia receiving ART in 2018 (Federal HIV/AIDS Prevention and Control Office of Ethiopia, 2018). As of January 2020, more than 1,230 health facilities were delivering ART services in Ethiopia, of which 909 were health centres, which in the Ethiopian healthcare system refers to a health facility with a capacity of 10 beds for emergency and delivery services. All first-line ART drugs are available in all health facilities, whereas second-line ART drugs are available only from hospitals (Getaneh et al., 2020).

2.3. Overview of malnutrition in Ethiopia

Malnutrition is a major public health problem in developing countries, including in Ethiopia. In 2017, Ethiopia was listed as having the second-highest malnutrition rate in East Africa behind Burundi (Akombi et al., 2017). Approximately 8.5 million Ethiopian people, representing 8% of the population, experienced food insecurity in 2017 (Mohamed, 2017). According to the 2019 Ethiopian Mini Demographic and Health Survey (EMDHS) report, 37%, 21%, and 7% of under-five children were stunted, underweight, and wasted, respectively (Central Statistical Agency of Ethiopia (CSA), 2019). According to the 2016 EDHS report, 22% of women in reproductive age (15-49 years) were undernourished, while adolescent girls (aged 15-19 years) were 29% more likely to be undernourished than women in reproductive age as a whole (Central Statistical Agency of Ethiopia (CSA), 2016). This report also indicated that undernutrition was higher among women who live in rural (25%) areas than those women live in urban (15%) areas (Central Statistical Agency of Ethiopia (CSA), 2016). Although childhood malnutrition has declined over the past 15 years, 28% of under-five deaths in Ethiopia are still attributed to malnutrition. Furthermore, approximately 16% of all repetitions in primary schools and 8% of the workforce lost in Ethiopia are due to undernutrition. Annual child undernutrition-related costs are estimated to be 55.5 billion Ethiopian birrs (ETB), equivalent to 16.5% of the country's gross domestic product (GDP) (Ethiopian Public Health Institute (EPHI), 2013).

2.4. Factors associated with mortality in adults living with HIV

Factors associated with mortality in ALHIV can generally be grouped into three categories: sociodemographic, clinical, and ART-medications related factors. Nutritional status is one of the clinical factors. Although the association between undernutrition and mortality among ALHIV has been reported from many SSA studies, results are widely scattered and inconclusive. For example, a multi-county-based retrospective cohort study found that as BMI increased by one unit, risk of death decreased by 8% (Palombi et al., 2009), while a Kenyan study showed that, as BMI increased by one unit, mortality risk reduced by 18% (Kendi et al., 2013). Similarly, a Ugandan study reported that ALHIV who had a BMI < 17.5 kg/m^2 were six-times more likely to die than well-nourished ALHIV (Masiira et al., 2014). Most SSA studies have shown that undernutrition significantly increases mortality risk in ALHIV (Damtew et al., 2015; Dao et al., 2011; Evans et al., 2012; Ferradini et al., 2006; Geng et al., 2013; Hanrahan et al., 2010; Hoffmann et al., 2011; Kouanda et al., 2012; Moh et al., 2007; Naidoo et al., 2018; Otwombe et al., 2014; Tchounga et al., 2016; Tesfamariam et al., 2016; Toure et al., 2008). However, some studies have reported that undernutrition had no significant association with mortality in this population morbidity (Brown et al., 2016; Hanrahan et al., 2010; Hussen et al., 2016; Nansera et al., 2012; Temesgen et al., 2019; Teshome et al., 2015). Most of the above studies used baseline BMI to determine the association between malnutrition and mortality. However, using a single BMI measurement has some limitations. First, a single BMI measurement may not reflect its impact on mortality, as body weight varies widely over time and weight history can provide important information about an individual`s health and mortality risk. Second, the association observed between a single BMI measurement and subsequent mortality may be due to underlying diseases and health conditions that can cause weight loss and increase mortality risk (Robins, 2008).

With respect to sociodemographic characteristics, being male (Bastard et al., 2013; Chen et al., 2008; Ferradini et al., 2006; Kouanda et al., 2012; Li et al., 2016; Palombi et al., 2009; Sieleunou et al., 2009), living in rural areas (Otwombe et al., 2014), and being of older age (age ≥ 35 years) (Brown et al., 2016) were significantly associated with a higher risk of mortality. Among clinical factors, low CD4 cell count (Bastard et al., 2013; Brown et al., 2016; Ferradini et al., 2006; Kouanda et al., 2012; Palombi et al., 2009), advanced WHO disease stage (stage III and IV) (Bastard et al., 2013; Chen et al., 2008; Ferradini et al., 2006; Jerene et al., 2006; Kouanda et al., 2012; Palombi et al., 2009; Tesfamariam et al., 2016), low

haemoglobin level (anaemia) (Johannessen et al., 2008; Palombi et al., 2009), having baseline OIs (Tesfamariam et al., 2016), bedridden or ambulatory functional status (Tesfamariam et al., 2016), participants with TB and cryptococcal antigenemia (Pac et al., 2015), and travel time to access ART (Geng et al., 2013) were factors significantly associated with higher mortality.

Medication-related factors, such as poor ART adherence (Abaasa et al., 2008; Joseph et al., 2019), not taking IPT (Badje et al., 2017; Kyaw et al., 2019), and not taking CPT (Hoffmann et al., 2010; Suthar et al., 2012), were significantly associate with higher mortality. A lower mortality risk was reported among participants taking fluconazole prophylaxis.

2.5. Factors associated with LTFU in adults living with HIV

Multiple risk factors of LTFU, such as sociodemographic, clinical, and treatment-related, have been reported in previous studies. Most of the studies were conducted in countries where HIV is highly prevalent, with studies conducted in Uganda (Opio et al., 2019), Malawi (Tweya et al., 2018), Guinea-Bissau (Honge et al., 2013), West Africa (Bernard et al., 2018), Tanzania (Kalinjuma et al., 2020), Nigeria (Agaba et al., 2017), Cambodia (Lay et al., 2017), and Ethiopia (Mekonnen et al., 2019) having shown that undernourished ALHIV were at a higher risk of LTFU. In addition, studies conducted in West Africa and Cambodia indicated that food insecurity is a strong predictor of LTFU (Benzekri et al., 2022; Chhim et al., 2018). However, some studies, including one from Ethiopia (Teshale et al., 2020) and one from Haiti (McNairy et al., 2017), found no association between undernutrition and LTFU. The study in Haiti had a relatively short follow-up period (12 months), which could be the reason for this study's insignificant association between nutritional status and LTFU. The study in Ethiopia included more participants who started ART through the test-and-treat approach. This approach recommends that all HIV-positive patients be able to initiate ART regardless of CD4 cell count and WHO stage. Therefore, the impacts of malnutrition may be masked because ART significantly improves a patient's nutritional status, and patients can start ART before their nutritional status deteriorates.

Multiple studies related to sociodemographic factors found that being of younger age (15-24 years (Megerso et al., 2016), 15-30 years (Teshale et al., 2020), 15-19 years (Jerene et al., 2019), and 15-28 years (Assemie et al., 2018)) were significantly associated with a higher risk of LTFU. However, studies from Tanzania (aged < 30 years) (Siril et al., 2017) and Togo (aged <35 years) (Saka et al., 2013) reported that younger age participants were at less risk of LTFU.

Most studies suggest that men are at higher risk of LTFU (Ochieng-Ooko et al., 2010; Seifu et al., 2018; Siril et al., 2017; Takarinda et al., 2015). This finding is consistent with a recent meta-analysis from LMICs demonstrated that men are generally at higher risk of LTFU (Frijters et al., 2020). However, a study from Togo showed women are at higher risk of LTFU (Saka et al., 2013). This study has some methodological limitations, such as the authors used convenient method to select the study clinics. This gender difference could be attributed to late presentations of males for ART care compared to females (Cornell et al., 2012; Mojumdar et al., 2010; Ochieng-Ooko et al., 2010).

Studies conducted in SSA countries reported that patients who did not disclose their HIV status were at higher risk of LTFU (Akilimali et al., 2017; Miller et al., 2010; Seifu et al., 2018; Sifa et al., 2019). Advanced WHO clinical disease staging (III and IV) (Assemie et al., 2018; Berheto et al., 2014; Megerso et al., 2016; Saka et al., 2013), and low CD4 cell count (Berheto et al., 2014; Megerso et al., 2016; Siril et al., 2017) are also clinical factors that significantly increased the risk of LTFU. An increased risk of LTFU has been reported in patients with poor ART adherence (Berheto et al., 2014; Megerso et al., 2016), those who received efavirenz-based ART regimen (Hong et al., 2022), and those whose baseline regimen has changed (Berheto et al., 2014). Lastly, patients who did not receive CPT (Teshale et al., 2020) and IPT (Assemie et al., 2018; Mekonnen et al., 2019; Teshale et al., 2020) were at higher risk of LTFU; whereas patients who took ART for longer duration were at lower risk of LTFU (Siril et al., 2017).

2.6. Factors associated with OIs in adults living with HIV

Several studies have shown that undernutrition is a proximal risk factor for OIs in ALHIV. Studies reported from Ethiopia (Ahmed et al., 2018; Alemu et al., 2020; Gedle et al., 2017; Getu et al., 2022; Hussen et al., 2017; Tiruneh et al., 2019), Uganda (Moore et al., 2007; Worodria et al., 2011), South Africa (Kufa et al., 2016), Tanzania (Sabasaba et al., 2019), and eight SSA HIV programs (Nicholas et al., 2011) found that undernutrition was significantly associated with higher risk of TB and other OIs among ALHIV. However, three SSA studies reported that undernutrition was not significantly associated with the occurrence of TB in ALHIV (Hanrahan et al., 2010; Moh et al., 2007; Temesgen et al., 2019). These studies reported nutritional status in different categories which can lead to insignificant associations and inconsistent results.

Urban residents (Gupte et al., 2019; Nicholas et al., 2011) and male patients (Gupte et al., 2019; Liu et al., 2015; Sabasaba et al., 2019) were found to be at higher risk of developing OIs. Common clinical factors that significantly increased the occurrence of OIs among ALHIV were low CD4 cell count (Akinyemi et al., 2017; Solomon et al., 2018; Weldegebreal et al., 2018), advanced WHO clinical disease staging (III and IV) (Dereje et al., 2019; Solomon et al., 2018), and poor ART adherence (Solomon et al., 2018). Taking ART for longer duration was reported as a protective factor for OIs (Coelho et al., 2016).

Additionally, advanced WHO clinical staging (III and IV) (Addis Alene et al., 2013; Ahmed et al., 2018; Liu et al., 2015; Sabasaba et al., 2019; Temesgen et al., 2019), low cell CD4 count (Addis Alene et al., 2013; Bjerrum et al., 2016; Greenhalgh, 1997; Gupte et al., 2019; Liu et al., 2015; Mupfumi et al., 2019; Nicholas et al., 2011; Pathmanathan et al., 2017; Sabasaba et al., 2019), high viral load (Mupfumi et al., 2019), not taking IPT (Ahmed et al., 2018; Alemu et al., 2020; Dravid et al., 2019; Maokola et al., 2021; Sabasaba et al., 2019; Temesgen et al., 2019), not taking CPT (Tiruneh et al., 2019), being anaemic (low Hgb) (Ahmed et al., 2018; Temesgen et al., 2019), and having a history of TB (Nicholas et al., 2011; Pathmanathan et al., 2017) were factors that significantly increased the risk of developing TB among ALHIV.

2.7. Weight change in adults living with HIV after ART initiation

Studies showed that weight gain after ART initiation in patients living with HIV is a common phenomenon and a sign of good prognosis, notably in LMICs. The rate of weight gain is also higher in the first year of ART follow-up (Madec et al., 2009; Tang et al., 2011). For example, a Vietnamese study found that the average weight gain in the first six months of ART was higher than after the first six months (3.1kg vs 0.8 kg) (Tang et al., 2011). Additionally, a cohort study from the United States reported that the median weight change after one year of ART was 2.7 kg (IQR: -1.3 to 7.7kg) (Yuh et al., 2015). A pooled analysis of eight clinical trials documented that after 96 weeks of follow-up, the median weight gain was 2.0 kg (IQR: -0.9, 5.9 kg) (Sax et al., 2020). A five-year retrospective study from Ethiopia showed that the mean weight of ALHIV on ART increased from 53.5 kg at baseline to 55.5 kg at the end of the study (Weldesenbet et al., 2020). However, the main limitation of this study is that it did not use stratified analysis because the pattern of weight gain before two years and after two years is different.

A significant difference in weight gain between men and women has been reported in different studies (Bares et al., 2018; Sax et al., 2020; Weldesenbet et al., 2020). For example, a three-year retrospective longitudinal study conducted in the United States has suggested that women living with HIV gained more weight (mean BMI= 1.91 kg/m^2; 95% CI: 1.64 to 2.19 kg/m^2) than men living with HIV (mean BMI= 1.39 kg/m^2; 95% CI: 1.30 to 1.48) (Bares et al., 2018). A pooled analysis of eight clinical trials also found that weight gain was higher among women compared to men and black people compared to white people (Sax et al., 2020). Similarly, a study conducted in low resource settings showed that weight gain in the first 12 months was higher in men; but, after the second year of ART follow-up, weight gain was higher in women (Huis, 2015). In contrast, a study from Ethiopia found that females have lower weight gain than males (Weldesenbet et al., 2020). As this study used a five-year follow-up data, a missed opportunity was noted in that weight trajectories for the first two year and after two years could have been analysed and reported separately because PLHIV generally gain weight rapidly during the initial period of ART (two years), and subsequently loss or gain less weight after two years of follow-up.

Apart from gender, various clinical factors significantly influence the weight of ALHIV on ART. A higher weight gain was consistently documented in patients with poor clinical status (Huis, 2015), lower BMI (Koethe et al., 2010), low baseline weight (Yuh et al., 2015), low CD4 cell count (Sax et al., 2020; Tang et al., 2011; Yuh et al., 2015), good ART adherence (Tang et al., 2011), and low haemoglobin (Yuh et al., 2015). The use of integrase strand transfer inhibitors was also significantly associated with more weight gain than protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTIs) (Sax et al., 2020). Similarly, DGT-based regimens have been associated with higher weight gains than efavirenz-based regimes (Ando et al., 2021; Kanters et al., 2022; Vizcarra et al., 2020).

2.8. Body mass index variation (BMI) and mortality after ART initiation

Although there are limited studies on the association between BMI variation and mortality after ART initiation, these studies suggest that weight gain may protect against mortality in this population. A study conducted in the United States found that weight gain after initiation of ART was associated with lower mortality in undernourished and well-nourished patients (Yuh et al., 2015). This study also suggested a minimal weight gain threshold of 10.0 to 19.9 pounds

(4.5 to 9.0 kg) was beneficial for under and normal-weight patients (HR: 0.56; 95% CI: 0.41, 0.78); however, there was no apparent benefit for overweight/obese patients (Toure et al., 2008). Similarly, a cohort study of 2,451 Cambodians and 2,618 Kenyans on ART showed that weight gain three months after starting ART was associated with a lower mortality rate (Madec et al., 2009). A study in Zambia also reported that weight gain after initiation of ART was associated with improved survival and reduced clinical failure rates, particularly in lower BMI strata (Koethe et al., 2010). Lastly, a Tanzanian study found that weight loss after one month of ART initiation was independently associated with higher subsequent mortality (Sudfeld et al., 2013).

2.9. Summary of identified knowledge gaps in the existing literature

Knowledge Gap I: Although several studies have been conducted on the effects of undernutrition on mortality and morbidity among ALHIV in SSA, most of the studies included small sample sizes, were highly fragmented, and often presented inconclusive findings. Many of the studies found that undernutrition significantly increased the risk of mortality and morbidity. However, some studies reported that undernutrition has no significant association with mortality and morbidity. There is currently no systematic approach to summarise the literature in this area.

Knowledge Gap II: Although studies conducted in SSA have shown that undernutrition is significantly associated with LTFU among ALHIV, no studies have yet investigated the actual effect of undernutrition on LTFU. In particular, no Ethiopian study existed, especially since implementation of the test-and-treat approach.

Knowledge Gap III: There are methodological limitations identified in the current body of literature, specifically concerning the analytical approach used by studies conducted on the association between undernutrition and OIs. Although these studies attempted to control for confounding variables using multivariable analysis, none used treatment effects analysis to show the actual (exact) effect of undernutrition on OIs. Furthermore, almost all studies were conducted on the association between undernutrition and OIs focused on TB, but little attention has been given to the impact of undernutrition on other OIs.

Knowledge Gap IV: Another important research gap is the issue of weight change after initiation of ART. First, most of the studies were descriptive and focused on absolute weight

gain or loss rather than longitudinal weight change. This approach is recommended since the weight of PLHIV is highly variable after ART initiation due to many factors. Second, most studies were conducted before the introduction of dolutegravir (DGT), an antiretroviral medication that is often associated with higher weight gain. Third, although weight gain after ART initiation is quite common, not all patients gain weight, and the extent of weight gain varies from person to person.

Knowledge Gap V: Although sufficient evidence exists on the association between low BMI and mortality in ALHIV, almost all studies were based on baseline nutritional status. However, a baseline measurement of BMI may not reflect its impact on mortality because weight varies widely over time, and weight history can be an important predictor of a person's health and mortality risk. Improving nutritional status (weight and BMI) after ART initiation is a desirable outcome for HIV treatment, particularly in under- and normal-weight patients: however, little attention has been paid to its impact on mortality.

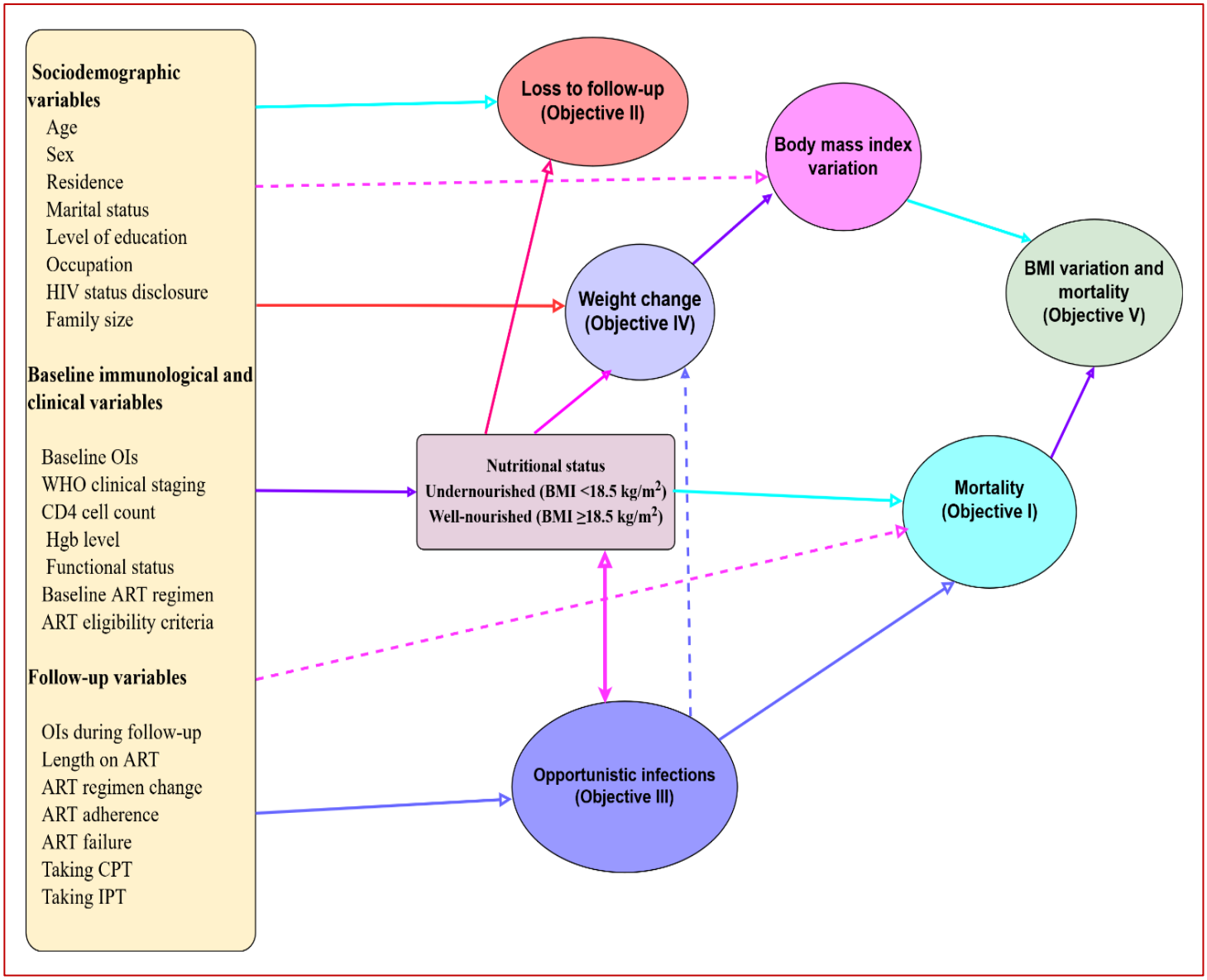

Figure 1. Conceptual framework to assess effects of undernutrition on treatment outcomes among adults living with HIV on ART in Northwest Ethiopia, developed from different literatures HIV.

Chapter 3 │Methodology

3.1. Chapter introduction

This chapter provides an overview of the methodology of the thesis, starting from the aim and objectives and then a brief introduction to the different study designs used in each objective. The chapter also includes a method summary for systematic reviews and meta-analyses study and retrospective longitudinal studies. Finally, the detailed methodological approaches for longitudinal studies, including study setting, population, sample size estimation, sampling procedures, study variables, statistical analyses, and ethical considerations, are described.

3.2. Aim and objectives of the study

3.2.1. Aim

The overall aim of the research presented in this thesis was to assess the overall effects of undernutrition on treatment outcomes of ALHIV after ART initiation in Ethiopia.

3.2.2. Objectives

The thesis has five objectives:

1) To examine the effects of undernutrition on mortality and morbidity among ALHIV on ART in SSA since 2002;
2) To determine the effect of undernutrition on loss to follow-up among ALHIV on ART;
3) To determine the effects of undernutrition on OIs among ALHIV on ART at Debre Markos Comprehensive Specialized Hospital (DMCSH), Ethiopia;
4) To assess weight change during the two years of ART among ALHIV on ART at DMCSH, Ethiopia; and
5) To examine the association between body mass index variation and early mortality among ALHIV on ART at DMCSH, Ethiopia.

The objectives that addressed previously identified gaps in the current body of literature are presented below (see Figure 2).

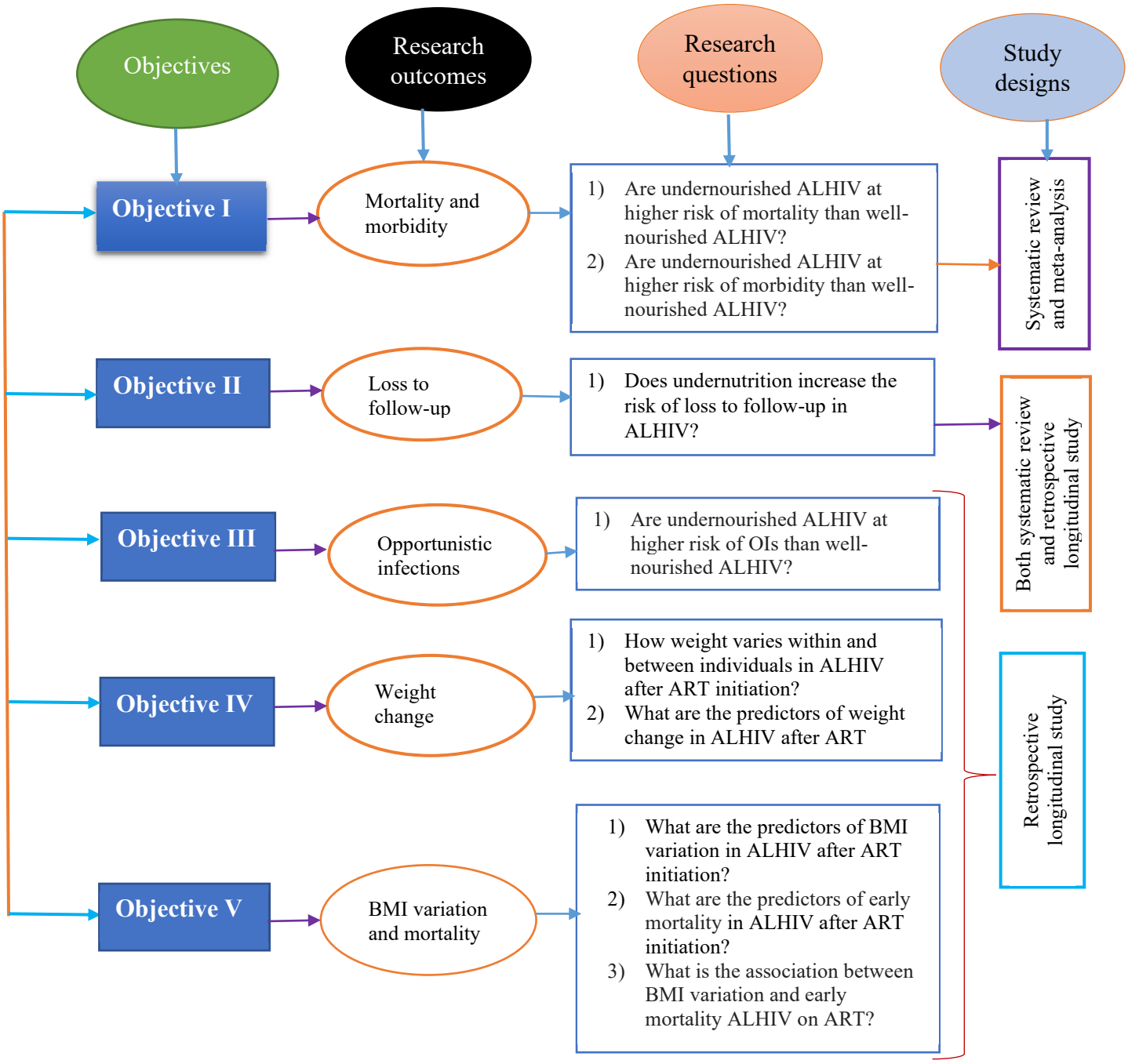

Figure 2. Schematic presentation of research objectives, outcomes, and study designs of this thesis, which examined the effects of undernutrition on treatment outcomes among ALHIV.

3.3. Overview of employed study designs

A quantitative study design was employed for all five objectives of this thesis, this design is predominantly used in medical research (Norman & Eva, 2010). Two quantitative methods were employed: (1) a systematic review and meta-analysis: and (2) a retrospective longitudinal study (see Figure 2). A systematic review and meta-analysis design was used to address

objective I, summarising the current evidence on the effects of undernutrition on mortality and morbidity in ALHIV on ART in SSA. This study design has several advantages as a time-efficient research method that improves the generalisability and consistency of results, generates new hypotheses, and increases precision of results (Greenhalgh, 1997). The remaining four objectives were addressed through a retrospective longitudinal study design using the medical records of ALHIV on ART between June 2014 and June 2020 at DMCSH, Northwest Ethiopia. A retrospective follow-up is the most appropriate design for these objectives considering resource constraints within the candidature, the Ethiopian context (time and cost), and ethical considerations that prevent using other methods such as randomised controlled trial.

3.4. Method summary for a systematic reviews and meta-analysis study

To address Objective I, a systematic review and meta-analysis was conducted to summarise the current body of evidence and identify gaps in the literature regarding the effects of undernutrition on mortality and morbidity in ALHIV. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO), University of York Centre for Reviews and Dissemination (ID: CRD42020161822; see Appendix A). The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline (Liberati et al., 2009). Studies published between 2002 and 2019 were systematically searched from four major databases (i.e., PubMed, EMBASE, CINAHL, and Scopus). All observational studies reporting the effects of undernutrition on mortality and morbidly among ALHIV in SSA were considered for inclusion. The quality of included studies was appraised using the Newcastle-Ottawa Scale (NOS) risk-of-bias assessment tool for cross-sectional, cohort, and case-control studies (Peterson et al., 2011). A standardized data extraction form was adopted and prepared based on the Joanna Briggs Institute (JBI) data extraction format (Peters et al., 2019).

A meta-analysis was performed using Stata™ Version 16 statistical software to estimate effect sizes. Heterogeneity between included studies was assessed using the Cochrane Q-test and I^2 statistics. Publication bias was also assessed using Egger's and Begg's tests at a 5% significance level (Lin & Chu, 2018). Finally, a random-effects meta-analysis model was employed to estimate the overall adjusted hazard ratio. The detailed methodology of this manuscript is available in Chapter four.

3.5. Methods for retrospective longitudinal studies

3.5.1. Study setting and period

The remaining four longitudinal studies presented in this thesis used secondary data obtained from a hospital in Northwest Ethiopia (DMCSH). Ethiopia is a SSA country, located in the horn of Africa (Figure 3). It is bordered by Eritrea to the north, Djibouti and Somalia to the east, South Sudan and Sudan to the west, and Kenya to the south. Ethiopia is the second most populous country in Africa after Nigeria, with an estimated population of 121,232,805. The country is divided into eleven administrative regions and two administrative cities (see Figure 3). Amhara is one of the eleven regions located in the northwest and north-central parts of Ethiopia and is the second most populous region, with 27% of Ethiopia's population (see Figure 3). East Gojjam Zone is one of the 11 administrative zones in the Amhara region. DMCSH is located in this administrative zone and is currently the only referral hospital serving over 3.5 million people in East Gojjam and neighbouring zones. The hospital commenced offering chronic HIV care and ART services in 2005. As of March 2020, the ART clinic had eight nurses, three medical doctors, three data clerks, five case managers, and six ART adherence supporters. The total recorded number of PLHIV having ART initiated at DMCSH between June 2014 and June 2020 was 1,209, of which 1,177 (97.4%) were aged ≥ 15 years (defined as adults). The study was conducted between June 2014 and June 2020. The selection of the follow-up period for this study was a deliberate process based on several factors. Firstly, in 2014, a significant guideline update for adults living with HIV was introduced. In order to align with this update, the follow-up was initiated in that particular year, serving as a crucial reference point. Secondly, the follow-up period was extended until June 2020. This endpoint was specifically chosen because it coincided with the year when ethical clearance was obtained from both UTS and the Amhara Public Health Institution after the confirmation of the first stage of candidature. This ensured compliance with ethical considerations and provided a well-defined endpoint for the follow-up. The decision to implement a six-year follow-up period was driven by a key consideration. Recognizing that HIV is a chronic disease, it was acknowledged that certain outcomes, particularly mortality rates, may not become evident within a short follow-up duration. Consequently, a follow-up period of more than five years is recommended to get a valid outcome.

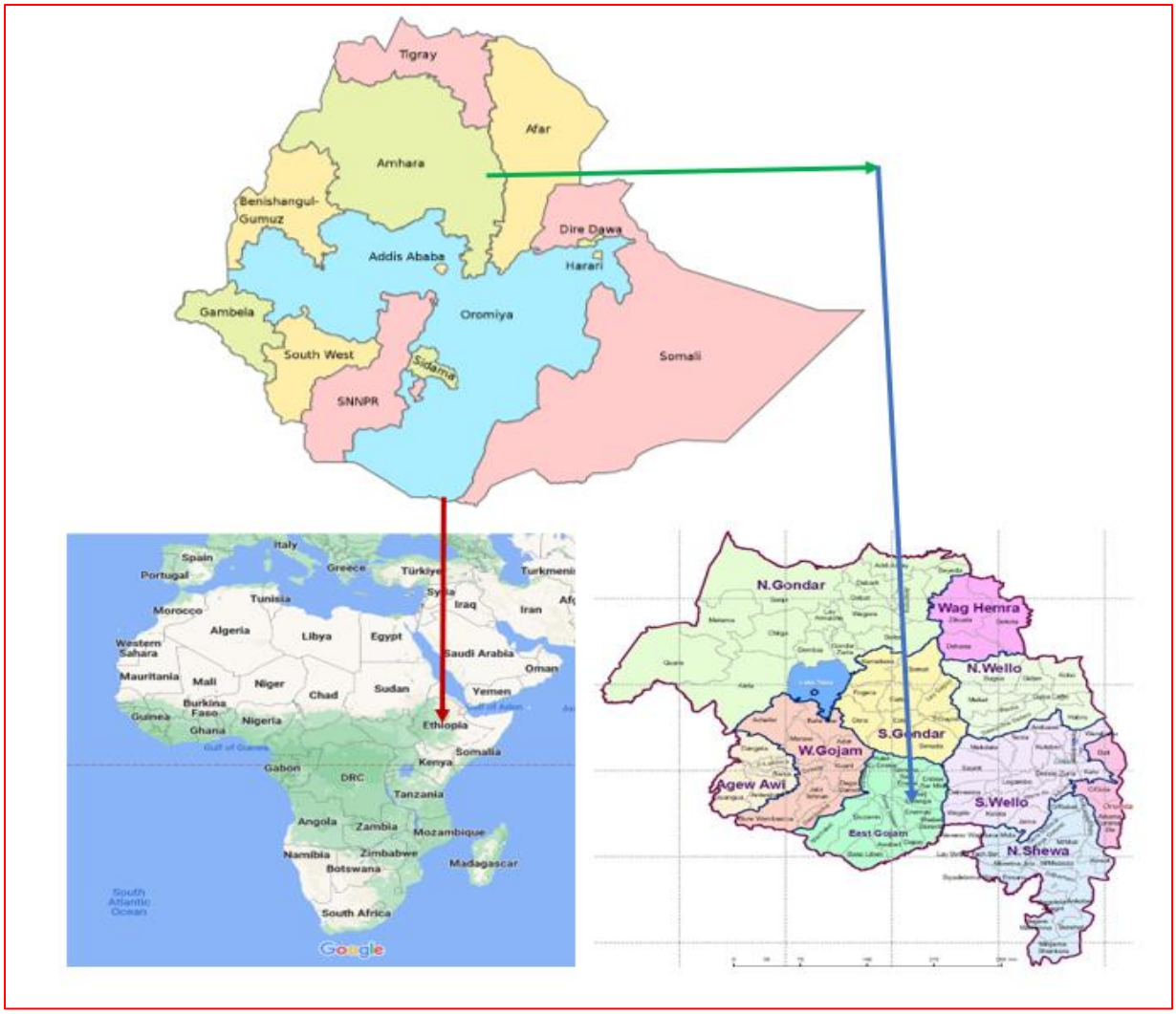

Figure 3. Map of the study area where the data for the longitudinal studies was obtained (from Map data ©2023 Google, INEGI).

3.5.2. HIV care in the ART clinics of Ethiopian hospitals

According to the current Ethiopian ART guidelines, all PLHIV are eligible to start ART immediately, regardless of WHO clinical disease staging and CD4 cell count (Ministry of Health Ethiopia, 2017). Activities provided by a team of physicians and nurses at the initial visit include, as necessary and available, patient counselling, CPT, treatment of OIs, management of co-morbidities and referrals, as well as the continuation of ART for transfer-ins. Laboratory tests at baseline included CD4 cell count, complete blood count, alanine transaminase and creatinine, cryptococcal antigen, Gene Xpert test in case of suspected TB, pregnancy test, and other indicated tests. Follow-up appointments are scheduled (two weeks post-first visit) and then every month for the next three months. After four months, patients

attend every two months (Ministry of Health Ethiopia, 2017). After six months, appointments at three-month intervals are scheduled, as necessary, for refilling ART and other medications, managing drug toxicities, treating OIs, providing ART drug adherence support, referring to other services, and setting a next appointment.

3.5.3. Study participants

The medical records of adults (defined as those aged ≥ 15 years) living with HIV who received ART between June 2014 and June 2020 at DMCSH were eligible for inclusion. All ALHIV, who started ART between June 2014 and June 2020, and had at least one month of ART follow-up were included to assess OIs (Objective III) and loss to follow-up (Objective II). All ALHIV receiving ART between June 2014 and June 2020 who had at least two weight measurements (two visits) during the ART follow-up period were included to evaluate the longitudinal weight change (Objective IV). Finally, all ALHIV who received ART between June 2014 and June 2020 at DMCSH for at least one month and who had at least two weight and height measurements were included to assess the association between BMI variation and early mortality (Objective V).

Patients transferred into DMCSH from other health institutions without baseline information and pregnant women were excluded from all objectives. Pregnant women were excluded as pregnancy inherently leads to weight gain, and nutritional assessment for pregnant women differs from other ALHIV (Ververs et al., 2013). Participants with the outcomes of interest (i.e., OIs, LTFU, and death) with dates not recorded were also excluded from Objectives II, III, and V (see Figure 4).

3.5.4. Sample size estimation and sampling procedures

3.5.4.1. Sample size estimation

The minimum sample size required for the study was calculated based on the objectives of the research. Accordingly, sample sizes for the second and third objectives were calculated using a sample size calculation method for an independent cohort study (Kelsey et al., 1996), as shown below, and estimated using OpenEpi Version 3.0.1. The values for each parameter used to calculate the second objective sample size were obtained from a previous study in Ethiopia that reported the incidence of LTFU in ALHIV (Teshale et al., 2020). Similarly, the values of parameters to calculate the sample size for the third objective were taken from a previous

Ethiopian study, which examined the incidence of TB in ALHIV (Ahmed et al., 2018) (Table 1).

$$\mathbf{N_{Kelsey}} = \frac{\left(\mathbf{z_{\alpha/2}} + \mathbf{z_{\beta}}\right)^2 \mathbf{p(1-p)\ (r+1)}}{\mathbf{r(P_0 - P_1)^2}}$$

- **α**: The probability of type I error (significance level) is the probability of rejecting the true null hypothesis;
- **β**: The probability of type II error (1-power of the test) is the probability of failing to reject the false null hypothesis;
- **P_0**: Proportion of unexposed group with outcome;
- **P_1**: proportion of exposed group with outcome;
- **r**: Ratio of unexposed to exposed in sample (one unexposed to r exposed); and
- **N_{Kelsey}**: required sample size for unexposed group using Kelsey formula (Kelsey et al., 1996).

The sample size for the fourth objective was calculated using a sample size calculation for a longitudinal study with repeated measurements, as presented below.

$$\boldsymbol{m} = {\mathbf{4}\sigma^2}/{nd^2}\ (\mathbf{1} + (\boldsymbol{n} - \mathbf{1})\boldsymbol{\rho})\left(\boldsymbol{z}_{\frac{\boldsymbol{\alpha}}{\mathbf{2}}} + \boldsymbol{z}_{\boldsymbol{\beta}}\right)^2$$

Two groups of equal size (m/2 subjects each); constant within-subject correlation ρ= 0.5; σ^2= 1; we want 80% power to detect a difference (d) of 0.25 at the two-sided 0.05 level; and all subjects measured at n= 9 time points (no drop-out). As the study (Objective IV) investigated weight change over two years, each patient had a maximum of nine repeated weight measurements. This assumption was taken from the current Ethiopian adult ART guidelines (Ministry of Health Ethiopia, 2017) that stipulate that patients have appointments every three months for ART follow-up. Therefore, within 24 months, one patient had a maximum of nine weight measurements. Finally, the sample size for the fifth objective was estimated by combining the two formulas above, as the study had two outcomes (BMI variation and mortality). The sample size for mortality outcome was also estimated using a sample size calculation for an independent cohort study, as described in objectives II and III. The value of each parameter to calculate the sample size for this objective were obtained from a previous Ethiopian study conducted on mortality in ALHIV. For the second (BMI variation) outcome, the same assumptions and calculations were used (Damtew et al., 2015).

After comparing the sample sizes of the four objectives, the sample size calculated for the second objective resulted in the largest sample size (n = 892) and was taken as the final minimum required sample size (see Table 1).

Table 1. Sample sizes to assess the effects of undernutrition on treatment outcomes of ALHIV at DMCSH, Northwest Ethiopia, between June 2014 and June 2020.

Objectives	Outcome(s)	Exposure variable	Parameters	Calculated sample size	With 10% contingency
Objective II	Loss to follow-up	Nutritional status	P_0= 19% P1=27% r=1 α=5% β=80%	Total=802 Exposed=401 Non-exposed=401	**Total=892** Exposed=446 Non-exposed=446
Objective III	Opportunistic infections	Nutritional status	P_0= 10% P1= 18% r=1 α=5% β=80%	Total=608 Exposed=304 Non-exposed=304	Total=676 Exposed=338 Non-exposed=338
Objective IV	Weight change	Nutritional status	m=9 σ^2 =1 ρ=0.5 α=5% β=80%	Total=376 Exposed=188 Non-exposed=188	Total=418 Exposed=209 Non-exposed=209
Objective V	Mortality	Nutritional status	P_0= 6.9% P1=14% r=1 α=5% β=80%	Total=560 Exposed=280 Non-exposed=280	Total=622 Exposed=311 Non-exposed=311
	BMI variation	Nutritional status	m=9	Total=376	Total=418

	σ^2 =1 ρ=0.5 α=5% β=80%	Exposed=188 Non-exposed=188	Exposed=209 Non-exposed=209

3.5.4.2. Sampling procedures

A computer generated simple random sampling technique was used to select the study participants. First, a list containing the medical registration number (MRN) of all ALHIV (n =1,177) who started ART between June 2014 and June 2020 was obtained from the health management information system unit of DMCSH. Second, a random number was generated for each patient using Microsoft™ Excel. In the final step, a sample of 892 participants from all ALHIV who started ART at DMCSH between June 2014 and June 2020 was selected using randomly generated numbers.

Of the 892 selected adult records, 844 were included in Objective II to assess the effect of undernutrition on LTFU in ALHIV after initiation of ART. This objective excluded 48 records; reasons for the exclusion are outlined in Figure 3. Objective III included 841 participants after excluding 51 records to examine the effect of undernutrition on time to develop OIs after ART initiation. Objective IV followed 848 participants retrospectively for two years to evaluate the longitudinal weight change after ART initiation, excluding 44 records. Lastly, after excluding 58 records, the fifth objective included 834 adult records in the final analysis (see Figure 4).

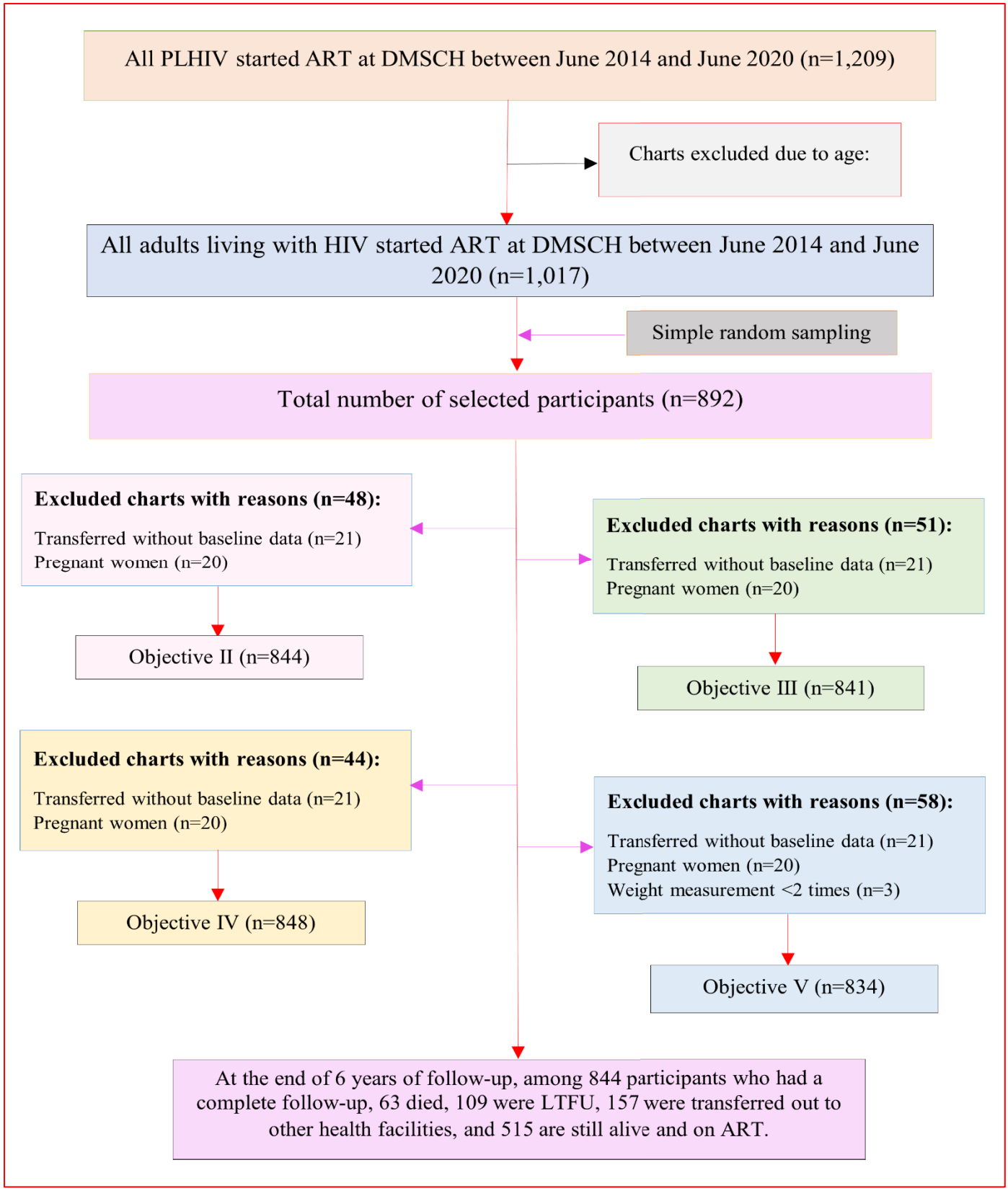

Figure 4. Flow chart showing the study participants recruitment process at DMCSH in Northwest Ethiopia, between June 2014 and June 2020.

3.5.5. Data collection procedures

Project-specific standardised data abstraction tools were developed based on the Ethiopian ART entry and follow-up forms that are currently used by Ethiopian hospitals to ensure data quality (Ministry of Health Ethiopia, 2017) (see Appendix 3.1). These tools included sociodemographic, clinical, immunological, follow-up, and medication-related variables. All sociodemographic and some clinical and immunological variables recorded at ART initiation or within one month after ART initiation were considered baseline values. The values of variables, such as OIs during follow-up, ART adherence, history of ART regimen change, taking CPT and IPT, HIV treatment failure, and duration of ART, were extracted from follow-up data. All required data were manually extracted from patient records. Two epidemiologists with HIV research experience working at the study hospital were employed as data collectors. In addition, a biostatistician with extensive experience in secondary data collection closely supervised the entire data collection process.

3.5.6. Study variables and measurements

3.5.6.1. Outcome variables

The retrospective longitudinal data contained information on five outcome variables. These variables were: (1) time to LTFU; (2) time to develop new OIs; (3) weight change; (4) BMI variation; and (5) time to death. Outcomes (. i.e., mortality, LTFU, OIs) were ascertained by reviewing the patient medical record written by a managing physician. Participants were followed for six years to assess time to OIs and LTFU outcomes (Objective II and III). However, they were followed for two years (24 months) to assess weight change, BMI variation, and time to death (Objective IV and V). Follow-up time was calculated in months from the date of ART initiation until the date of events (i.e., OIs, LTFU, and death) or censoring (other than events or end of the study). Weight was measured in kilogram (kg) at ART initiation (baseline) and then measured repeatedly every three months for 24 months. The corresponding BMI for each visit was calculated by dividing weight in kilograms by the height in meters squared (kg/m^2). The exposed group included undernourished (nutritional status measured at baseline was used to establish the cohort) ALHIV, defined as having a BMI of less than 18.5 kg/m^2.

3.5.6.2. Explanatory (covariates) variables

Independent variables included socio-demographic variables, baseline immunological and clinical variables, and follow-up variables. Socio-demographic variables included age, sex, level of education, residence, marital status, occupation, family size, and HIV-status disclosure. Baseline immunological and clinical variables included baseline OIs, CD4 cell counts, WHO clinical disease staging, Hgb level, nutritional status, functional status, ART eligibility criteria, and baseline ART regimen. Follow-up variables were OIs during follow-up, ART adherence, ART regimen change, taking CPT and IPT, HIV treatment failure, and length of time on ART.

3.5.6.3. Operational definitions

Table 2. Classifications and operational definitions of outcome and explanatory variables.

Variables	Classification/definition
Early mortality	When patients died from any causes within the first 24 months after starting ART.
Loss to follow-up	Loss to follow-up (LTFU) was defined patients missing an ART appointment for at least one month (Ministry of Health Ethiopia, 2017).
ART Adherence	ART adherence was classified as good, fair, or poor, calculated from the total monthly dose of ART drugs (n=60). Good is compliance equal to or greater than 95% or ≤ 3 missed doses per month; fair 85-94% compliance or between 4 and 8 missing doses per month; and poor as less than 85% compliance or ≥ 9 missed doses per month (Ministry of Health Ethiopia, 2017)
Common OIs	According to the Ethiopian ART guidelines, common OIs are herpes zoster, bacterial pneumonia, pulmonary and extra-pulmonary TB, oral and oesophageal candidiasis, mouth ulcer, diarrhea, pneumocystis pneumonia, toxoplasmosis, cryptococcal meningitis, non-Hodgkin's lymphoma, Kaposi's sarcoma, cervical cancer, and others (Ministry of Health Ethiopia, 2017).
Functional status	Functional status was classified as working, ambulatory, or bedridden. Patients were classified as working functional status if they can go out of home and do routine activities, including daily work. Patients were classified as ambulatory functional status if they are capable of self-care and use the toilet without support.

	Lastly, patients are classified under bedridden functional status if they are incapable of essential self-care (i.e., not able to use the toilet without support).
Degree of immunodeficiency	The WHO staging of HIV has four levels to determine the degree of immunodeficiency based on CD4 cell count: no significant immunosuppression (CD4 > 500 cells/mm^3), mild immunosuppression (CD4: 350−499 cells/mm^3), advanced immunosuppression (CD4: 200−349 cells/mm^3), and severe immunosuppression (CD4<200 cells/mm^3).
Nutritional status	Undernutrition was defined as a BMI of less than 18.5 kg/m^2. The severity of undernutrition is further classified as severe (BMI < 16 kg/m^2), moderate (BMI 16 -16.99 kg/m^2), and mild (BMI 17-18.48 kg/m^2) (Purnell, 2018).
HIV-status disclosure	According to current Ethiopian ART guidelines, patients are considered as disclosed their HIV status if they have disclosed their HIV status to at least one person (i.e., sexual partner or family member) (Ministry of Health Ethiopia, 2017).

3.5.7. Statistical analyses

Table 2 provides an overview of the statistical methods used in the longitudinal studies. A detailed statistical analysis plan and justification are included in each manuscript from Chapter five to Chapter eight.

Table 3. Summary of statistical approaches used in the longitudinal studies included in this thesis.

Objectives	**Outcomes**	**Statistical approaches**	**Tests used for model assumptions**	**Missing data handling**
OBJECTIVE II	Time to LTFU	Proportional hazards regression	Schoenfeld residual for proportional assumption	Multiple imputation (MI) was used for CD4 and Hgb
OBJECTIVE III	Time to new OIs	Logistic regression and Log-normal models for propensity score estimation	Overlap plots (positivity assumption)	Multiple imputation (MI)

		& Invers probability weighting (IPW) for treatment effects estimation	and covariate balance tests	was used for CD4 and Hgb
OBJECTIVE IV	Weight change	Linear mixed-effects model (LMM)	Q-Q plot for normality assumption	
OBJECTIVE V	BMI variation and time to death	Joint modelling of linear mixed-effects model and relative risk model with a piecewise-constant baseline risk function (piecewise PH-GH)	Q-Q plot for normality assumption & Schoenfeld residual test for Cox-proportional assumption	Multiple imputation (MI) was used for CD4 and Hgb

3.5.8. Ethical approval

A permission letter was secured from DMCSH Medical Director's Office (see Appendix 3.2). Ethical approvals for secondary data use were granted from the University of Technology Sydney Health and Medical Research Ethics Committee (*ETH20-5044*) and the Amhara Regional Public Health Research Ethics Review Committee (*Ref. no: 816*) (see Appendix 3.3). As the study was based on existing medical records of PLHIV, participants' verbal or written informed consent was not feasible, and a waiver of consent was granted through the UTS Medical Research Ethics Committee. However, since the participant's unique ART number and name were not included in the data abstraction tool, the data was completely de-identified to authors.

3.6. Chapter summary

This chapter briefly described different methodological approaches used for the five objectives of the thesis. This study used the medical records of ALHIV, who received ART between June 2014 and June 2020 at DMCSH in Northwest Ethiopia. This chapter provided brief information on sample size estimation, participants' selection, and data collection. Finally, study variables were also operationalised, and different statistical analyses used in all studies were also summarized. Detailed methodological approaches are included in each manuscript, starting from Chapter four. The next chapter presents the results of a published study that examined the effects of undernutrition on mortality in ALHIV.

Chapter 4 │Effects of undernutrition on mortality and morbidity among ALHIV on ART in SSA

4.1. Chapter introduction

This chapter includes findings from a published systematic review and meta-analysis. The review (Manuscript I) used a meta-analysis approach to examine the effects of undernutrition on mortality and morbidity in ALHIV in SSA. This systematic review addressed the first objective by summarizing the best available evidence based on 53 published primary studies conducted in SSA. Objectives, detailed methodology and results of the study are presented in the following pages. The manuscript has been published and is available in *BMC Infectious Diseases.*

4.2. Publication (Published in *BMC Infectious Diseases*):

Peer review process:

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Manuscript-Version 2 submitted----------24 August 2020
Manuscript-Version 3 submitted----------30 November 2020
Manuscript accepted for publication----------11 December 2020
Manuscript published----------4 January 2021

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Authors' contributions for this study

The candidate is the primary author of this manuscript and conceived the research idea, involved in study design, literature search, quality assessment, data extraction, data analysis, interpretation, and manuscript writing. The second and fourth authors participated in designing the study protocol, quality assessment, and reviewing and editing the manuscript. The third author was involved in interpreting the results and reviewing and editing the manuscript.

Effects of undernutrition on mortality and morbidity among adults living with HIV in Sub-Saharan Africa: A systematic review and meta-analysis

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Abstract

Background: Undernutrition is one of the most common problems among people living with HIV, contributing to premature death and the development of comorbidities within this population. In Sub-Saharan Africa (SSA), the impacts of these often-inter-related conditions appear in a series of fragmented and inconclusive studies. Thus, this review examines the pooled effects of undernutrition on mortality and morbidities among adults living with HIV in SSA.

Methods: A systematic literature search was conducted from PubMed, EMBASE, CINAHL, and Scopus databases. All observational studies reporting the effects of undernutrition on mortality and morbidity among adults living with HIV in SSA were included. Heterogeneity between the included studies was assessed using the Cochrane Q-test and I^2 statistics. Publication bias was assessed using Egger's and Begg's tests at a 5% significance level. Finally, a random-effects meta-analysis model was employed to estimate the overall adjusted hazard ratio.

Results: Of 4,309 identified studies, 53 articles met the inclusion criteria and were included in this review. Of these, 40 studies were available for the meta-analysis. A meta-analysis of 23 cohort studies indicated that undernutrition significantly (AHR: 2.1, 95% CI: 1.8, 2.4) increased the risk of mortality among adults living with HIV, while severely undernourished adults living with HIV were at higher risk of death (AHR: 2.3, 95% CI: 1.9, 2.8) as compared to mildly undernourished adults living with HIV. Furthermore, the pooled estimates of ten cohort studies revealed that undernutrition significantly increased the risk of developing tuberculosis (AHR: 2.1, 95% CI: 1.6, 2.7) among adults living with HIV.

Conclusion: This review found that undernutrition has significant effects on mortality and morbidity among adults living with HIV. As the degree of undernutrition became more severe, mortality rate also increased. Therefore, findings from this review may be used to update the nutritional guidelines used for the management of PLHIV by different stakeholders, especially in limited-resource settings.

Keywords: Adults living with HIV, PLHIV, Sub-Saharan Africa, undernutrition

Background

Human Immunodeficiency Virus (HIV) continues to be a significant global public health problem, with Sub-Saharan Africa (SSA) being the most significantly affected region (Kharsany & Karim, 2016; World Health Organization, 2018). Globally, in 2018, an estimated 37.9 million people were living with HIV (PLHIV), and 1.1 million people died from Acquired Immunodeficiency Syndrome (AIDS) related illnesses worldwide (UNAIDS, 2019b), with 54% of PLHIV located in East and Southern Africa, 13% in Western and Central Africa, 16% in Asia and Pacific, and 6% in Western and Central Europe and North America (UNAIDS, world AIDS day 2019). Low and middle-income countries (LMICs), especially SSA, are the most affected region accounted for 68% of PLHIV in 2018 (UNAIDS, world AIDS day 2019; World Health Organization, 2018). Although there is no cure for HIV, antiretroviral therapy (ART) suppresses viral replication and increases the CD4 counts sufficiently to improve the survival rates and quality of life (Centers for Disease Control and Prevention (CDC), Last update 14 July 2019). Despite these benefits, 23.3 million (62%) PLHIV were accessing ART in 2018 (UNAIDS, world AIDS day 2019; World Health Organization, 2019a) with low ART coverage in LMICs is mainly attributable to inaccessibility of health coverage (Kharsany & Karim, 2016).

Malnutrition refers to both undernutrition and overnutrition. Undernutrition is a state of inadequate intake of energy or nutrients to support the physiological function of the body. Due to the high prevalence of undernutrition, malnutrition often refers to undernutrition and the associated complications (Maleta, 2006; World Health Organization, 2009a). Therefore, this review focused on undernutrition, which is the most common form of malnutrition in LMICs.

Despite the use of ART having been effective in reducing AIDS-related mortality and morbidities (Edmonds et al., 2011), not all patients living with HIV have the same response to therapy. Thus, additional factors, such as nutritional status, and potential negative effects on the immunologic response of PLHIV must be considered (Duggal et al., 2012). Undernutrition is the most common problem among PLHIV and a significant factor potentiating morbidities and mortality (Duggal et al., 2012). Although undernutrition and HIV are global challenges, once more, we see a higher prevalence of undernutrition in SSA (Trehan et al., 2012). Accordingly, in 2018, about 22.8% of undernourished people and 68% of PLHIV were living in SSA (Food and Agriculture Organization of the United Nations, 2019; UNAIDS, world AIDS day 2019; World Health Organization, 2018).

Undernutrition and HIV are found to be interwoven in a vicious cycle (Thimmapuram et al., 2019). PLHIV are more vulnerable to developing undernutrition by different mechanisms. HIV is often accompanied by reduction in food intake due to: food insecurity, cognitive impairment or depression, medication-related nausea, and opportunistic infections (OIs) of mouth and oesophagus, which bring about painful swallowing (Weiser et al., 2011). In addition, HIV increases the energy requirements of HIV-infected adults by 10% for asymptomatic, and by 20-30% for symptomatic patients (L. Kosmiski, 2011). Conversely, undernutrition weakens the immune system and increases the risk of early mortality and morbidities (Enwonwu, 2006; França et al., 2009). Previous studies have shown that undernutrition has a significant impact on mortality and morbidity in ALHIV (Damtew et al., 2015; Liu et al., 2011), with even a minimal weight loss of up to 5% significantly increasing the risk of death (Hu et al., 2011). Studies conducted elsewhere confirmed that low body mass index (BMI) at ART initiation hastened disease progression and increased the risk of OIs (Ayele et al., 2017; Edmonds et al., 2011).

To inform health program planners and policymakers, current evidence-based findings are required. Although there is a general understanding that undernutrition and HIV are interrelated, a comprehensive systematic review and meta-analysis estimating the pooled effects of undernutrition on mortality and morbidity among adults living with HIV is lacking. Although there are primary studies reporting the effects of undernutrition on mortality and morbidity among ALHIV in SSA, they are highly fragmented and inconclusive. For example, some studies showed that undernutrition (BMI< 18.5kg^2) has a significant effect on mortality and morbidity (Ahmed et al., 2018; Ayele et al., 2017; Bastard et al., 2013; Evans et al., 2012; Ferradini et al., 2006; Hanrahan et al., 2010; Kouanda et al., 2012; Kufa et al., 2016; Moh et al., 2007; Moore et al., 2007; Naidoo et al., 2018; Ssebutinde et al., 2018; Tiruneh et al., 2019; Toure et al., 2008), while others showed no significant impact on mortality and morbidity (Brown et al., 2016; Hanrahan et al., 2010; Hussen et al., 2016; Nansera et al., 2012; Temesgen et al., 2019; Teshome et al., 2015). To the best of our knowledge, the above inconsistencies have not been well investigated. Therefore, this review aims to examine the effects of undernutrition on mortality and morbidities among adults living with HIV in SSA. Results obtained from this review will provide evidentiary inputs for program planners and decision-makers in designing strategies to reduce undernutrition related mortality and morbidities among PLHIV, particularly in LMICs.

Methods

Data sources and searching strategies

This systematic review and meta-analysis is designed to examine the effects of undernutrition on mortality and morbidity among adults living with HIV in SSA. The study protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO), University of York Centre for Reviews and Dissemination (ID: CRD42020161822). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline was followed to report our results (Appendix 4.1) (Liberati et al., 2009). We searched articles published between 2002 and 2019, aligning with the first year in which the first WHO ART guidelines were distributed for developing countries (World Health Organization, 2002). A comprehensive search was conducted in the following databases: PubMed (contains MEDLINE), EMBASE (Elsevier), CINAHL (EBSCO), and Scopus (Appendix 4.2). Searches were limited to articles published in English and conducted on humans. Finally, the reference lists of included studies were screened for additional articles. Articles identified through the electronic search were exported and managed using Covidence, a primary screening and data extraction tool provided by Cochrane. The search from the above-mentioned databases was done using the following search terms:

Line1: "malnutrition" OR "undernutrition" OR "nutritional deficienc*" OR "malnourish*" OR "low Body Mass Index" OR "low BMI" OR "underweight" OR "nutritional status" "stunting" OR "Wasting" OR "underweight" OR "micronutrient deficienc*"

AND

Line2: "HIV Infections" OR "HIV" OR "HIV-1" OR "HIV-2" OR "HIV infect*" OR "human immunodeficiency virus" OR "human immunedeficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR "((human immun*)OR (deficiency virus))" OR "acquired immunodeficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immunodeficiency syndrome" OR "acquired immune-deficiency syndrome" OR "((acquired immun*) OR (deficiency syndrome))" OR "HIV-positive" OR "Sexually Transmitted Diseases, Viral"

AND

Line3: "Mortalit*" OR "incidence" OR "survival" OR "death rate" OR "risk factors" OR "time to death" OR "case fatality rate" OR "determinates" OR "mortality rate" OR "predictors" OR "opportunistic infect*" OR "AIDS related opportunistic infecti*" OR "morbidit*" OR "hospital admissions" OR "hospitalization" OR "herpes zoster" OR "bacterial pneumonia" OR "pulmonary TB" OR "extra-pulmonary TB" OR "tuberculosis" OR "TB" OR "oral candidiasis" OR "oesophageal candidiasis" OR "mouth ulcer" OR "diarrh*" OR "pneumocystis pneumonia" OR "central nervous system toxoplasmosis" OR "toxoplasmosis" OR "cryptococcal meningitis" OR "non-Hodgkins lymphoma" OR "Kaposi's sarcoma" OR "cervical cancer" OR "herpes simplex" OR "cytomegalovirus" OR "AIDS defining disease"

AND

Line 4: "Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cameroon" OR "Cape Verde" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Republic of the Congo" OR "Democratic Republic of the Congo" OR "Cote d'Ivoire" OR "Djibouti" OR "Equatorial Guinea" OR "Eritrea" OR Ethiopia" OR "Gabon" OR "The Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Liberia" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome and Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "Tanzania" OR "Togo" OR "Uganda" OR "Zambia" OR "Zimbabwe"

The PICO framework was used to determine the eligibility for the study:

- ✓ **P**articipants/population: adults (defined as those aged ≥ 15 years) living with HIV.
- ✓ **I**ntervention(s)/exposure(s) group: undernourished adults living with HIV.
- ✓ **C**omparator(s)/control group: well-nourished adults living with HIV.
- ✓ **O**utcomes of interests: mortality and morbidities among adults living with HIV.

Inclusion and exclusion criteria

The study selection was done by the primary author (AA) using a two-stage approach. Initially, studies were screened based on titles and abstracts. At this stage, all studies reporting mortality and morbidity among PLHIV were considered. Then, a full-text assessment based on the predetermined inclusion criteria was performed (Figure 5). All observational studies (i.e., cross-sectional, case-control, and cohort) reporting effects of undernutrition on mortality and

morbidly among adults living with HIV in SSA were considered for inclusion. However, only cohort studies reporting the adjusted hazard ratio were included in the meta-analysis as determination of cause-and-effect relationships requires a robust study design. Excluded were systematic reviews, animal studies, studies not reporting the outcome of interests, conference papers, and editorial comments. The reason for excluding conference papers was due to the inability to assess the quality of studies in the absence of their full texts. Furthermore, studies conducted among HIV-infected pregnant women were excluded as pregnancy by itself increased the risk of undernutrition, and nutritional assessment tools used for pregnant women are different from tools used for other adults (Ververs et al., 2013). Studies involving both HIV-infected and HIV-uninfected adults were excluded, unless data for HIV-infected adults were reported separately. Articles included only malnourished adults living with HIV were also not considered for this review as these lacked controls (i.e., well-nourished adults living with HIV).

Measurement of outcome variables

This systematic review focused on two outcomes. The first outcome was the effect of undernutrition on mortality among adults living with HIV. Undernutrition (underweight) was defined as a BMI of less than 18.5 kg/m^2. The severity of undernutrition was classified as severe (BMI < 16 kg/m^2), moderate (BMI 16-16.99 kg/m^2), and mild (BMI 17-18.48 kg/m^2) (Purnell, 2018). The second outcome was the effect of undernutrition on morbidities. Morbidity refers to the occurrence of any type of opportunistic infection, incidence of AIDS defined diseases, hospital admissions, and other types of illnesses related to HIV-infection as reported by each primary study. The pooled effects of undernutrition on mortality and morbidity were determined using the (adjusted) hazard ratios reported from primary studies. For the meta-analysis, only cohort studies reporting the adjusted hazard ratios were included, as described previously.

Quality appraisal

The quality of included studies was appraised using the Newcastle-Ottawa scale (NOS) risk-of-bias assessment tool for cross-sectional, cohort, and case-control studies (Peterson et al., 2011). The NOS is validated for case-control and cohort studies with grading from zero to ten for cross-sectional, and zero to nine for case-control and cohort studies (Luchini et al., 2017). The three components of the tool are: selection, comparability, and outcome/exposure. The

selection part of this tool was graded from zero to five stars for cross-sectional studies, and zero to four stars for cohort and case-control studies. The comparability was graded from zero to two stars for all study designs. Lastly, the outcome/exposure was primarily related to the statistical analysis and cofounding handling mechanisms, which was graded from zero to three stars for all study designs.

During the quality appraisal, three (AA, DD, and DS) authors were involved, ensuring each study was appraised by two authors, with any disagreements between authors resolved through discussion. Finally, the quality score of each study was calculated as the sum of scores, thus ranging from zero to ten for cross-sectional studies, and zero to nine for cohort and case-control studies. Accordingly, articles receiving three or four stars in the selection, one or two stars in comparability, and two or three stars in outcomes were categorized as "good quality". Articles with two stars in the selection, one or two stars in comparability, and two or three stars in outcomes, were classified as "fair quality", whereas, a "poor quality" score was considered if the articles got zero or one-star(s) in the selection, or zero stars in comparability, or zero or one-star(s) in outcomes (Penson et al., 2012).

Data extraction

A standardized data extraction format was adopted and prepared based on the Joanna Briggs Institute (JBI) data extraction format (Peters et al., 2019). The data extracted included the following: primary author, publication year, country/countries where the study was conducted, study design, study/follow-up period, sample size, sex/ gender of participants, mortality rate/morbidity rate, and adjusted hazard ratio/ adjusted odds ratio with 95% confidence intervals (CI). If further information or clarification was needed, the primary author of the original article was contacted through email. The article was excluded if, after at least two email attempts, the author did not respond. Before combining in a meta-analysis, the hazard ratios were transformed into a logarithmic scale as the hazard ratio was measured on a ratio (exponential) scale.

Data synthesis

A narrative synthesis approach was employed to present results, which were not included in the meta-analysis. A meta-analysis was performed using Stata™ Version 16 statistical software to estimate effect sizes. Effect sizes were expressed as log-adjusted hazard ratios (AHR) with

their 95% CIs. In this meta-analysis, well-nourished adults living with HIV were considered as a reference (control) category. However, some primary studies reported AHR by considering undernourished adults living with HIV as a reference category, so to ensure consistency and uniformity, new AHRs with their 95% CIs were calculated by taking the reciprocal of the reported AHRs (Kleinbaum et al., 2010). Primary studies reporting the AHR based on the severity of undernutrition were included in our subgroup analysis because they reported nutritional status in three (mild, moderate, and severe) categories rather than two categories (undernutrition versus well-nourished). Studies reporting nutritional status (BMI) as a continuous variable were addressed in the narrative review.

Heterogeneity, publication bias, and subgroup analyses

The presence of heterogeneity between included studies was assessed using Cochrane Q-test and I^2 statistics. The I^2 value can be interpreted as: 0% to 40% (might not be important); 30% to 60% (may represent moderate heterogeneity); 50% to 90% (may represent substantial heterogeneity); and 75% to 100% (considerable heterogeneity) (Cumpston et al., 2019). In the case of significant heterogeneity, possible sources were investigated by performing univariate meta-regression analyses, and a random-effects meta-analysis model estimated the final effect size. Furthermore, to minimize random variations between primary studies, subgroup analyses were performed based on different variables (i.e., country where studies were conducted, degree of malnutrition, sample size, publication year, and quality score). We selected these variables because of the availability of data for these variables from most included studies. At last, the presence of publication bias was assessed using Egger's and Begg's tests at a 5% significance level (Lin & Chu, 2018).

Results

Identification of studies

A total of 4,309 articles were identified from PubMed, EMBASE, Scopus, and CINAHL (Figure 5). After the removal of 898 duplicates, 3,411 studies remained and were screened for title and abstract. In the next step, 3,320 articles were excluded based on titles and abstracts as these were not relevant for this review. The full text of 91 studies were downloaded and assessed based on the predefined inclusion criteria. An additional 43 full texts were excluded for the following reasons: 17 studies did not report data on the outcome(s) of interest (Bezabhe

et al., 2015; Boullé et al., 2015; Bucciardini et al., 2015; Herce, Kalanga, Wroe, et al., 2015; Hoffmann et al., 2014; Hosseinipour et al., 2010; Koethe et al., 2013; Lawn et al., 2005; Molfino et al., 2014; Nakanjako et al., 2010; Russell et al., 2010; Stete et al., 2018; Van Der Sande et al., 2004; Van Rie et al., 2011), eight studies reported only descriptive results (Bebell et al., 2017; Donovan & Massingue, 2007; Estopinal et al., 2012; Giri et al., 2013; Henostroza et al., 2016; Holmes et al., 2006; Kasonka et al., 2006; McCarthy et al., 2006; Oyella et al., 2012; Sørensen et al., 2016; Tadege, 2018), six studies were conference presentations (Adebamowo et al., 2017; Asiimwe et al., 2014; Hector et al., 2017; Herce, Kalanga, Crocker, et al., 2015; Kilama et al., 2015; Umanah et al., 2016), six studies were not conducted in SSA (Argemi et al., 2012; Benova et al., 2012; Choun et al., 2013; Jiang et al., 2019; Kumar et al., 2017; Sharma et al., 2015), two studies focused on children (aged <15 years) (Ebissa et al., 2015; Frigati et al., 2011), two studies focused on pregnant women (Li et al., 2014; Liotta et al., 2013), one study included only malnourished adults (Woodd et al., 2016), and one was a review paper (Chandrasekhar & Gupta, 2011). Five articles were added from the reference lists of included articles, leading to 53 included studies. Of these, 33 studies were conducted on mortality, 18 studies on morbidity, and two on both morbidity and both morbidity. Finally, 40 studies were available for the meta-analysis. Of these, 23 studies were used to estimate the pooled effects of undernutrition on mortality. Seven studies were included in the subgroup analysis to determine the effects of the severity of undernutrition (mild, moderate, and severe) on mortality. The remaining ten studies were used to estimate the pooled effects of undernutrition on tuberculosis.

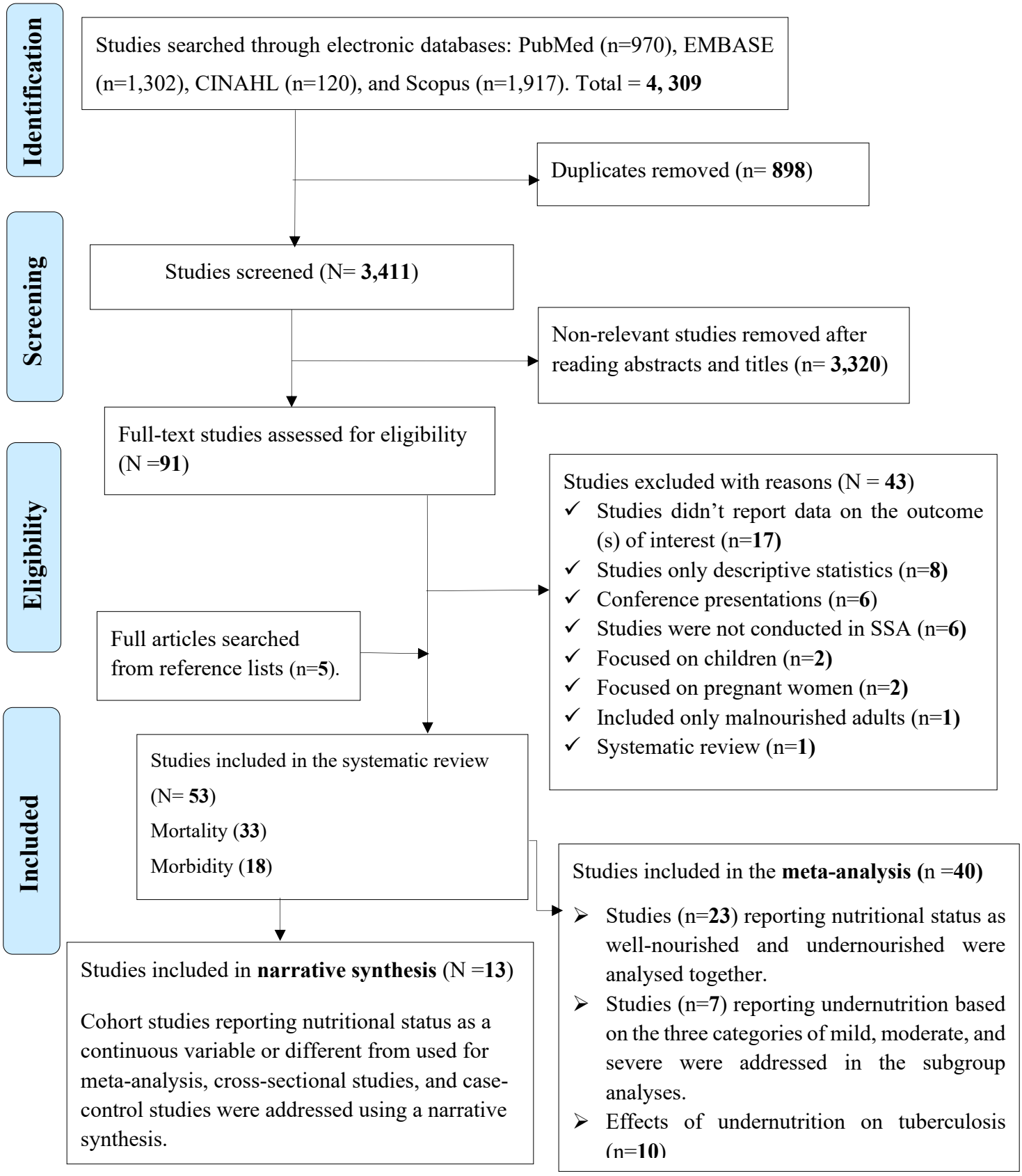

Figure 5. Flow chart of study selection for a systematic review and meta-analysis of the effects of undernutrition on mortality and morbidity among adults living with HIV in SSA.

Description of included studies

In this systematic review, 367,680 adults living with HIV were included across included articles with more than three quarters (76.2%) being females. Publication year of the included studies ranged from 2006 to 2019. The sample size of the included studies ranged from 71 in Kenya (Kendi et al., 2013) to 68,378 in Tanzania (Sabasaba et al., 2019). Most were cohort studies (n=47, 88.7%). From the 32 studies that reported the number of deaths or proportion of mortality, the highest (38%) mortality was reported from a study done in Kenya (Kendi et al., 2013); whereas the lowest (2%) proportion mortality was reported from a study done in Cote d'Ivoire (Moh et al., 2007). From the 19 included studies to assess the effects of undernutrition morbidities, 14 studies were done on TB, two studies on anaemia, and one study each for intestinal parasite (IP), AIDS-defining disease, and OIs. Of the18 studies that reported the number of morbidities or proportion of morbidity, the highest proportion of morbidity (65%) was recorded in a study conducted in Uganda (Kyeyune et al., 2014). Conversely, the lowest (2.4%) proportion of morbidity was reported from a study conducted in South Africa (Kufa et al., 2016) (**Table 4**). In this review, 13 SSA countries and six multi-country-based studies were represented. In this regard, more than half (55%) of the studies were conducted in Uganda (n=8), Ethiopia (n=13), and South Africa (n=8) (Figure 6).

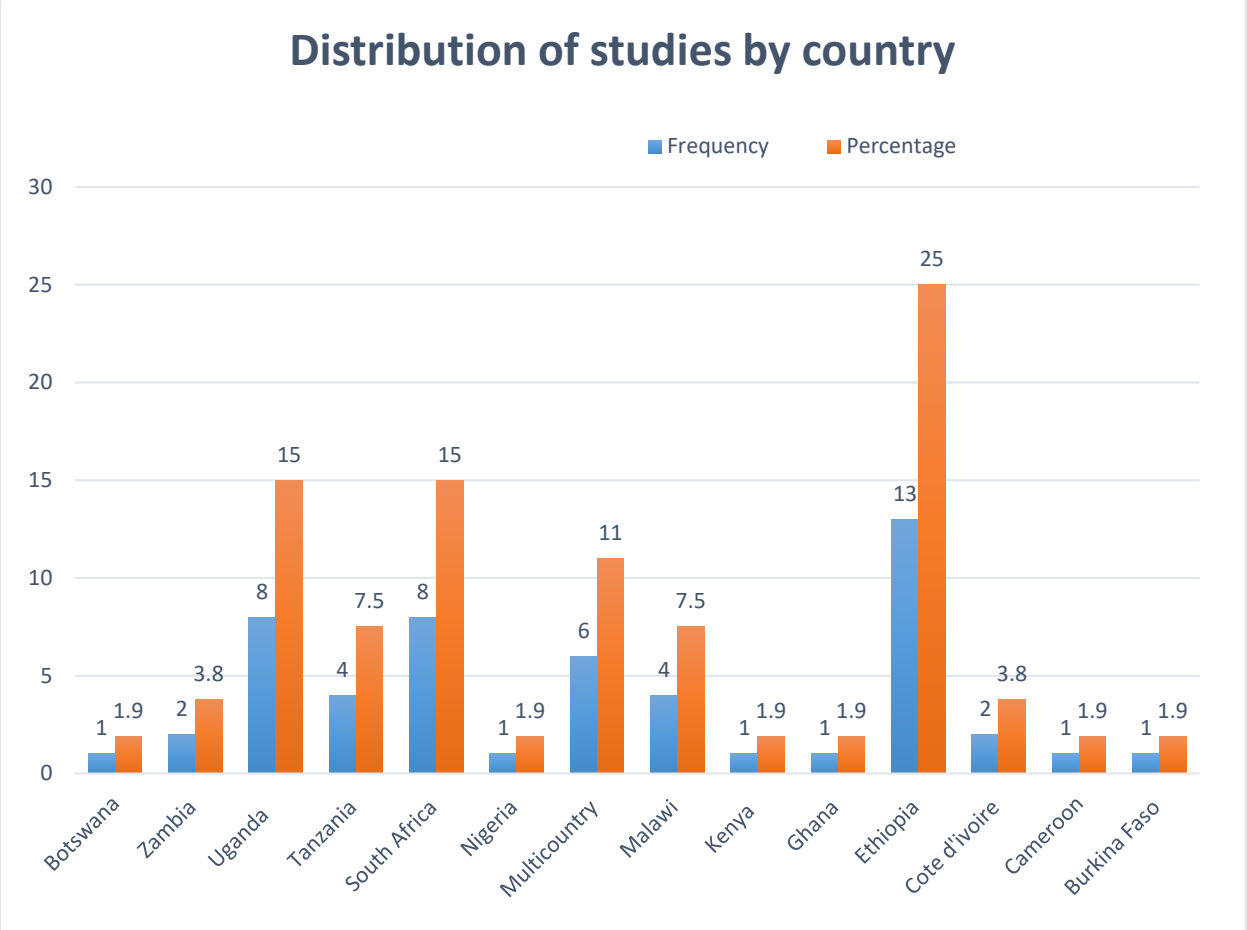

Figure 6. The distribution of included studies across countries in SSA.

Table 4. Descriptive summary of 53 included studies in the systematic review of the effects of undernutrition on mortality and morbidity among adults living with HIV, between 2002 and 2019.

No	Author (Publication Year)	Study Design	Study/ follow-up period	Quality score	Sample size	Female N (%)	Mortality N (%)	Adjusted confounders for mortality
	Studies included assessing the effect of undernutrition on mortality							
1.	Ferradini et al., (2006)	Retrospective cohort	2001-2004	5	1, 308	827 (63.2)	243(19)	Age, year of HAART initiation, type of ART regimen, follow-up site, sex, and baseline CD4 count
2.	Evans et al., (2012)	Retrospective cohort	2004-2009	8	8,409	5,204 (61.9)	661(7.9)	Hgb, CD4 count, aspartate transaminase, TB, age, and sex
3.	Palombi et al., (2009)	Retrospective cohort	NR	6	3, 749	2,325 (62)	393 (10.5)	Sex, age, baseline Hgb, baseline CD4 count, baseline HIV RNA level, WHO staging, ART adherence, and length of ART follow-up.
4.	Jerene et al., (2006)	Cohort	2003-2005	6	152	66 (43.4)	24 (15.8)	TLC, WHO staging and Hgb
5.	Johannessen et al., (2008)	Prospective cohort	2003-2006	7	320	223 (69.7)	95 (29.7)	Sex, WHO staging, ART start year, Hgb, TLC, and platelet count
6.	Moh et al., (2007)	Cohort	2002-2004	7	792	606 (76.5)	18 (2)	WHO staging, Hgb, viral load, baseline CD4 count, follow-up CD4 count and follow-up viral load
7.	Brown et al., (2016)	Cohort	2008-2015	8	432	243 (56.3)	74 (17.2)	Sex, age at enrolment, CD4 count at enrolment, year of enrolment, and route of HIV testing
8.	Tesfamariam et al., (2016)	Retrospective cohort	2006-2013	8	489	254 (51.9)	87 (17.8)	Educational status, functional status, WHO staging, CD4 count, Hgb, previous OI, HIV related counselling
9.	Bastard et al., (2013)	Cohort	2004-2010	8	55,789	36,508 (65.4)	1843 (3.3)	Sex, age, WHO staging, CD4 count, diagnosis of TB, eligibility to ART, and mode of entry to ART
10.	Dao et al., (2011)	Prospective cohort	2005-2007	7	661	661 (100)	53 (8)	Country, age, WHO staging, diagnosis of TB, CD4 count, viral load, prophylaxis, Hgb, WBC, neutrophils count, platelet counts, potassium, chloride, sodium, hyponatremia, creatinine clearance, AST/ALT, and albumin
11.	Kouanda et al., (2012)	Retrospective cohort	2003- 2008	8	5,608	3926 (70)	690 (12.3)	Age, sex, occupation, WHO staging, ART regimen, CD4 count, year of HAART initiation, and intensity of intervention
12.	Masiira et al., (2014)	Prospective cohort	1992-2011	8	374	204 (54.5)	27 (7.21)	Age, sex, marital status, alcohol consumption, tobacco use, Hgb, CD4 count, WHO staging, viral load, malaria infection during follow-up, diarrhea, and viral load
13.	Teshome et al., (2015)	Retrospective cohort	2011-2012	6	1,173	649 (55.3)	47 (4)	Sex, gap b/n test and treatment, marital status, family size, facility type, CD4 count, age, INH prophylaxis, CPT prophylaxis, side effects, functional status, HIV status disclosure, educational status, TB, and WHO staging
14.	Chen et al., (2008)	Retrospective cohort	2004-2006	7	2, 838	1,716 (60.5)	376 (13.2)	Sex, age, and WHO staging

15.	Sieleunou et al., (2009)	Retrospective cohort	2001-2006	7	1, 187	660 (55.6)	338 (28.5)	Sex, WHO staging, CD4 count, and Hgb
16.	Liu et al., (2011)	Retrospective cohort	2004-2009	7	8,271	11,927 (65.3)	1673 (9.2)	Hgb and MUAC
17.	Ssebutinde et al., (2018)	Retrospective cohort	2006-2012	7	8,364	5,308 (63.5)	180 (2.1)	Age, sex, WHO staging, CD4 count, and level of education
18.	Maskew et al., (2013)	Retrospective cohort	2004-2010	8	7,354	4,621(62.8)	333 (4.5)	Sex, age, CD4 count, and Hgb
19.	Geng et al., (2013)	Retrospective cohort	2007-2011	7	2,633	1,563 (59.4)	42 (1.6)	Age, sex, CD4 count, baseline TB diagnosis, pregnancy at ART initiation, WHO staging, income, employment status, education, and distance from ART clinic
20.	Hoffmann et al., (2011)	Retrospective cohort	2003-2008	7	15,060	5,455 (36.2)	2,658 (18)	Sex, age, WHO staging, TB symptoms, Hgb, viral load, and CPT
21.	Toure et al., (2008)	Retrospective cohort	2004-2007	6	10,211	7,187 (70.4)	1,140 (11)	Sex, age, CD4 count, WHO staging, ART regimen, Type of HIV, and Hgb
22.	Damtew et al., (2015)	Retrospective cohort	2007-2011	6	784	485 (61.9)	87 (11.1)	Marital status, educational status, functional status, WHO staging, CD4 count, anaemia, and TB co-infected
23.	Ayele et al., (2017)	Retrospective cohort	2012-2014	7	280	183 (65.4)	NR	Sex, age, educational level, residence, religion, occupation, marital status, alcohol, WHO staging, CD4 count, TB treatment, type of ART regimen, and prophylaxis
24.	Maman et al., (2012)	Retrospective cohort	2001-2010	7	24, 037	16,355 (68)	568 (2.4)	HIV program, sex, age, WHO staging, initial CD4 count, updated CD4 count, and year of ART initiation
25.	Naidoo et al., (2018)	Retrospective cohort	2008-2010	6	948	547 (57.7)	56 (5.9)	Age, sex, CD4 count, WHO staging, and TB
26.	Stringer et al., (2006)	Cohort	2004-2005	7	21,755	13,646 (62.7)	1, 120 (5.1)	Age, ART non-adherence, sex, Hgb, CD4 count, WHO staging, and TB infection
27.	Hussen et al.,(2016)	Retrospective cohort	2006-2011	8	340	200 (58.8)	42 (12.4)	Age, marital status, CD4 count, WHO staging, occupation, educational level, Fluconazole prophylaxis, and Baseline HAART
28.	Pac et al., (2015)	Prospective cohort	2010-2012	7	540	324 (60)	39 (7.2)	Age, sex, CD4 count, Hgb, TB infections, and positive serum Cr Ag
29.	Tchounga et al., (2016)	Cohort	2014-2015	7	1,825	1,102 (60.4)	221 (12.1)	Sex, age, year of ART initiation, WHO staging, CD4 count, and Hgb
30.	Nansera et al., (2012)	Retrospective cohort	2007-2010.	6	386	142 (36.8)	53 (13.7)	Sex, anaemia, CD4 cell count, and WHO staging

31.	Otwombe et al., (2014	Prospective cohort	2003-2010	8	2,221	1,555 (70)	242 (11)	Sex, time on ART, CD4 count, employment status, ever smoking, and ever TB
		Prospective cohort	2003-2010		4,469	3,480 (77.9)	324 (7.2)	
32.	Kendi et al., (2013)	Retrospective cohort	2005-2009	6	71	35 (49.3)	27 (38)	Age, sex, CD4 count, on ART, and any anti-fungal therapy
33.	Zachariah et al., (2006)	Cross-sectional	2003-2005	9	1, 507	990 (65.7)	190 (12.6)	Sex, age, WHO staging, CD4 count, and active TB
34.	Umanah et al., 2015)	Cross-sectional	2007-2010	8	947	490 (51.7)	NR	ART regimen, age, sex, site of TB, CPT prophylaxis, CD4 categories, Hgb, infiltrative cavitation change on X-ray, fibrotic change on X-ray, other OIs, comorbidity, and adverse events to medication
		Studies included assessing the effect of undernutrition on morbidity						
No	**Author**	**Study Design**	**Study/ follow-up period**		**Sample size**	**Female N (%)**	**Morbidity N (%)**	**Adjusted for confounders for morbidities**
35.	Moore et al., (2007)	Prospective cohort	2003-2005	6	1042	765 (73.4)	53 (5.1)	Sex, median age, CD4 count, viral load, prior TB treatment, participation in previous safe water/co-trimoxazole study
36.	Kufa et al., (2016)	Prospective cohort	2011-2012	7	634	513 (80.9)	15 (2.4)	Sex, age, employed, ever smoked, alcohol drinking, duration since HIV test, on ART, current or prior ART use, current CPT use, previous TB treatment, and CD4 count
37.	Sabasaba et al., (2019)	Retrospective cohort	2011-2014	8	68,378	51,486 (75.3)	3,124 (4.6)	Age, sex, marital status, CD4 categories, WHO staging, CPT use, IPT status, ART status, and functional status at enrolment
38.	Worodria et al., (2011)	Prospective cohort	NR	7	219	157 (71.7)	6 (3.8)	Age, Sex, TB ski test, C-reactive protein, Hgb, CD4 count, and WHO staging
39.	Ahmed et al., (2018)	Retrospective cohort	2010-2015	8	451	267 (59.2)	119 (26.4)	Marital status, family size, substance use, previous TB, OIs, bed ridden, length of follow-up, WHO staging, Hgb, CD4 count, and IPT
40.	Tiruneh et al., (2019)	Retrospective cohort	2009-2012	8	600	356 (59.3)	53 (8.8)	Age, CD4 count, sex, weight, WHO staging, functional status, CPT, previous TB treatment, and OI
41.	Nicholas et al., (2011)	Prospective cohort	2006-2008	7	28,323	18,968 (67.0)	780(9) pre 933(5) post	Residence, sex, age, history of ART use, TB history, and CD4 count
42.	Liu et al., (2015)	Prospective cohort	2004-2012	8	67,686	50,633 (74.8)	7,602 (11.2)	Age, sex, district, family size, years of enrolment, season of visit, MUAC, anaemia, CD4 count, WHO staging, ALT, CPT, IPT, non-adherence to ART, month on ART, ART regimen, and NNRTI

43.	Chang et al., (2015)	Retrospective cohort	2004 -2012	8	32,611	22,106 (67.8)	2,021 (6.2)	Sex, ART at enrolment year, ART regimen, WHO staging, CD4 count, viral load, anaemia, and ART adherence
44.	Bjerrum et al., (2016)	Prospective cohort	2013-2014	7	473	304 (64.3)	60 (12.7)	Age, sex, CD4 count, cough ≥ 2 weeks, and fever ≥ 2 weeks
45.	Temesgen et al., (2019)	Retrospective cohort	2012-2017	7	492	264 (53.7)	83 (16.9)	Sex, CD4 count, WHO staging, functional status, Hgb, OIs, CPT, and IPT
46.	Mupfumi et al., (2018)	Retrospective cohort	2008-2011	7	254	172 (67.7)	13 (5)	Sex, age, Hgb, CD4 count, viral load, and hepatitis B infection
47.	Hanrahan et al., (2010)	Prospective cohort	2003-2008	9	3, 456	2704 (78.2)	226 (6.5)	On HAART, CD4 count, CPT use, income, employment status, and smoking ever
48.	Melkamu et al., (2013)	Case-Control Study	2011-2012	9	357	192 (53.8)	NR	Marital status, educational status, having diabetes mellitus, WHO clinical staging, and having separate kitchen
49.	Gedle et al., (2017)	Cross-sectional	April-June 2016	10	323	204 (63.2)	142 (35.9)	Residence, educational status, income, presence of animals, presence of toilet, source of water, WHO staging, and CD4 count
50.	Kyeyune et al., (2014)	Cross-sectional	2010-2012	9	400	277 (69.3)	260 (65)	Sex, CD4 count, age, HART status, educational status, and employment status
51.	Ageru et al., (2019)	Cross-sectional	October-December 2016	10	411	258 (62.8)	150 (36.5)	Sex, marital status, educational level, HAART status, year live with virus, frequency of eating, CD4 count, and infection with intestinal parasite
52.	Chen et al., (2019)	Prospective cohort	2007-2009	8	572	334 (58.4)	75 (13.1)	Loss of appetite, handgrip strength, sphygmomanometer test
53.	Hussen et al. (2017)	Retrospective cohort	2006-2011	8	340	200 (58.8)	83 (24.4)	Educational level, baseline HAART, and INH prophylaxis

ALT: Alanine Transaminase, **ART**: Antiretroviral Therapy, **AST**: Aspartate Aminotransferase, **CD4**: Cluster of Differentiation 4, **CPT:** Cotrimoxazole Preventive Therapy, **HAART**: Highly Active Antiretroviral Therapy, **Hgb**: Hemoglobin, HIV: Human Immunodeficiency Virus, **INH**: Isoniazid, **IPT:** Isoniazid Preventive Therapy, **MUAC**: Mid Upper Arm Circumference, **NNRTI**: Non-Nucleoside Reverse Transcriptase Inhibitor, **NR**, Not reported, **OI**: Opportunistic Infection, **RNA**: Ribonucleic Acid, **TB:** Tuberculosis, **TLC**: Total Lymphocyte count, and **WHO**: World Health Organization.

Quality appraisal results

NOS quality scores ranged from five to nine for cohort studies, and eight to ten for cross-sectional studies (Table 4). The mean quality score of the included studies was 7.34 (SD: 0.14). More than two-thirds (71.7%) of the included studies had good quality. Fair or poor-quality scores of the cohort studies were mainly due to the following reasons: lack of descriptions of loss to follow-up (n=14, 29.8%), shorter follow-up period (n=30, 63.8%), lack of description of the derivation of the exposed group (n=19, 40.4%), and lack description of the derivation of the non-exposed group (n=16, 34%). All included studies-controlled confounders through multivariable regression analysis. However, most of the cohort studies employed a single-arm study design (no control group). From 47 cohort studies included in our review, 14 (29.8%) of the studies lacked a description of the loss to follow-up. Furthermore, six cohort studies reported that their loss to follow-up rate was more than 20%. About 63.8% of the included cohort studies had a follow-up period of less than five years for mortality and/or less than two years for morbidities.

Narrative Analysis

The effects of undernutrition on mortality

Five studies (Kendi et al., 2013; Masiira et al., 2014; Palombi et al., 2009; Umanah et al., 2015; Zachariah et al., 2006), which were not suitable for the meta-analysis, were included in the narrative analysis. A multi-county based retrospective cohort study involving 3,749 adults living with HIV found that, as BMI increased in one unit, the hazard of death was reduced by 8% (AHR: 0.92, 95% CI: 0.87, 0.96) (Palombi et al., 2009). A Kenyan retrospective cohort study followed 71 adults living with HIV with a median follow up time of 201 days found that as BMI increased in one unit, the hazard of death decreased by 18% (AHR: 0.82, 95% CI: 0.68, 0.99) (Kendi et al., 2013). Another retrospective cohort study including 374 adults living with HIV from Uganda reported that adults living with HIV who had BMI < 17.5 kg/m^2 were six-fold (AHR: 6.11, 95% CI: 2.3, 16.2) more likely to die as compared to well-nourished adults living with HIV. This study also documented that HIV positive adults, who had BMI between 17.5 and 18.49kg/m^2, were four times (AHR: 4.5, 95% CI: 1.54, 13.32) more likely to die than well-nourished adults living with (Masiira et al., 2014). Furthermore, a cross-sectional study involving 1,507 participants conducted in Malawi reported that mild (AOR: AOR: 2.1, 95% CI: 1.2, 3.8), moderate (AOR: 2.4, 95% CI: 1.7, 6.3) and severe (AOR: 6, 95% CI: 4.6, 12.7)

undernutrition were significantly associated with mortality (Zachariah et al., 2006). Lastly, a cross-sectional study involving 947 adults living with HIV reported from South Africa found that severe undernourishment (AOR: 3.71, 95% CI: 1.89, 7.29) and BMI between 16 and 18.49 kg/m^2 (AOR: 2.35, 95% CI: 1.3, 4.26) were significantly associated with mortality in PLHIV (Umanah et al., 2015).

The effects of undernutrition on tuberculosis

From the 15 studies assessed respecting the effects of undernutrition on tuberculosis (TB), five studies were not suitable for meta-analysis (Bjerrum et al., 2016; Chang et al., 2015; Liu et al., 2015; Melkamu et al., 2013; Mupfumi et al., 2018). A Tanzanian prospective cohort study followed 67,685 adults living with HIV with a median follow-up time of 24 months indicated that patients living with HIV with a BMI<17 kg/m^2 (AHR: 1.96, 95% CI: 1.83, 2.09), and BMI between 17 and 18.49 kg/m^2 (AHR: 1.69, 95% CI: 1.58, 1.8) were at higher risk of TB (Liu et al., 2015). An additional retrospective cohort study on 32,611 Nigerian adults living with HIV noted that within a median follow-up time of 29.2 months severely underweight [(BMI<16 kg/m^2 (AHR: 3.85, 95% CI: 2.75, 5.38)], and underweight [(BMI: 16-18.49 kg/m^2 (AHR: 2.18, 95% CI: 1.80, 2.65)] adults living with HIV had a higher risk to be diagnosed with TB (Chang et al., 2015). Furthermore, a retrospective cohort study conducted among 254 adults living with HIV in Botswana documented that, as BMI increased in one unit, the risk of TB reduced by 19% (AHR: 0.81, 95% CI 0.66, 1.00: P=0.05) (Mupfumi et al., 2018). A case-control study undertaken with 357 adults living with HIV in Ethiopia reported that undernourished HIV positive adults had a higher risk of TB (AOR: 3.8, 95% CI: 2.39, 6.08) (Melkamu et al., 2013). Another prospective cohort study done among 473 adults living with HIV in Ghana found that undernutrition significantly increased the risk of TB (AOR: 2.51, 95% CI: 1.15, 5.51) (Bjerrum et al., 2016).

The effects of undernutrition on other morbidities

Five studies reported the effects of undernutrition on various morbidities in PLHIV (Ageru et al., 2019; Chen et al., 2019; Gedle et al., 2017; Hussen et al., 2017; Kyeyune et al., 2014). Two cross-sectional studies from Uganda involved 400 participants (Kyeyune et al., 2014), and Ethiopia involved 411participants (Ageru et al., 2019) showed that undernutrition significantly increased the risk of anaemia among PLHIV with prevalence ratio (PR): 2.43 (95% CI: 1.01, 5.26) and AOR: 2.96 (95% CI: 1.36, 6.39), respectively. A cross-sectional study conducted

among 323 Ethiopian adults living with HIV reported that undernutrition was significantly associated with parasitic intestinal infections (AOR: 2.59, 95% CI: 1.36, 4.95) (Gedle et al., 2017). Furthermore, a Zambian prospective cohort study involving 572 participants found that moderate wasting was significantly associated with AIDS-defining illnesses (AOR: 2.40, 95% CI: 1.13, 5.10) (Chen et al., 2019). At last, a retrospective cohort study conducted with 340 Ethiopian adults living with HIV showed that undernutrition was a significant risk of OIs (AHR: 2.27, 95% CI: 1.4, 3.6) (Hussen et al., 2017).

Meta-analysis of the effects of undernutrition on mortality

Thirty cohort studies were included in the meta-analysis. Of these, 23 studies reporting nutritional status as well-nourished (BMI between 18.5 kg/m^2 and 24.9 kg/m^2) and undernourished (BMI<18.5 kg/m^2) were analysed together. The remaining seven studies reporting undernutrition based on the three categories of mild, moderate, and severe were addressed in the subgroup analyses (Table 5). Of the 23 studies included in the meta-analysis, 17 studies showed that undernutrition has a significant effect on mortality in adults living with HIV (Damtew et al., 2015; Dao et al., 2011; Evans et al., 2012; Ferradini et al., 2006; Geng et al., 2013; Hanrahan et al., 2010; Hoffmann et al., 2011; Kouanda et al., 2012; Moh et al., 2007; Naidoo et al., 2018; Otwombe et al., 2014; Tchounga et al., 2016; Tesfamariam et al., 2016; Toure et al., 2008). However, six studies reported that undernutrition has no significant effect on mortality in this population (Brown et al., 2016; Hussen et al., 2016; Jerene et al., 2006; Nansera et al., 2012; Ssebutinde et al., 2018; Teshome et al., 2015). Finally, the pooled AHR of 23 cohort studies involving 125,790 individuals showed that undernourished adults living with HIV were two-fold (AHR: 2.1, 95% CI: 1.8, 2.4) more likely to die as compared to their well-nourished counterparts. The included studies exhibited substantial heterogeneity (I^2 =66.4% and Cochrane chi-squared test p-value <0.001). As a result, a random-effects meta-analysis model was conducted to estimate the final pooled effect size (Figure 7).

The possible sources of heterogeneity were explored using a meta-regression model considering the following continuous variables as moderators: publication year, sample size, and quality. None of these factors were significantly associated with heterogeneity. Publication bias was assessed using a funnel plot. Since the funnel plot had a symmetric inverted shape, it is unlikely that there is publication bias (Figure 8). To confirm this finding, objective statistical tests (Begg's rank correlation and Egger's linear regression tests) were conducted, which

confirmed that there was no publication bias among studies used to estimate the effect of undernutrition on mortality with p=0.5 and p=0.8.

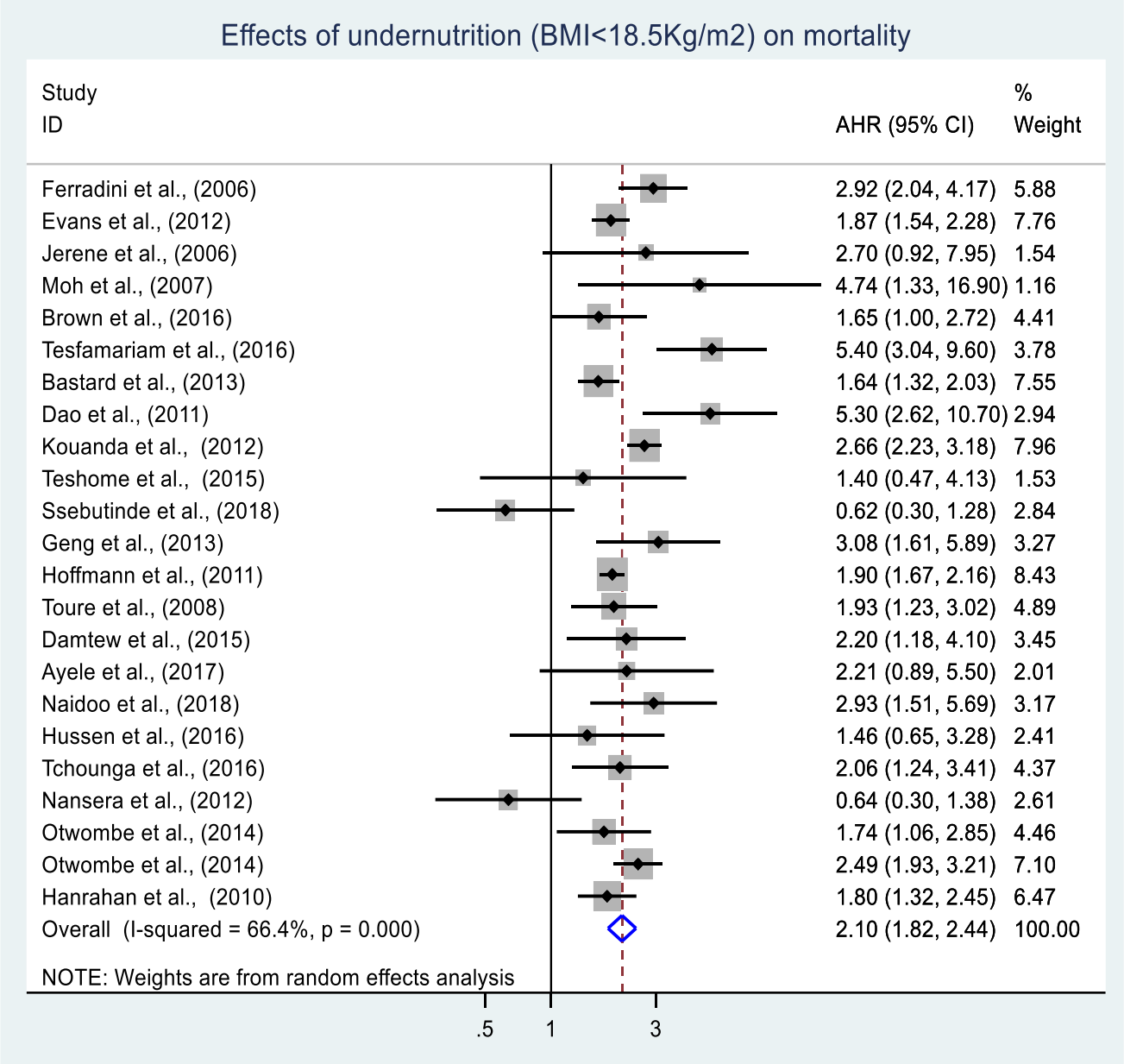

Figure 7. Forest plot of the effects of undernutrition on mortality among adults living with HIV in SSA.

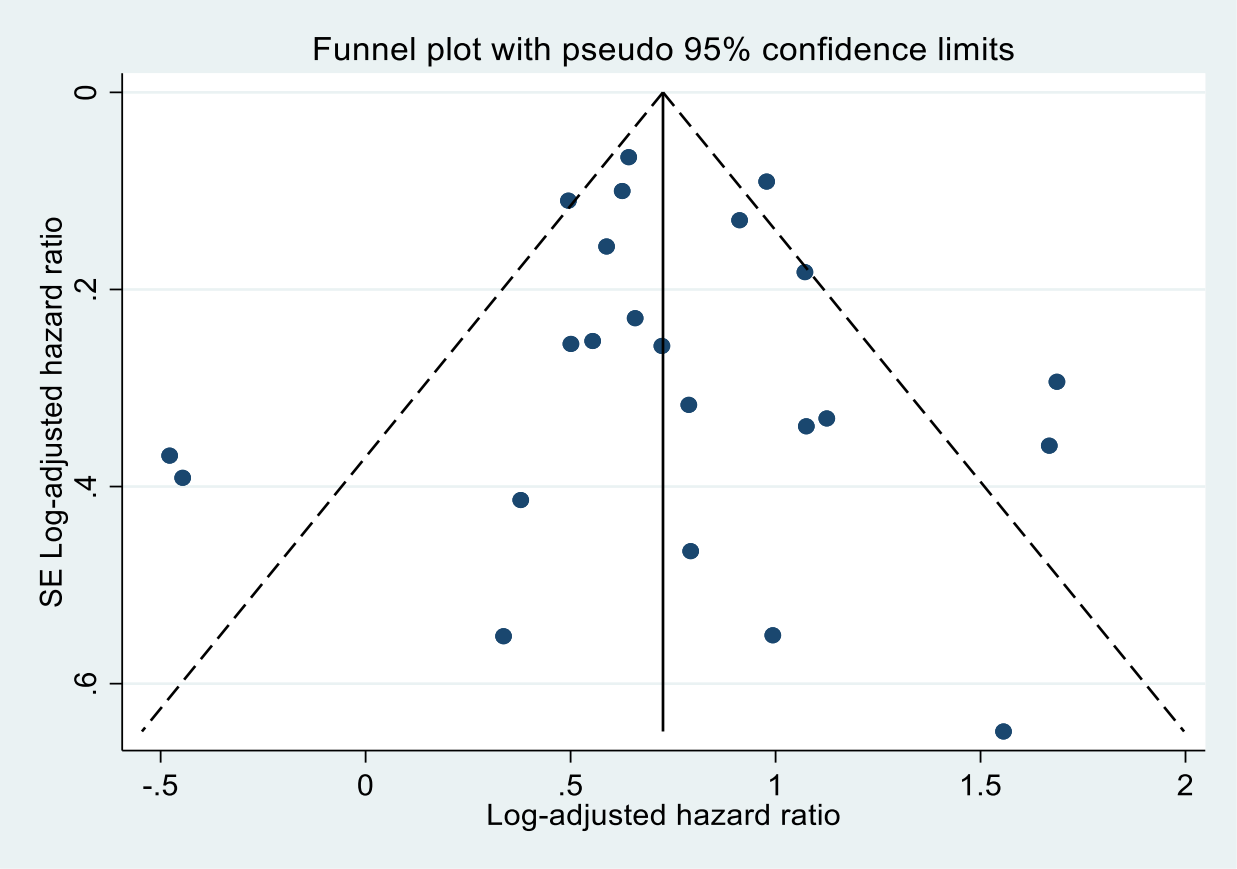

Figure 8. Funnel plot of the effects of undernutrition on mortality among adults living with HIV in SSA.

Subgroup analyses of effects of undernutrition on mortality

The subgroup analyses of this review showed that severely undernourished adults living with HIV were at higher risk of death (AHR: 2.3, 95% CI: 1.9, 2.8) as compared to mildly undernourished adults living with HIV (using six studies) (Johannessen et al., 2008; Liu et al., 2011; Maman et al., 2012; Pac et al., 2015; Sieleunou et al., 2009; Stringer et al., 2006). However, the mortality rate between moderately undernourished (two studies) and mildly undernourished (four studies) adults living with HIV was not statistically significant [(AHR: 1.8, 95% CI: 1.5, 2.5) (Liu et al., 2011; Maman et al., 2012), and (AHR: 1.4, 95% CI: 1.1, 1.8)] (Chen et al., 2008; Kouanda et al., 2012; Liu et al., 2011; Maman et al., 2012), respectively. Moreover, undernutrition on mortality is exacerbated in Western Africa as compared to other parts of SSA (AHR: 2.5, 95% CI: 1.9, 3.3) (Kouanda et al., 2012; Moh et al., 2007; Toure et al., 2008). The subgroup analyses also indicated that undernutrition has a more significant effect on mortality in studies published before 2012 (AHR: 2.3, 95% CI: 1.9, 2.7) (Dao et al.,

2011; Evans et al., 2012; Ferradini et al., 2006; Hanrahan et al., 2010; Hoffmann et al., 2011; Jerene et al., 2006; Kouanda et al., 2012; Moh et al., 2007; Toure et al., 2008) (Table 5).

Table 5. Subgroup analyses of the effect of undernutrition on mortality among adults living with HIV in SSA, between 2002 and 2019.

Variables	Subgroup	No of studies	Population (N)	AHR (95%CI)	(I^2 (%) and Cochrane chi-squared test p-value)
Severity of undernutrition	Severe	6	66, 110	2.3 (1.9, 2.8)	(45.5, 0.102)
	Moderate	2	42, 308	1.8 (1.5, 2.5)	(52.3, 0.145)
	Mild	4	50, 754	1.4 (1.1, 1.8)	(60.9, 0.053)
Geographical locations	Eastern Africa	9	14, 601	1.8 (1.1, 3.0)	(75.9, <0.001)
	Western Africa	3	16, 611	2.5 (1.9, 3.3)	(23, 0.273)
	Sothern Africa	8	36, 303	2.1 (1.8, 2.3)	(35.3, 0.147)
	Multicounty	3	58, 275	2.4 (1.3, 4.4)	(80, 0.007)
Sample size	≥ 5, 470	6	103, 441	1.8(1.5, 2.3)	(79.3, <0.001)
	< 5, 470	17	22, 349	2.3 (1.9, 2.9)	(56.6, 0.002)
Publication year	≤ 2012	9	45, 657	2.3 (1.9, 2.7)	(65.6, 0.003)
	> 2012	14	80, 133	1.9 (1.5, 2.4)	(68.2, <0.001)
Quality score	Good	13	93, 236	2.05 (1.7, 2.5)	(73.3, <0.001)
	Fair/ poor	10	32, 554	2.2 (1.7, 2.8)	(51.5, 0.029)

Meta-analysis of effects of undernutrition on TB

Ten cohort studies involving 104,387 adults living with HIV were included in the meta-analysis. Of these ten studies, seven studies found that undernutrition has a significant effect on the occurrence of TB (Ahmed et al., 2018; Kufa et al., 2016; Moore et al., 2007; Nicholas et al., 2011; Sabasaba et al., 2019; Tiruneh et al., 2019; Worodria et al., 2011). The remaining three studies found that undernutrition has no significant effect on the occurrence of TB (Hanrahan et al., 2010; Moh et al., 2007; Temesgen et al., 2019). The final overall pooled effect found that undernutrition has a significant effect on the occurrence of TB among adults living

with HIV (AHR: 2.1, 95% CI: 1.6, 2.7) (Figure 9). Significant heterogeneity (I^2 = 75.2% and Cochrane chi-squared test p-value <0.001) was observed; therefore, a random-effects meta-analysis model was computed to estimate the pooled effect. To investigate the possible sources of heterogeneity, a univariate random-effects meta-regression was done using continuous variables of publication year, sample size, quality as covariates [(Coefficient: -0.03, p: 0.524), (Coefficient: -2.71, p: 0.736) and (Coefficient: 0.31: 0.307) respectively]. Finally, publication bias between the included studies was also assessed using the funnel plot (Figure 10) with confirmatory tests of publication bias done using Begg's rank correlation and Egger's linear regression tests. Accordingly, both test sets indicated there was no publication bias across included studies (p= 0.325 and p= 0.767).

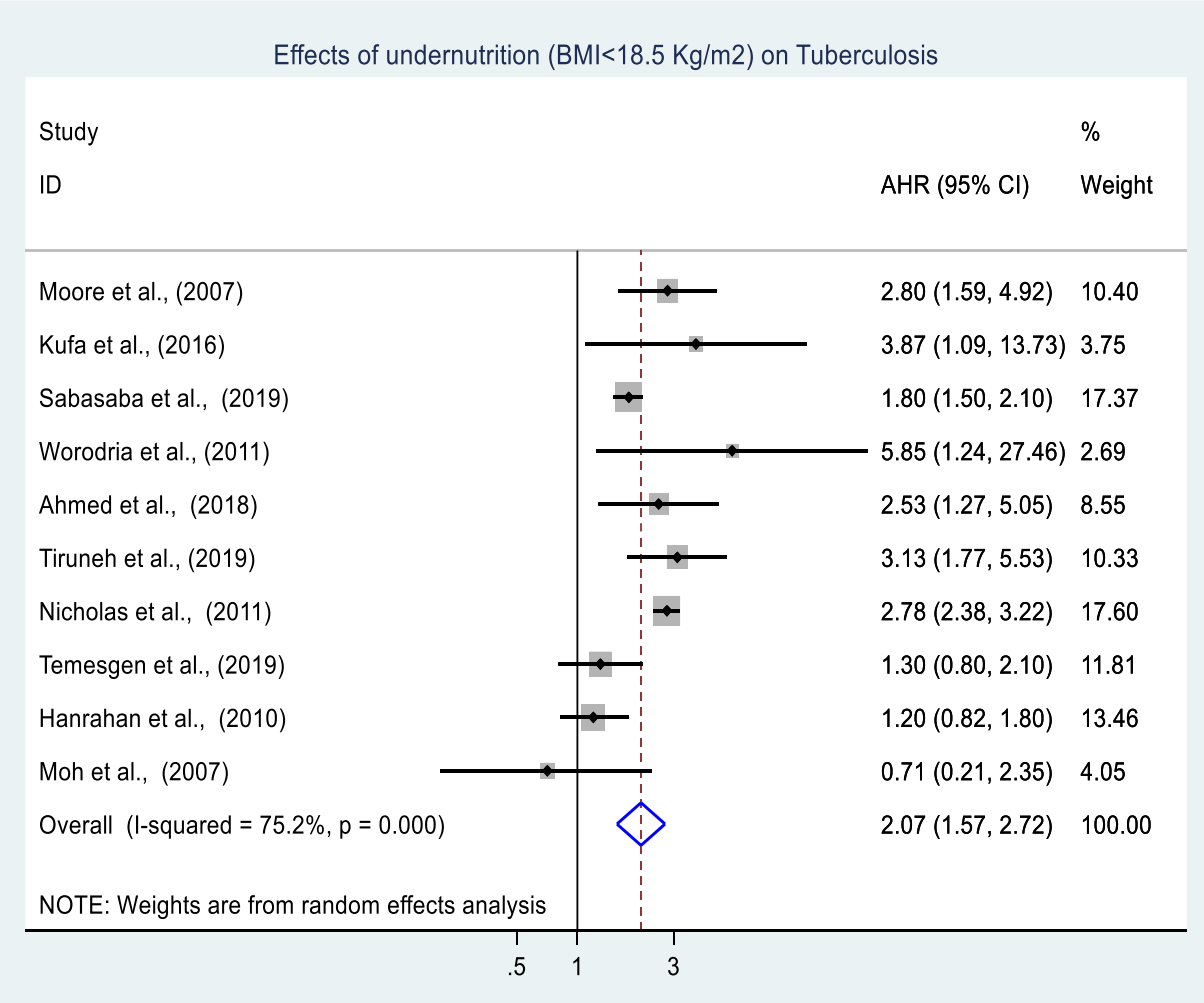

Figure 9. Forest plot of the effects of undernutrition on TB among adults living with HIV in SSA.

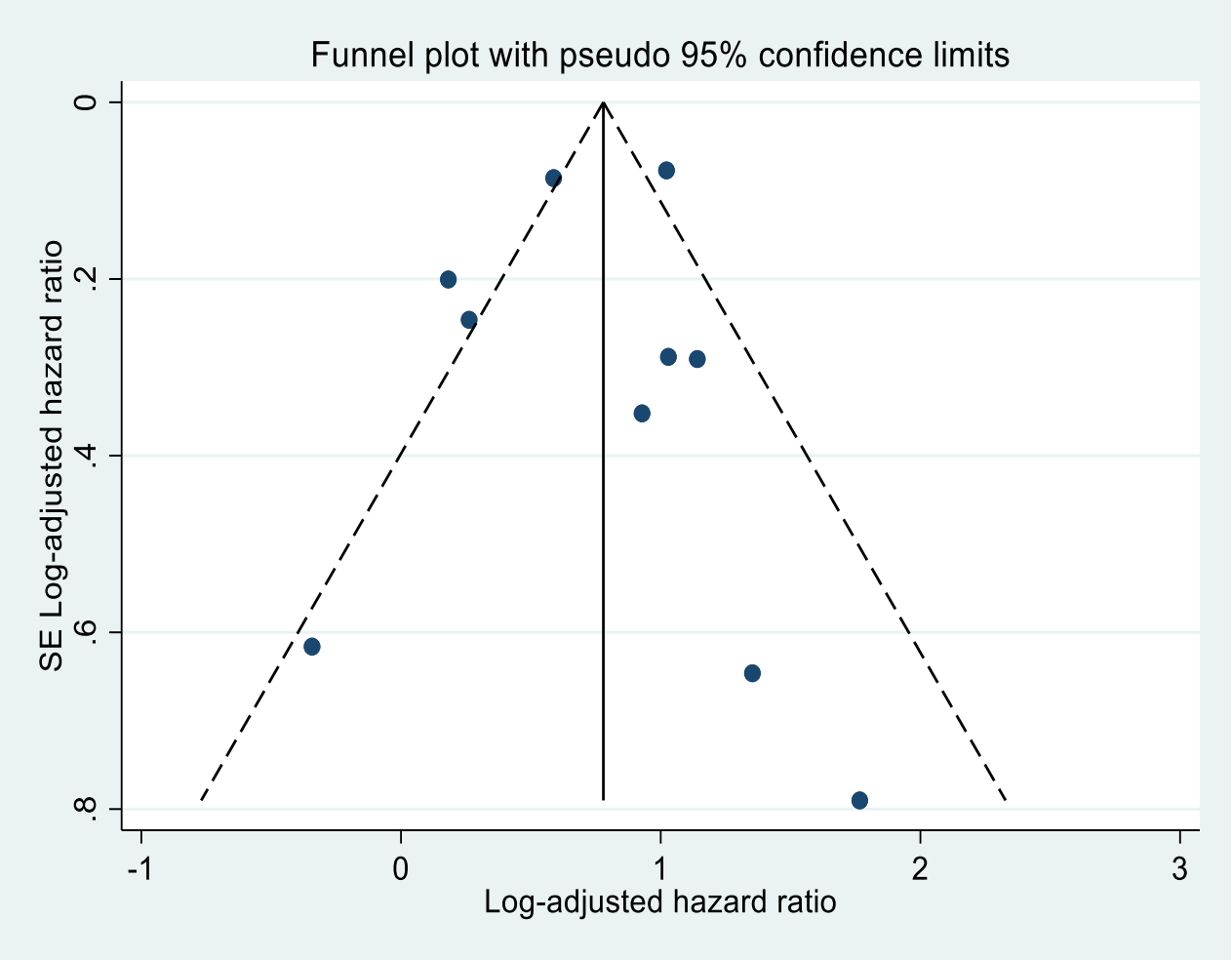

Figure 10. Funnel plot of the effects of undernutrition on TB among adults living with HIV in SSA.

Subgroup analyses of effects of undernutrition on TB

Subgroup analyses were performed based on geographical locations, sample size, and year of publication. Our subgroup analyses indicated that undernutrition has a higher effect (AHR: 2.2, 95% CI: 1.6: 2.9) on the occurrence of TB among adults living with HIV in studies done in Eastern Africa as compared to other parts of SSA. Interestingly, insignificant heterogeneity (I^2 =51%, p-value = 0.069) was observed between studies conducted in Eastern Africa. The subgroup analysis based on publication year and sample size found no significant difference in undernutrition's effect on the occurrence of TB among adults living with HIV. However, a considerable heterogeneity difference was observed across these factors (Table 6).

Table 6. Subgroup analyses of the effect of undernutrition on TB among adults living with HIV in SSA, between 2002 and 2019.

Variables	Subgroup	No of studies	Population (N)	AHR (95%CI)	(I^2 (%) and Cochrane chi-squared test p-value)
Geographical locations	Eastern Africa	6	71, 182	2.2 (1.6, 2.9)	51, 0.069
	Other countries	4	33, 205	1.8 (0.9, 3.5)	84.9, <0.001
Sample size	≥ 1, 000	4	101, 199	2.02 (1.4, 2.9)	87.8, <0.001
	< 1, 000	6	3, 188	2.2 (1.3, 3.6)	56.8, 0.041
Publication year	≤ 2012	5	33, 832	2.02 (1.2, 3.4)	80.7, <0.001
	> 2012	5	70, 555	2.02 (1.5, 2.8)	46.8, 0.111

Discussion

Despite encouraging recent scale-up of ART, nutrition-related early mortality from HIV is a persistent concern in SSA. Therefore, this systematic review and meta-analysis aimed to estimate the pooled effects of undernutrition on mortality and morbidity among adults living with HIV in SSA. To the best of our knowledge, this review is the first of its kind. The findings of this review highlighted that undernutrition significantly increases the risk of mortality and morbidity in adults living with HIV in SSA, and that, as the degree of undernutrition became more severe, mortality rate also increased.

The overall pooled estimate of 23 cohort studies involving 125,790 adults living with HIV indicated that undernourished adults living with HIV were two times (AHR: 2.1, 95% CI: 1.8, 2.4) more likely to die as compared to their well-nourished counterparts. Different mechanisms could explain the observed association between undernutrition and mortality. Undernutrition significantly impairs the immune response, which could increase the risk of developing and recurrence of OIs in the early phase of ART and ultimately contributing to early mortality. There is evidence that malnutrition adversely affects both innate and adaptive immunity systems, which are essential for defence against infections (Hughes & Kelly, 2006). OIs are the leading cause of mortality among PLHIV, being responsible for more than 94% of AIDS-related deaths (Candiani et al., 2007; Mermin et al., 2008).

Another mechanism explaining the effect of undernutrition on mortality could be due to its impact on the adherence level of ART. Different studies revealed that undernutrition is significantly associated with poor ART adherence levels (Berhe et al., 2013; Young et al.,

2014). The effectiveness of HIV treatment depends on ART drug adherence. PLHIV are recommended to take their medications continuously and daily (Iacob et al., 2017) as ART drug adherence is the proximal predictor of mortality (Biset Ayalew, 2017; Rai et al., 2013). An additional possible explanation for the observed effect of undernutrition on mortality might be due to its impact on ART treatment failure (Ahmed et al., 2019). PLHIV, who had a history of treatment failure or not taking their ART drug properly, are at higher risk of death as compared to those who had good treatment response or good adherence level to their ART drugs (Pettersen et al., 2015; Pujades-Rodriguez et al., 2010).

This review found that, as the degree of undernutrition became more severe, mortality rate also increased. This dose-response relationship of undernutrition and mortality could result from the severity of malnourishment increasing the occurrence of OIs, which are the leading cause of mortality among PLHIV (França et al., 2009). It is postulated that malnutrition and infection are interrelated in a vicious cycle (Scrimshaw, 2003). Infections contribute to malnutrition through different means: increased metabolic demand, loss of appetite, and decreased absorption. On the contrary, malnutrition increases the risk of infections by causing immune deficiency, resulting in the persistence of malnutrition as the most common cause of immunodeficiency (França et al., 2009; Walson & Berkley, 2018).

The second outcome of this review demonstrated that undernutrition significantly increased the risk of developing morbidities among adults living with HIV. A meta-analysis of ten cohort studies involving 104,387 adults living with HIV showed that undernourished adults living with HIV were twice as likely to develop TB as compared to their well-nourished counterparts. Our finding is in line with a systematic review of cohort studies, which reported that a higher risk of TB was observed among adults with BMI < 18.5 kg/m^2 (Lonnroth et al., 2010). This finding might be due to malnutrition's weakening of the immune system and the concomitant increased risk of comorbidities including TB infections (Bourke et al., 2016).

The relationship between malnutrition and TB has been well documented (Padmapriyadarsini et al., 2016). The bidirectional relationship is more accentuated among adults living with HIV, because HIV further weakened the immune system and increased the risk of TB. Evidence suggests that malnutrition increases the risk of disease progression from latent TB to active TB by weakening the immune system among adults living with HIV (Chandrasekaran et al., 2017). Besides, food insecurity may delay the health-seeking behaviour, which results in late diagnosis and poor treatment adherence of TB (Gupta et al., 2009). This problem is more severe

in SSA, where 68% of the PLHIV in 2018 lived (UNAIDS, world AIDS day 2019; World Health Organization, 2018), and 23.2% of the world's food-insecure people in 2015 lived (FAO, 2015). On the other hand, TB can cause loss of appetite, malabsorption, and increase metabolic demand (World Health Organization, 2013).

Finally, subgroup analyses confirmed that undernutrition appears to have a more deleterious effect on the occurrence of TB among adults living with HIV in Eastern Africa as compared to other parts of SSA. The possible explanation for this variance might be due to the economic differences across included countries. Likewise, the studies included in Eastern Africa were obtained from Ethiopia, Tanzania, and Uganda. According to the 2019 World Bank report, all three countries were classified as low-income (United Nations, 2019). Even though the clear association is not well known, poverty is widely recognized as the leading risk factor for TB (Young et al., 2014). Moreover, the accentuated effect of undernutrition on TB could be due to the clinical profile of the participants included in primary studies. As an example, more than half (54.6%) of the participants involved in an Ethiopian study were classified as WHO clinical stage III and IV (Ahmed et al., 2018). Furthermore, about 44.5% of the participants involved in a Tanzanian study were classified as WHO clinical stage III and IV (Sabasaba et al., 2019). The more advanced HIV/AIDS disease stage coincides with the increased occurrence and the recurrence of OIs, including TB (Zanoni & Gandhi, 2014). According to the recent Ethiopian National ARV treatment guidelines, adults living with HIV presenting with pulmonary TB are classified as WHO stage III and with extra pulmonary TB are classified as WHO stage IV (Ministry of Health Ethiopia, 2017).

What does this study add to what is known?

Although different clinical trials showed nutritional interventions have no effect on mortality (Filteau et al., 2015; França et al., 2009; Mallewa et al., 2018), the lancet HIV commentary paper strongly recommended that nutritional supplementations for patients on ART should be continued because it could increase body weight, hasten physical and functional recovery, and improve work capacity and quality of life (PrayGod et al., 2018). Similarly, the WHO recommends that severely undernourished adults living with HIV should be treated with therapeutic foods. Moderately undernourished adults living with HIV can be treated with supplementary foods. Besides, nutritional assessments for PLHIV should be done regularly (World Health Organization, 2008a). Although undernutrition is the proximal risk factor increasing mortality and morbidity among adults living with HIV (Lawn et al., 2008), a

comprehensive review estimating the effects of undernutrition on mortality and morbidity in this vulnerable population in SSA is lacking. Our results showed that undernutrition increased the risk of death and TB among adults living with HIV by two-fold. For policy makers and program planners, highly credible evidence obtained from systematic reviews and meta-analyses are vital. Therefore, findings from this review may be used to update the nutritional guidelines used for the management of PLHIV by different stakeholders, especially in limited-resource settings.

Strengths and limitations

There are a number of strengths with this review. An extensive search strategy was undertaken. Explicit inclusion and exclusion criteria regarding population, exposure, control, and outcomes were used. Three authors were involved in the quality assessment. A homogenous exposure category (BMI < 18.5 kg/m^2) was used rather than including studies that used different categories for the meta-analysis. Attempts were made to control the confounders by taking the AHR for the meta-analysis. Since the included studies exhibited considerable heterogeneity, advanced statistical analyses such as meta-regression were performed to identify possible heterogeneity sources. Most of the included studies used measured weight and height to calculate BMI from medical records rather than self-reported weight and height thereby avoiding recall biases.

Despite the above-mentioned strengths, this review has some constraints that must be considered before interpreting results. This review included some studies with small sample sizes, potentially influencing findings. Our search limited to studies published in the English language, which may have resulted in the exclusion of a few essential studies. Many studies reported BMI in different categories making it difficult to include all studies in our meta-analysis. However, this variance has been addressed through subgroup analyses and qualitative analysis. Despite the use of AHR for our meta-analysis, most of the included primary studies used retrospective data. Thus, these studies did not include some important nutritional variables like socioeconomic status and dietary diversity. Furthermore, undiagnosed acute diseases could confound the actual effect of undernutrition on mortality. This review included studies reported from 13 SSA countries and six multicounty based studies, which may yield underrepresentation of other SSA countries. Lastly, the majority of included studies used baseline BMI, but it changed continuously over time. Therefore, this result may not reflect the actual effects of malnutrition on mortality and morbidity.

Conclusion

This review found that undernutrition has significant effects on mortality and morbidity among adults living with HIV**.** As the degree of undernutrition became more severe, mortality rate also increased. Based on our findings, we recommended that nutritional assessment among adults living with HIV needs to be done regularly. Moreover, early screening of morbidities like TB among undernourished adults living with HIV is recommended. Furthermore, besides the management of malnutrition, comprehensive nutritional counselling to improve diet by consuming locally available needs to be reinforced at each visit for HIV care. Further studies are needed to examine the impact of nutritional interventions to improve nutritional status on mortality and morbidities among adults living with HIV. Finally, further follow-up studies considering malnutrition as exposure variable are needed to examine its actual effects on mortality and morbidities.

List of abbreviations

AHR: Adjusted hazard ratio, **AIDS: Acquired Immunodeficiency Syndrome, ART**: Antiretroviral Therapy, **BMI**: Body mass Index, **CI**: Confidence Interval, **HAART**: Highly Active Antiretroviral Treatment, **HIV: Human Immunodeficiency Virus, LMICs**: Low and Middle-income Countries, **NOS**: Newcastle-Ottawa scale, **OIs**: Opportunistic Infections, **PLHIV**: People Living with Human Immunodeficiency Virus, **SSA**: Sub-Saharan Africa, **TB**: Tuberculosis, and **WHO**: World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The data sets used and/or analysed for this review are available from the corresponding author on reasonable request.

Competing interests

The authors have declared that they have no competing interests.

Funding

Funding was not available for this study.

Authors' contributions

AA: Conception of research protocol, study design, literature review, quality assessment, data extraction, data analysis, interpretation and drafting the manuscript. DD and DS: Conception of research protocol, study design, quality assessment, reviewing and editing the manuscript. PP: Interpretation of the data, reviewing, and editing the manuscript. All authors have read and approved the manuscript.

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4.3. Chapter summary

This chapter described the findings of a published systematic review and meta-analysis that determined the overall effects of undernutrition on mortality and morbidity among adults living with HIV in SSA using 53 primary studies. The findings suggested that undernutrition significantly increased the risk of mortality and morbidity among adults living with HIV in SSA. The study also showed that as the degree of undernutrition became more severe, the mortality rate also increased. The following chapter presents the results of a cohort study examining the effects of undernutrition on LTFU among ALVIH. Moreover, a published systematic review protocol examining the impact of undernutrition on LTFU among ALVIH in SSA is also included as a supplementary paper.

Chapter 5 │The effect of undernutrition on LTFU among ALHIV on ART in Ethiopia

5.1. Chapter introduction

This chapter included two published articles (one systematic review protocol (Manuscript II) and one original study (Manuscript III). However, the chapter mainly describes the findings from the original study (Manuscript III). The study included the records of 844 ALHIV receiving ART to address the second objective. This manuscript is published and available in *Scientific Reports*. Moreover, a published (*BMJ Open)* systematic review and meta-analysis protocol is also included as a supplementary article to Manuscript III. The protocol is designed to examine the effect of undernutrition on LTFU among adults living with HIV in the context of SSA.

5.2. Publication (Published in *BMJ Open*):

Peer review process:

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Authors' contributions for this study

The candidate is the primary author of this manuscript and conceived the review protocol, designed the study methodology, drafted and revised the protocol, and designed the statistical analyses plan. The second and fourth authors were involved in developing the review protocol, reviewing and editing the protocol, and reviewing the statistical analyses plan. The third author was involved in reviewing and editing the manuscript.

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Authors' contributions for this study

The candidate is the primary author of this manuscript and was involved in the conception of the research idea, designing, data analysis, interpretation, and drafting of the manuscript. The second, third, and fourth authors participated in designing, interpreting results, and reviewing and editing the manuscript.

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

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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 (BMI< 18.5 kg/m^2) is one of the main factors that significantly increases the risk of loss 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 summarize 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 (NOS) will be used for quality assessment. Data from eligible studies will be extracted using a standardized data extraction tool. Heterogeneity between included studies will be assessed using Cochrane Q-test and I^2 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 hazard ratio (AHR) 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.

Keywords: Adults living with HIV, loss to follow up, sub-Saharan Africa, undernutrition

Strengths and limitations of the 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 LTFU among adults living with HIV in SSA.
- 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 hazard ratio to control for potential confounding factors.
- The protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) 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.

Introduction

Human immunodeficiency virus (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) (World Health Organisation, 2020). Though there is no cure for HIV, antiretroviral (ARV) drugs can suppress viral replication and reduce or eliminate HIV transmission risk (Günthard et al., 2016). ARV also assists people living with HIV (PLHIV) to live comparably healthy (Mayer & Venkatesh, 2010). 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 (Fauci & Eisinger, 2018). Globally, access to ART has increased dramatically from 7% in 2005 to 67% in 2019 (World Health Organisation, 2019, 2020).

ART is a daily medication (Brinkhof et al., 2009; Deeks et al., 2013), requiring a lifelong commitment to be effective (Hughes et al., 2014). Loss 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 (World Health Organization, 2008b). It has become an emerging problem in many low- and middle-income countries (LMICs), including SSA (Fox & Rosen, 2015; Levi et al., 2016). 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 (Fox & Rosen, 2015). An additional meta-analysis from SSA has shown that up to 40% of patients were LTFU or died (Rosen et al., 2007). PLHIV lost to ART are at higher risk of treatment failure, viral rebound, mortality, and opportunistic infections (OIs) (Luebbert et al., 2012; Schaecher, 2013). 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))(Berheto et al., 2014; Hassan et al., 2015; Karcher et al., 2007; Megerso et al., 2016;

Mutasa-Apollo et al., 2017; Ochieng-Ooko et al., 2010; Seifu et al., 2018; Siril et al., 2017; Takarinda et al., 2015).

Undernutrition is considered a marker for poor prognosis among PLHIV, particularly in SSA, where both undernutrition and HIV are highly prevalent (Süttmann et al., 1995). 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.(Food and Agriculture Organization of the United Nations, 2019; UNAIDS, 2019a) Undernutrition is characterized by a deficit in macronutrients and/or micronutrients, leading to body composition changes and diminished function (Seres, 2005; Soeters et al., 2008). HIV and undernutrition are interrelated. HIV reduces food intake, reduces nutrient absorption, and increases energy requirements (Dikman et al., 2015; Duggal et al., 2012; Lisa Kosmiski, 2011). At the same time, undernutrition hastens disease progression and increases the occurrence and recurrence of OIs (De Pee & Semba, 2010; Duggal et al., 2012). Undernutrition significantly increases the risk of mortality, treatment failure, and LTFU among PLHIV (Ahoua et al., 2011; Geng et al., 2013; Gupta et al., 2011; Naidoo et al., 2018; Otwombe et al., 2014; Silverman et al., 2019; Tchounga et al., 2016; Tesfamariam et al., 2016).

Studies have shown that undernutrition (i.e. BMI <18.5 kg/m^2) is one of the main factors that significantly increases the risk of LTFU among adults living with HIV (Bernard et al., 2018; Hønge et al., 2013; Kalinjuma et al., 2020; Mekonnen et al., 2019; Teshome et al., 2015; Tweya et al., 2018). 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 (Kiwanuka et al., 2020). 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 (Alebel et al., 2021). 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 (Opio et al., 2019). Additional study from Uganda has reported that overweight (BMI >30 kg/m^2) patients living with HIV are at lower risk of LTFU compared to well-nourished patients living with HIV (Kiwanuka et al., 2020).

There have been extensive primary studies on the relationship between undernutrition and LTFU among adults living with HIV in SSA (Bernard et al., 2018; Hønge et al., 2013; Kalinjuma et al., 2020; Kiwanuka et al., 2020; Mekonnen et al., 2019; Moyo et al., 2016; Opio et al., 2019; Teshale et al., 2020; Teshome et al., 2015; Tweya et al., 2018; Vinikoor et al.,

2014; Wekesa et al., 2020). However, these individual studies have reported inconsistent findings. Some studies showed that undernutrition significantly increases the risk of LTUF among adults living with HIV (Bernard et al., 2018; Hønge et al., 2013; Kalinjuma et al., 2020; Mekonnen et al., 2019; Teshome et al., 2015; Tweya et al., 2018). Conversely, a few studies found that undernutrition and LTFU among adults living with HIV have no significant association (Tweya et al., 2018). Estimating the pooled effect of undernutrition on LTFU among adults living with HIV is important to provide evidence for healthcare workers and policymakers in designing specific interventions to minimize undernutrition related LTFU among adults living with HIV. However, to the best of our knowledge, there is no systematic review and meta-analysis, which summarized 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 loss to follow-up among adults living with HIV in SSA?

The PICO framework:

- ✓ **P**articipants/population: adults (aged ≥ 15 years) living with HIV
- ✓ **I**ntervention(s)/exposure(s) group: undernourished adults living with HIV
- ✓ **C**omparator(s)/control group: well-nourished adults living with HIV
- ✓ **O**utcome(s) of interest: loss to follow-up 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-P) checklist (Appendix 5.1) (Shamseer et al., 2015). The following databases will be searched: PubMed, EMBASE (Elsevier), Web of Science, Scopus, and, for grey literature, Google Scholar (Appendix 5.2) 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 hazard ratio (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 (Ververs et al., 2013). Articles including only malnourished adults living with HIV will also not be considered for this review due to a lack of controls (i.e., well-nourished adults living with HIV).

The primary author (Animut Alebel (AA)) will assess the titles and abstracts of potentially relevant studies. Then, two reviewers, (AA and Daniel Demant (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 11.

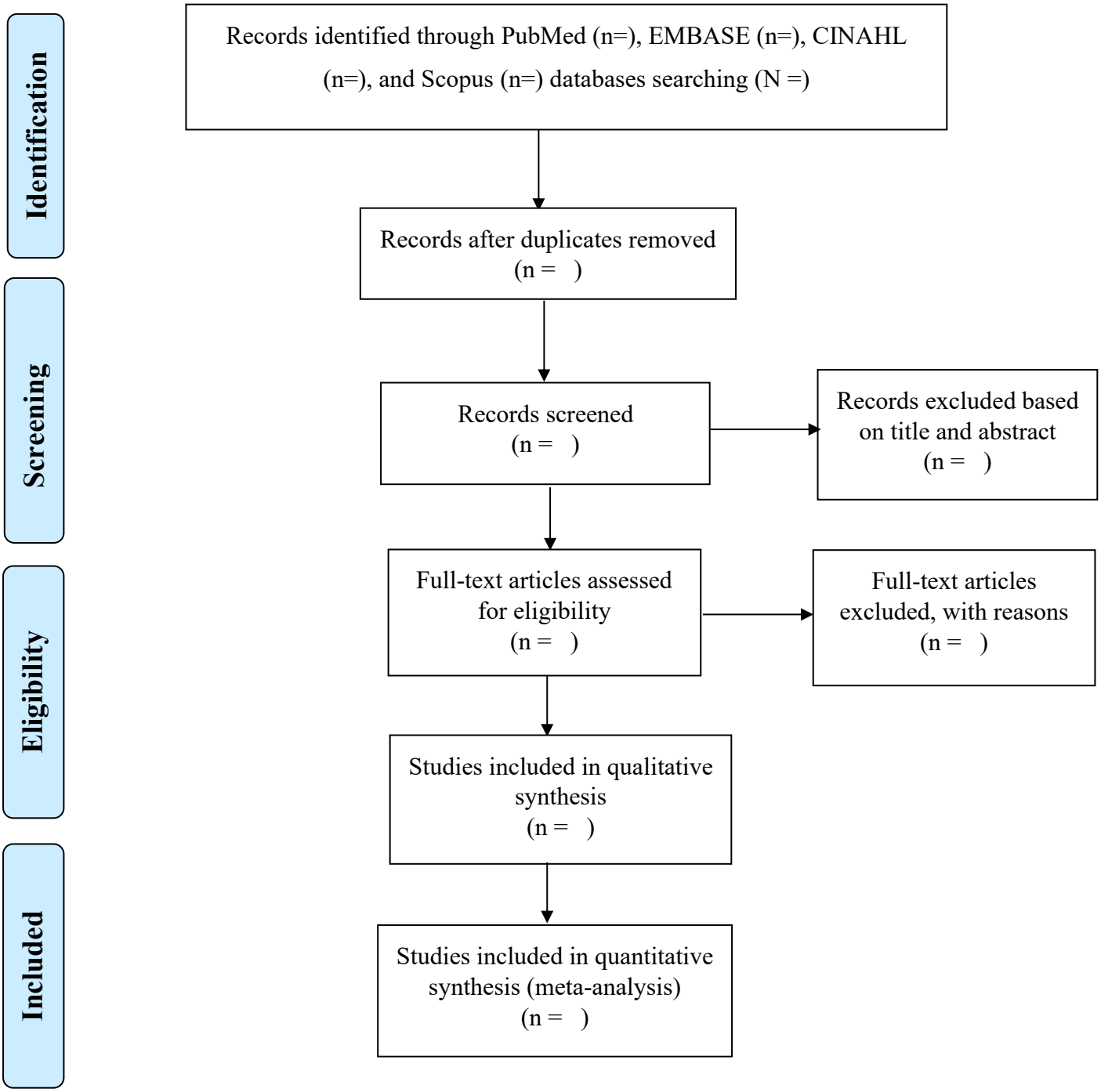

Figure 11. Flow chart of study selection for a systematic review and meta-analysis of the effect of undernutrition on LTFU in adults living with HIV in SSA.

Data extraction and management

A standardized data extraction tool will be adapted from the Joanna Briggs Institute (JBI).(Peters et al., 2019) 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 (i.e., sex, residence, age, distance from health facility, ART regimen, functional status, CD4 cell count, WHO clinical staging, ART adherence, opportunistic infections (OIs), cotrimoxazole preventive therapy (CPT), and isoniazid preventive therapy (IPT)), and adjusted hazard ratio (AHR) for time-to-event analysis/adjusted odds ratio (AOR)/ adjusted risk ratio (ARR) with 95% confidence intervals (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 (World Health Organization, 2008b). 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 body mass index (BMI) of less than 18.5 kg/m^2. The severity of undernutrition is further classified as severe (BMI < 16 kg/m^2), moderate (BMI 16-16.99 kg/m^2), or mild (BMI 17-18.48 kg/m^2) (Purnell, 2018).

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 (Peterson et al., 2011). The NOS is a validated tool with grading from zero to nine for case-control and cohort studies (Luchini et al., 2017). 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 cofounding handling mechanisms, which is

scored from zero to three stars. Furthermore, to minimize the subjective interpretation of bias from scoring the NOS, three reviewers (AA, DD, and David Sibbritt (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™ (version 16) statistical software. The effect of undernutrition on LTFU will be estimated using the AHR by considering undernutrition as exposure variable. Relative risks, rate ratios, and incidence density ratios will be directly used as hazard ratios. Adult HIV patients with BMI $\geq$ 18.5 kg/m^2 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 (Kleinbaum et al., 2010). 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 (i.e., RR=exp(β)) (Wiest et al., 2015). The effect size (pooled AHR) will be estimated based on two nutritional status categories (undernutrition versus 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 odds ratios 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 I^2 statistics. The I^2 value will be interpreted as: 0% to 40% (might not be important); 30% to 60% (may represent moderate heterogeneity; 50% to 90% (may represent substantial heterogeneity); and 75% to 100% (considerable heterogeneity) (Cumpston et al., 2019). As heterogeneity is anticipated, the pooled effect size and 95% confidence interval 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 ($I^2 \geq 75\%$) 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 (Sutton et al., 2000). The Egger's and Begg's tests at a 5% significance level will be used to confirm publication bias (Lin & Chu, 2018). 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 (Fauci & Eisinger, 2018; Fox & Rosen, 2015; Levi et al., 2016). Evidence shows that undernutrition significantly increases the risk of LTUF among living with HIV (Bernard et al., 2018; Hønge et al., 2013; Kalinjuma et al., 2020; Mekonnen et al., 2019; Teshome et al., 2015; Tweya et al., 2018). Therefore, understanding the impact of undernutrition on LTFU is essential in designing appropriate interventions. However, there is no systematic review and meta-analysis summarizing 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 synthesize 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 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009). 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. Not all studies included in our systematic review might 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.

Authors' contributions

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. **PP**: Critically reviewed the protocol and made revisions. All authors read and approved the final manuscript.

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Competing interests: The authors declare that they have no competing interests**.**

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Undernutrition increased the risk of loss to follow-up among adults living with HIV on ART in Northwest Ethiopia: A retrospective cohort study

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Abstract

This study aims to examine the effect of undernutrition on loss to follow-up (LTFU) in adults living with human immunodeficiency virus (HIV) receiving antiretroviral therapy (ART) in Ethiopia. We conducted an institution-based retrospective cohort study using medical records of 844 adults living with HIV receiving ART between June 2014 and June 2020 at Debre Markos Comprehensive Specialized Hospital (Northwest Ethiopia). The effect of undernutrition on LTFU was examined using a proportional hazards regression model after adjusting potential confounders. The significance level was set at $p < 0.05$. At the end of the study period, 109 (12.9%) participants were considered LTFU, with an overall LTFU incidence of 5.3 per 100 person-years (95% CI: 4.4, 6.4). The incidence of LTFU was higher in undernourished participants (8.2 per 100 person-years) compared to well-nourished participants (4.3 per 100 person-years). After adjusting for potential confounders, the adjusted risk of LTFU among undernourished participants was two times higher than in their well-nourished counterparts (AHR [adjusted hazard ratio]: 2.1, 95% CI: 1.4, 3.2). This study found that undernutrition significantly increased the risk of LTFU among adults living with HIV on ART.

Introduction

Although the human immunodeficiency virus (HIV) is a global public health concern, sub-Saharan Africa (SSA) is the most affected region. Of the 37.7 million people living with HIV (PLHIV) worldwide in 2020, more than two-thirds (67%) were from SSA (UNAIDS, 2020). Ethiopia is one of the SSA countries with a high prevalence of HIV (Central Statistical Agency of Ethiopia (CSA), 2016). Although there is no cure for HIV infection, antiretroviral therapy (ART), a combination of three or more antiretroviral drugs, enables PLHIV to live longer, healthier lives (World Health Organisation, 2021b). Since 2016, all PLHIV have been eligible to start ART as soon as possible, regardless of their clinical status (World Health Organisation, 2021b). As of December 2020, 25.7 million (73%) PLHIV were on ART worldwide (UNAIDS, 2020).

Despite the dramatic increase in access to ART, high rates of loss to follow-up (LTFU) remain a significant challenge, especially in resource-limited settings, with HIV-care related LTFU emerging as a public health issue in low- and middle-income countries (LMICs) (Fox & Rosen, 2015; Levi et al., 2016) including SSA (Akilimali et al., 2017). A collaborative analysis has

shown that 18.8% of adults living with HIV in SSA were lost to ART follow-up (Haas et al., 2018). A systematic review and meta-analysis from Ethiopia found that LTFU among adults living with HIV was 15.2% throughout follow-up (Abebe Moges et al., 2020). LTFU has been associated with various unfavourable treatment outcomes, such as frequent hospitalizations, high risk of treatment failure, high rate of mortality, and high risk of opportunistic infections (OIs) (Schaecher, 2013). SSA based studies have shown that the most common risk factors of LTFU in adults living with HIV are poor ART adherence, being younger, being male, not disclosing HIV-status, advanced World Health Organization (WHO) clinical disease stage (III and IV), low CD4 cell count, not taking co-trimoxazole preventive therapy (CPT), not taking isoniazid preventive therapy (IPT), and being undernourished (Kalinjuma et al., 2020; Megerso et al., 2016; Sifa et al., 2019; Takarinda et al., 2015; Teshale et al., 2020).

Various studies conducted in Africa have shown that undernutrition is significantly associated with a higher risk of LTFU in adults living with HIV receiving ART (Bernard et al., 2018; Hønge et al., 2013; Kalinjuma et al., 2020; Tweya et al., 2018; Wekesa et al., 2020). Undernutrition may indirectly increase the risk of LTFU as it accelerates disease progression from HIV to acquired immunodeficiency syndrome (AIDS) and increases the occurrence and recurrence of OIs (De Pee & Semba, 2010; Duggal et al., 2012). Undernourished patients may not return to the health facility for ART refill and miss their appointments due to frequently being sick or feeling generally unwell (Opio et al., 2019). Furthermore, a Ugandan study also showed that overweight (BMI >30 kg/m^2) participants are at lower risk of LTFU (Kiwanuka et al., 2020). This could be explained as being overweight is the leading risk factor of non-communicable diseases (NCDs), especially hypertension and diabetes (World Health Organisation, 2021c). Overweight HIV-infected patients may benefit from the program, as regular health education on medication adherence is a component of care for patients with NCDs (Correia et al., 2019).

The United Nations Sustainable Development Goal (SDG #3) aimed to end the epidemic of HIV/AIDS by 2030 (Sachs, 2012). To meet this ambitious target, optimizing retention in ART care is an effective strategy. In line with this agenda, the Ethiopian government has adapted various strategies to reduce LTFU in PLHIV, such as adherence support through phone calls and tracing patients who have missed their appointments. Despite these interventions, LTFU from ART is still a significant challenge for health care professionals. As mentioned above, undernutrition is one of the main factors significantly associated with LTFU among PLHIV.

Understanding the impact of undernutrition on LTFU is essential for designing and implementing evidence-based interventions. However, studies examining the actual impact of undernutrition on LTFU in this population are scarce in SSA, and none has been conducted in Ethiopia. Thus, this study aimed to examine the impact of undernutrition on LTFU in adults living with HIV receiving ART by considering undernutrition as an exposure variable. The findings of this study will help clinicians to develop targeted interventions to reduce undernutrition related LTFU. It will also inform further interventional studies.

Methods

Study design, area, and period

This study used a part of data came from a large retrospective cohort study conducted to examine the effects of undernutrition on treatment outcomes among adults living with HIV on ART between June 2014 and June 2020 at Debre Markos Comprehensive Specialized Hospital (DMCSH), Northwest Ethiopia. Therefore, the detailed methodology was described in our previously published two papers (Alebel et al., 2022a; Alebel et al., 2022b). DMCSH is the only referral hospital in the East Gojjam Zone in the Amhara Region, located 300 km from Addis Ababa, the capital of Ethiopia, and 255 km from Bahir Dar, the capital of the Amhara region. It serves over 3.5 million people in East Gojjam Zone and neighbouring zones. The hospital commenced offering chronic HIV care and ART services in 2005. Out of the total 1,209 PLHIV who started ART at DMCSH between June 2014 and June 2020, 1,177 (97.4%) were adults. Adulthood was defined as patients' ≥ 15 years of age since this population is considered and treated as adults in Ethiopia for treatment purposes.

Study participants

The study population was all adults living with HIV who started ART at DMCSH between June 2014 and June 2020 and received ART for at least one month. All patients aged 15 years or older were defined as adults, consistent with the Ethiopian ART treatment guidelines (Ministry of Health Ethiopia, 2017). Patients were excluded from the study if they were transferred to DMCSH without baseline information and without a recorded date for the outcome of interest (LTFU). Furthermore, pregnant women were excluded as the nutritional assessment is different from other HIV-positive adults (Ververs et al., 2013).

Sample size and sampling procedures

The minimum required sample size was determined using an independent cohort study formula and calculated using Open Epi Version 3 (Kelsey et al., 1996). Undernourished participants were considered as the exposed group, and their well-nourished counterparts were considered as the unexposed group. The following parameters were taken into consideration: proportion of unexposed (well-nourished) group with lost to follow-up (P_0 = 19%); proportion of exposed (undernourished) group with lost to follow-up (P_1 = 27%); r of 1:1; α of 5%; power of 80%; and $Z_{\alpha/2}$ of 1.96. The P_0 and P_1 values were taken from a previous Ethiopian study (Teshale et al., 2020). The sample size calculated based on the above parameters was 802. Allowing for 10% contingency, the records of 892 study participants were selected from the total records of HIV-positive adults who started ART at DMCSH between June 2014 and June 2020 (n =1,177) using a computer-generated simple random sampling technique. Initially, a list containing the medical registration number (MRN) of all adults living with HIV initiated ART between June 2014 and June 2020 was obtained from the health management information system unit of the DMCSH. Then, a random number was generated for each patient using Microsoft™ Excel. Lastly, randomly generated numbers were used to select a sample of 892 participants from all adults living with HIV who started ART at DMCSH between June 2014 and June 2020. The final sample included 844 records after 48 records were excluded (see Figure 12).

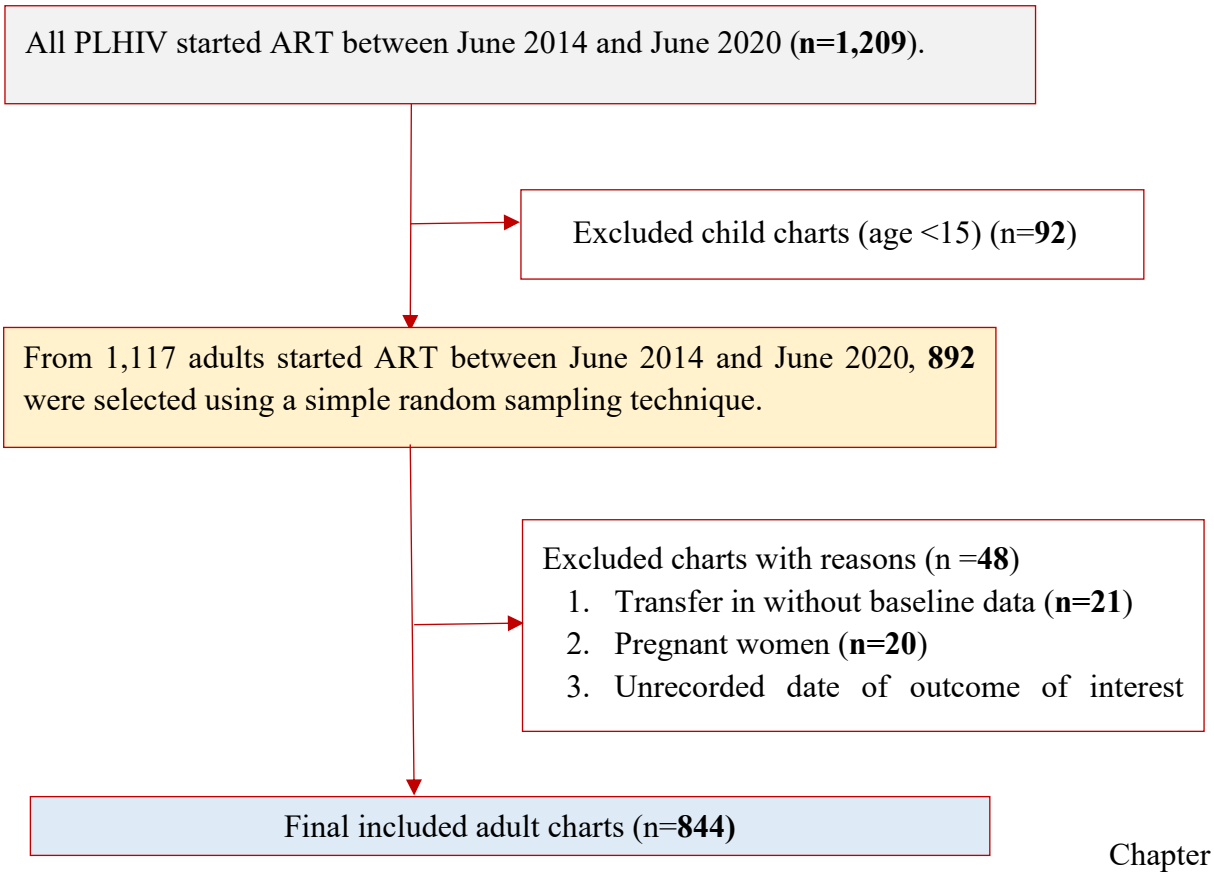

Figure 12. Study participants' recruitment process to assess the effect of undernutrition on loss to follow-un at Debre Markos Comprehensive Specialized Hospital in Northwest Ethiopia, between June 2014 and June 2020.

Data collection and quality control

Data from the medical records of HIV patients were extracted using a standardized data extraction checklist developed using the current Ethiopian ART treatment guidelines. The data extraction checklist included sociodemographic characteristics, clinical and immunological characteristics, and follow-up characteristics. Variables included in the sociodemographic characteristics were age, sex, marital status, level of education, occupation, residence, HIV-status disclosure, and family size. Clinical and immunological variables included baseline OIs, nutritional status, functional status, CD4 cell counts, WHO clinical staging, and haemoglobin (Hgb) level. Variables extracted from the follow-up data included ART eligibility criteria, ART regimen, OIs during follow-up, ART adherence, regimen change, CPT, IPT, treatment failure, and patient outcomes. Sociodemographic measurements recorded at ART initiation were considered as baseline data. However, for other variables, such as laboratory tests, the most recent values were used as predictors. Two epidemiologists specialized in HIV currently working at DMCSH were recruited as data collectors.

Outcome of the study

The outcome of this study was the occurrence of loss to follow-up (LTFU) after ART initiation. LTFU was defined as patients missing an ART appointment for at least one month (Ministry of Health Ethiopia, 2017). At the end of follow-up, participants were classified as event (lost) or censored (not lost). Censored was considered when participants died or were still alive under ART at the end of follow-up (30th of June 2020) or formally transferred to other health facilities. The follow-up time was calculated in months from the date of ART initiation until the date of event (LTFU) or censoring (other than lost).

Expose variable

Undernutrition was diagnosed when participants had a body mass index (BMI) below 18.5 kg/m^2 (Cederholm et al., 2015). All participants (n=227) with a BMI of below 18.5 kg/m^2 were the exposure group of this cohort.

Covariates and operational definitions

Covariates (confounders) included sociodemographic variables, clinical and immunological variables, and follow-up variables, as mentioned in the data collection section.

Residency was classified as urban and rural. Under the Ethiopian Central Statistical Agency (CSA), urban is considered if the local area contains 2,000 or more inhabitants. In addition, urban areas include all administrative capitals of regions, zones, and woredas (districts), with at least 1,000 people primarily engaged in non-agricultural activities or areas that the administrative official declares to be urban (Schmidt & Kedir, 2009). Family size refers to the number of individuals in the family. Family size was classified as < three or ≥ three standards established by previous research (Temesgen et al., 2019).

Disclosure of HIV status was recorded as disclosed and not disclosed. According to current Ethiopian ART guidelines, patients are considered as disclosed their HIV status if they have disclosed their HIV status to at least one person (i.e., sexual partner or family member) (Ministry of Health Ethiopia, 2017). ART adherence was classified as good, fair, or poor, calculated from the total monthly dose of ART drugs (n=60). Good is compliance equal to or greater than 95% or ≤ 3 missed doses per month; fair is defined as 85-94% compliance or between 4 and 8 missing doses per month; and poor as compliance of less than 85% or ≥ 9 missed doses per month (Ministry of Health Ethiopia, 2017).

Functional status was classified as working, ambulatory, and bedridden. Working was defined as being capable of going out of home and do routine activities, including daily work. Ambulatory was defined as capable of self-care and being able to use the toilet unsupported. Bedridden was defined as incapable of basic self-care (i.e., not able to use toilet without support) (Ministry of Health Ethiopia, 2017).

The WHO staging of HIV has four levels to determine the degree of immunodeficiency based on CD4 cell count: no significant immunosuppression (CD4 > 500 cells/mm^3), mild immunosuppression (CD4: 350−499 cells/mm^3), advanced immunosuppression (CD4: 200−349 cells/mm^3), and severe immunosuppression (CD4<200 cells/mm^3) (World Health Organization, 2007). In addition, the WHO has implemented a clinical staging system based on clinical symptoms beyond CD4 cell count (Ministry of Health Ethiopia, 2017) listed herein:

Clinical stage I: Usually asymptomatic, except persistent generalized lymphadenopathy.

Clinical stage II: One of the following clinical presentations is present: moderate unexplained weight loss (5-10% of presumed or measured body weight), recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, and pharyngitis), herpes zoster, angular cheilitis, recurrent oral ulceration, papular pruritic eruption, fungal nail infections, and seborrheic dermatitis.

Clinical stage III: At least one of the following conditions is present: unexplained severe weight loss (>10% of presumed or measured body weight), unexplained chronic diarrhoea > one month, unexplained persistent fever (intermittent or constant > one month), persistent oral candidiasis, oral hairy leucoplakia, pulmonary tuberculosis, severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia), acute necrotizing ulcerative stomatitis, gingivitis or periodontitis, unexplained anaemia, neutropoenia, and/or chronic thrombocytopaenia.

Clinical stage IV: At least one of the following severe conditions is present: HIV wasting syndrome, pneumocystis jirovecii, recurrent severe bacterial pneumonia, chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site), oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs), extra pulmonary tuberculosis, Kaposi sarcoma, cytomegalovirus infection (retinitis or infection of other organs), central nervous system toxoplasmosis, HIV encephalopathy, extra pulmonary cryptococcosis, disseminated non-tuberculous mycobacterial infection, progressive multifocal leukoencephalopathy, chronic cryptosporidiosis, chronic isosporiasis, disseminated mycosis (extra-pulmonary histoplasmosis, coccidioidomycosis), lymphoma (cerebral or B-cell non-Hodgkin), symptomatic HIV-associated nephropathy or cardiomyopathy, recurrent septicaemia (including non-typhoidal salmonella), invasive cervical carcinoma, and atypical disseminated leishmaniasis.

Missing data handling

Data for 208 (24.6%) CD4 cell counts and 50 (5.9%) haemoglobin (Hgb) levels were not available from patient records. Multiple imputation (MI) was undertaken using a multivariate normal imputation model. Before MI, Little's MCAR test (Little, 1988) was performed to check if the values are missing at random (MCAR). Moreover, we checked the patterns and mechanisms of missing values. Variables included in the imputation model were sex, residence, WHO clinical disease staging, ART adherence, nutritional status, baseline OIs, CPT, and IPT.

Finally, diagnostic plots for multiple imputation were employed to assess the distributions of observed, imputed, and completed data (multiple imputation diagnostic test).

Statistical analysis

Chi-square (χ^2) tests were used to compare the frequencies of sociodemographic, clinical, and follow-up characteristics between undernourished and well-nourished groups. The Kaplan-Meier survival curve was used to was used to visualize the survival time of loss to follow-up. A generalized log-rank test was used to compare survival curves between undernourished (exposed) and well-nourished (non-exposed) groups. Bi-variable and multivariable proportional hazards regression models were fitted. The proportionality assumption of the proportional hazards regression model was assessed using the Schoenfeld residual test. In the bi-variable analysis, variables with p-values ≤ 0.25 were included in the multivariable analysis for adjusting confiders. Results from the final model were reported as adjusted hazard ratios (AHRs) with 95% confidence intervals (CIs). The significance level was set at $p < 0.05$. All statistical analyses were carried out using Stata™ Version 16.

Ethics approval and consent to participate

Ethical approvals and permissions were granted from the DMCSH Medical Director's Office, the University of Technology Sydney Medical Research Ethics Committee (ETH20-5044), and the Amhara Regional Public Health Research Ethics Review Committee (Ref. no: 816). All methods were performed in accordance with the relevant guidelines and regulations. As the study was based on existing medical records of PLHIV, participants' verbal or written informed consent was not feasible, and a waiver of consent was granted. Data were entirely de-identifiable for the authors and data collectors, as the data abstraction tool did not include participants' unique ART numbers and names.

Consent for publication

Not applicable

Results

Participants' sociodemographic characteristics

Of the 844 participants included in the final sample, more than three-quarters (78.4%; n=662) were from urban areas. The cohort included 227 (26.9%) undernourished and 617 (73.1%) well-nourished participants. The median age of participants at ART initiation was 32 years

(IQR: 14). More than half (59.0%; n=498) were female, 18.3% (n=154) had never married, and 25.8% (n=218) had attended at least primary school. Homemakers accounted for 16.9% (n=143) of the sample; 66.9% (n=565) had disclosed their HIV-status, and 55.3% (n= 447) were from a family of less than three people (see Table 7).

Table 7. Socio-demographic characteristics of undernourished and well-nourished participants at Debre-Markos Comprehensive Specialized Hospital, Northwest Ethiopia (n=844).

Variables	Undernourished n (%)	Well-nourished n (%)	Total n (%)	p-values
Residence				0.001**
Urban	161(70.9)	501 (81.2)	662 (78.4)	
Rural	66 (29.1)	116 (18.8)	182 (21.6)	
Age (years of age)				0.679
15-24	51 (22.5)	135 (21.9)	186 (22.0)	
25-34	73 (32.2)	208 (33.7)	281 (33.3)	
35-44	69 (30.4)	200 (32.4)	269 (31.9)	
≥45	34 (15.0)	74 (12.0)	108 (12.8)	
Sex				0.018**
Male	108 (47.6)	238 (38.6)	346 (41.0)	
Female	119 (52.4)	379 (61.4)	498 (59.0)	
Marital status				0.002**
Single	56 (24.7)	98 (15.9)	154 (18.3)	
Married	88 (38.8)	303 (49.1)	391 (46.3)	
Divorced	53 (23.4)	163 (26.4)	216 (25.6)	
Widowed	30 (13.2)	53 (8.6)	83 (9.8)	
Level of education				0.665
No formal education	70 (30.8)	186 (30.2)	256 (30.3)	

Primary	56 (24.7)	162 (26.3)	218 (25.8)	
Secondary	66 (29.1)	158 (25.6)	224 (26.6)	
Tertiary	35 (15.4)	111 (18.0)	146 (17.3)	
Occupation				0.003**
Daily labourer	37 (16.3)	102 (16.5)	139 (16.5)	
Merchant	37 (16.3)	130 (21.1)	167 (19.8)	
Farmer	48 (21.2)	70 (11.4)	118 (14.0)	
Employed	41 (18.1)	142 (23.0)	183 (21.7)	
Student	18 (7.9)	29 (4.7)	47 (5.6)	
Homemaker	32 (14.1)	111 (18.0)	143 (16.9)	
Others	14 (6.2)	33 (5.4)	47 (5.6)	
HIV-status disclosure				
Disclosed	155 (68.3)	410 (66.5)	565 (66.9)	0.616
Not disclosed	72 (31.7)	207 (33.5)	279 (33.1)	
Individuals/ household				
<3 individuals	125 (55.1)	342 (55.4)	447 (55.3)	0.925
≥3 individuals	102 (44.9)	275 (44.6)	377 (44.7)	

P-value obtained from chi-square test.

****Significant results from chi-square test.***

Clinical, immunological, and medication-related characteristics

Forty percent (n=337) of patients had at least one opportunistic infection at ART initiation, and most (83.3%; n=703) participants were classified as working functional status. Nearly a third (31.3%; n=264) had severe immunodeficiency, and 43.7% (n=369) were in WHO clinical stage I. the majority (80.2%; n=677) of patients were non-anaemic at ART initiation. More than half (55.5%; n=468) started ART through a test and treat approach. Most participants (89.8%; n=758) started an Efavirenz-based ART regimen, and 31.4% (n=264) had a regimen change

from baseline. CPT and IPT was not received by 26.9% (n=227) and 37.6% (n=317) of participants, respectively. During the study period, 23 (2.7%) patients experienced ART treatment failure, and 267 (31.6%) patients developed OIs (Table 8).

Table 8. Clinical, immunological, and medication-related characteristics of undernourished and well-nourished participants at Debre-Markos Comprehensive Specialized Hospital, Northwest Ethiopia (n=844).

Variables	Undernourished n (%)	Well-nourished n (%)	Total n (%)	p-value
Baseline OIs				< 0.001**
Yes	114 (50.2)	223 (36.1)	337 (39.9)	
No	113 (49.8)	394 (63.9)	507 (60.1)	
Functional status				< 0.001**
Working	160 (70.5)	543 (88.0)	703 (83.3)	
Ambulatory/ bedridden	67 (29.5)	74 (12.0)	141 (16.7)	
Immunodeficiency				< 0.001**
Not significant	95 (41.9)	169 (27.4)	224 (26.5)	
Mild	53 (23.4)	137 (22.2)	166 (19.7)	
Advanced	44 (19.4)	122 (19.8)	190 (22.5)	
Severe	35 (15.4)	189 (30.6)	264 (31.3)	
WHO clinical staging				< 0.001**
Stage I	74 (32.6)	295 (47.8)	369 (43.7)	
Stage II	60 (26.4)	180 (29.2)	240 (28.4)	
Stage III	74 (32.6)	114 (18.5)	188 (22.3)	
Stage IV	19 (8.4)	28 (4.5)	47 (5.6)	
Haemoglobin level				0.001**
Anaemic	62 (27.3)	105 (17.0)	167 (19.8)	

Non-anaemic	165 (72.7)	512 (83.0)	677 (80.2)	
ART eligibility criteria				0.174
Immunological	82 (36.1)	203 (32.9)	285 (33.8)	
Clinical	30 (13.2)	61 (9.9)	91 (10.8)	
Test and treat	115 (50.7)	353 (57.2)	468 (55.5)	
ART regimens				0.442
Efavirenz-based	199 (87.7)	559 (90.6)	758 (89.8)	
Nevirapine-based	7 (3.1)	16 (2.6)	23 (2.7)	
Dolutegravir-based	21 (9.3)	42 (6.8)	63 (7.5)	
ART adherence				0.015**
Good	157 (69.2)	477 (77.3)	634 (75.1)	
Fair/ poor	70 (30.8)	140 (22.7)	210 (24.9)	
ART regimen change				0.378
Yes	161 (70.9)	418 (67.8)	265 (31.4)	
No	66 (20.1)	199 (32.3)	579 (68.6)	
Taking IPT				0.007**
Yes	125 (55.1)	402 (65.2)	527 (62.4)	
No	102 (44.9)	215 (34.9)	317 (37.6)	
Taking CPT				0.022**
Yes	179 (78.9)	438 (71.0)	617 (73.1)	
No	48 (21.2)	179 (29.0)	227 (26.9)	
ART failure				0.297
Yes	4 (1.8)	19 (3.1)	23 (2.7)	
No	223 (98.2)	589 (96.9)	821 (97.3)	

OIs during follow-up			0.004**
Yes	89 (39.2)	178 (28.8)	267 (31.6)
No	138 (60.8)	439 (71.2)	577 (68.4)

P-value obtained from chi-square test.

****Significant results from chi-square test.***

Incidence of loss to follow-up

The minimum follow-up time was one month with a maximum of 72 months, and a total follow-up time of 24,850 person-months. At the end of follow-up, 7.5% (n=63) of participants had died, 13.0% (n=109) were lost to follow-up, 19.0% (n=157) were transferred out to other health facilities, and 61.0% (n=515) were alive and on ART (see Figure 13). Among the total lost cases, 84 (77.1%) were lost in the first year of follow-up. The overall incidence rate of LTFU in all participants was 5.3 per 100 person-years (95% CI: 4.4, 6.4). However, a higher rate of LTFU (LTFU=8.2; 95% CI: 6.0, 11.1) was recorded in undernourished participants than well-nourished participants (LTFU=4.3, 95% CI: 3.4; 5.5). As shown in Figure 14, the mean survival time of undernourished participants was significantly shorter than the mean survival time of well-nourished participants (p = 0.002).

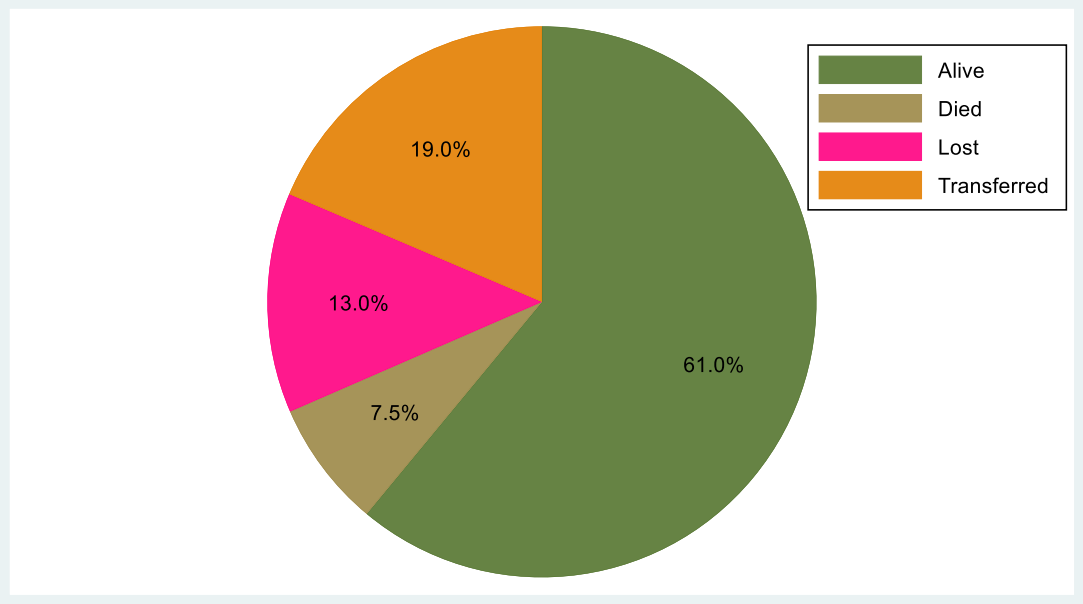

Figure 13. Treatment outcomes of adults living with HIV on ART at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia, 2021

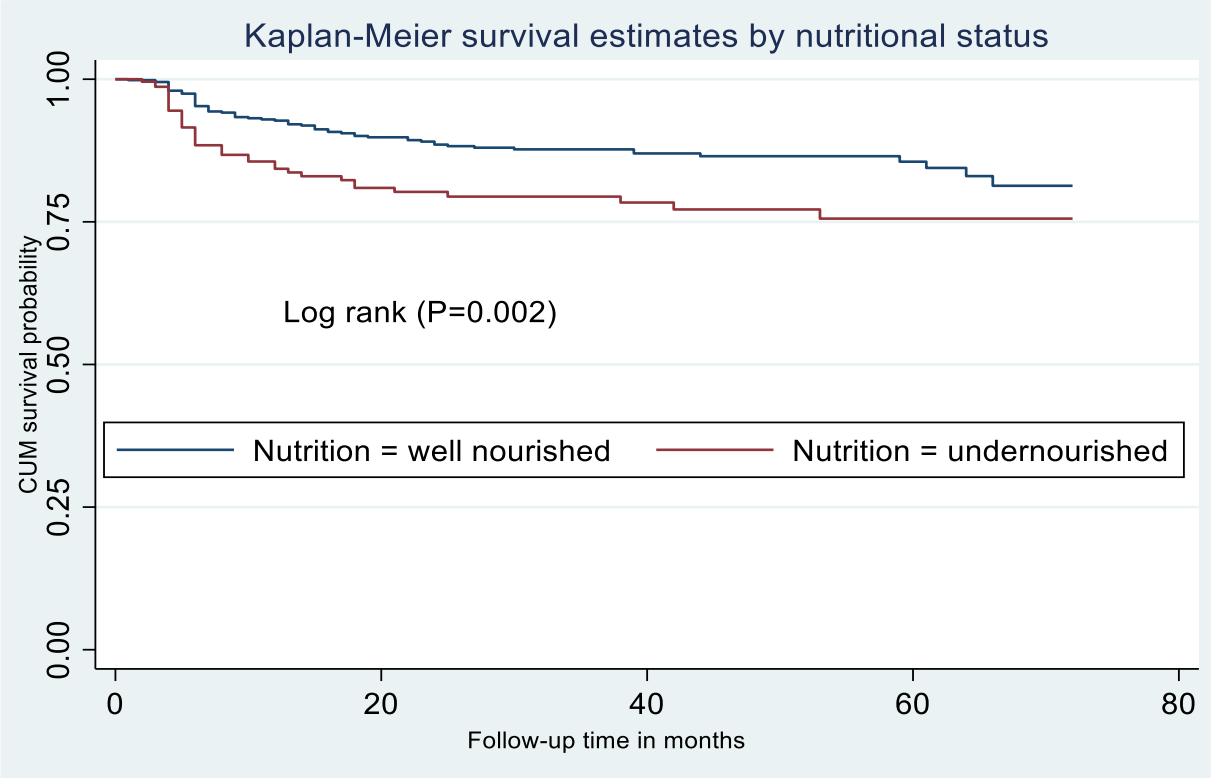

Figure 14. Kaplan-Meier survival curves to compare LTFU among undernourished and well-nourished adults living with HIV on ART at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia, 2021.

Effect of undernutrition on loss to follow-up

We performed a bi-variable analysis and variables with p-values ≤ 0.25 were included in the multivariable analysis to adjust for potential confounding variables. Variables included in the final model were residence, sex, functional status, baseline OIs, nutritional status, CD4 cell counts, WHO clinical stating, ART eligibility criteria, ART regimens, taking CPT, and taking IPT. After adjusting for potential confounders, the adjusted risk of LTFU among undernourished participants was two times higher than their well-nourished counterparts (AHR: 2.1, 95% CI: 1.4, 3.2) (Table 9).

Table 9. The effect of undernutrition on LTFU among adults living with HIV on ART at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia, 2021.

Variable	Loss to follow-up		CHR (95%CI)	AHR (95%CI)	P-value
	Event	Censured			
Nutritional status					
Undernourished	41	186	1.8 (1.2, 2.7)	2.1(1.4, 3.2)	<0.001
Well-nourished	68	549	Ref	_____	_____

Discussion

This retrospective cohort study examined the effects of undernutrition on LTFU among adults living with HIV initiated ART between 2024 and 2020 at DMCSH, Northwest Ethiopia. The study found that the rate of LTFU (8.2 per 100 person-years) in undernourished participants was higher compared to well-nourished participants (4.3 per 100 person-years); with the risk of LTFU in undernourished patients, being double that of well-nourished patients.

The overall incidence of LTFU in our study (5.3 per 100 person-years) is consistent with a study conducted in Zimbabwe (5.75 per 100 person-years) (Matsena Zingoni et al., 2020). However, our finding is lower than studies conducted in Uganda (7.5 per 100 person-years) (Kiwanuka et al., 2020) and Ethiopia (10.9 per 100 person-years) (Teshale et al., 2020). The above variations might be due to differences in sample sizes, follow-up periods, study settings, and population characteristics. In this regard, the follow-up periods of Ugandan (Kiwanuka et al., 2020) and previous Ethiopian studies (Teshale et al., 2020) were three and four years,

respectively. The follow-up period of our study was six years. In addition, our study included a referral hospital, whereas the Ugandan study included both hospital and health centres. Therefore, the lower LTFU rate in this study might be due to the differences in the quality of care provided at hospitals and health centres, as hospitals provide advanced care and commonly have more specialised staff.

The study found that of the total lost cases, more than three-fourths (n=84, 77.1%) were seen in the first year of follow-up. This finding is supported by a study conducted in Guinea, which reported LTFU at one year was 42% (Hønge et al., 2013). A study from South Africa also revealed that half of the lost cases were observed in the first six months of ART follow-up (Chauke et al., 2020). A Nigerian study also found that half (51%) of the LTFU cases occurred within the first 30 days following ART initiation. The high rate of LTFU in the early stage of ART follow-up might be because newly diagnosed individuals visiting ART clinics may not be fully prepared to engage in HIV care, as ART is a lifelong medicine, requiring repeated counselling, and psychological preparation (Ministry of Health Ethiopia, 2017). Although rapid ART initiation has improved the clinical outcomes of patients, particularly for those with very low CD4 cell counts, observational studies have shown that starting ART on the same day as HIV diagnosis may increase the risk of LTFU because patients need frequent counselling and psychological preparation before starting ART (Ford et al., 2018). The WHO guidelines also mentioned the limitation of the test and treat approach, such as it increases the risk of LTFU (World Health Organization, 2017). Another possible explanation of high LTFU in the first year of follow-up could be due to ART-associated adverse drug reactions that are very common during the first year of ART. Studies suggested that ART-related adverse reactions negatively affect adherence, indirectly affecting LTF (Bezabhe et al., 2015; Li et al., 2017; Shet et al., 2014).

Our study found that the risk of LTFU in undernourished patients was two times higher as compared to their well-nourished counterparts. This finding is in line with studies conducted in Tanzania (Kalinjuma et al., 2020), Uganda (Kiwanuka et al., 2020), South Africa (Evans et al., 2012), and Malawi (Tweya et al., 2018). This may be the results of undernourished patients being more likely to have underlying health conditions and eat less nutritious foods, which may directly impair clinic attendance (Opio et al., 2019). In addition, food insecurity and undernutrition are significant predictors of poor ART adherence (Berhe et al., 2013; Young et al., 2014). A qualitative study from Ugandan identified different mechanisms that explain how

food insecurity leads to poor ART adherence (Weiser et al., 2010). Accordingly, patients believe that in the absence of food, ART increases appetite and causes hunger. Patients also believe that the side effects of ART can be aggravated without access to adequate food. Another reason is that they experienced competing demands of paying for food costs, transportation costs, and medical expenses. Lastly, they forget or are unable to take ART while working or searching for food (Weiser et al., 2010).

Undernutrition could also indirectly contribute to a higher risk of LTFU by increasing disease progression from HIV to AIDS stage in PLHIV (Chen et al., 2019). A systematic review and meta-analysis from LMICs found that advanced WHO clinical disease staging was significantly associated with higher risk of LTFU (Frijters et al., 2020). Advanced WHO clinical disease stage increases the risk of LTFU in various ways. Patients with WHO stage III or IV are more likely to have OIs and are bedridden most of the time, which can make it difficult for them to stay engaged in HIV care. In addition, HIV patients with advanced disease stage are at higher risk of premature death from severe OIs, especially during the first year. Therefore, these patients may have died at home but were not reported due to a passive surveillance system.

Strengths and limitations of the study

One strength of our study is that it included a relatively large sample size (n=844). As we used a cohort study design, we were able to calculate the incidence rate of LTFU. However, this study has some limitations. Some important confounding factors, such as distance from the healthcare facilities and viral load, were unavailable due to data incompleteness. Moreover, the actual incidence of LTFU might be underestimated due to incomplete recording. Conversely, the actual incidence of LTFU may be overestimated because some patients classified as LTFU may have died or have started ART in other health care facilities without sufficient recording.

Conclusion

Although Ethiopia has achieved remarkable success in increasing access to ART, LTFU is still a significant concern. The study found that undernutrition significantly increased the risk of LTFU among adults living with HIV on ART. This finding implies that different stakeholders should undertake various nutritional interventions and practical approaches to reduce LTFU and improve treatment outcomes in adults living with HIV. In addition, efforts must be made to improve the food security of people living with HIV across the country. Finally, further

prospective studies by incorporating some confounders such as viral load and distance from health facilities are needed to examine the effects of undernutrition on LTFU.

Availability of data and material

The data sets used and/or analysed for this study are available from the corresponding author on reasonable request.

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Authors' contributions

AA: conception of the research idea, design, analysis, interpretation, and drafting the manuscript. **DD, PP**, and **DS**: Design, interpretation of results, reviewing and editing the manuscript. All authors have read and approved the final manuscript.

Competing interests

All authors have declared that they have no competing interests.

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5.4. Chapter summary

This chapter examined the effect of undernutrition on LTFU in 844 ALHIV receiving ART using a proportional hazards regression model. The study found a higher incidence of LTFU in undernourished participants (8.2 per 100 person-years) than in well-nourished individuals (4.3 per 100 person-years). Finally, after adjusting for potential confounders, the adjusted risk of LTFU in undernourished participants was two times higher than in their well-nourished counterparts. The next chapter reports the results of a published retrospective cohort study evaluating the effects of undernutrition on opportunistic infections in ALHIV on ART.

Chapter 6 │Effects of undernutrition on opportunistic infection among ALHIV on ART in Ethiopia

6.1. Chapter introduction

This chapter includes the findings of a published study (Manuscript IV) that determined the effects of undernutrition on the occurrences of OIs in a cohort of 841 adults living with HIV receiving ART at DMCSH in Northwest Ethiopia. This study employed a treatment effects analysis on time-to-event data to address the third objective. The study found that undernutrition significantly reduced the time to develop OIs in ALHIV receiving ART. This study provides empirical evidence that healthcare professionals and policymakers need to improve treatment outcomes and prevent OIs in undernourished people living with HIV. The manuscript has been published and is available in *PLoS One.*

6.2. Publication (Published in *PLoS One*)

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Authors' contributions for this manuscript

The candidate is the primary author of this manuscript and was involved in the conception of the research idea, methodology, software, formal analysis, investigation, project administration and drafting and editing of the manuscript. The second, third, and fourth authors participated in the interpretation of results, reviewing, and editing the manuscript.

Effects of undernutrition on opportunistic infections among adults living with HIV on ART in Northwest Ethiopia: A retrospective cohort study

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Abstract

Background: Opportunistic infections (OIs) are the leading causes of hospitalization, morbidity, and mortality (accounting for 94.1% of all deaths) in people living with human immunodeficiency virus (PLHIV). Despite evidence suggested that undernutrition significantly increases the risk of OIs in PLHIV, to our knowledge, no study has examined the actual effects of undernutrition on OIs in this population, particularly in low-income countries. Thus, this study examined the effects of undernutrition on OIs in adults living with HIV receiving antiretroviral therapy (ART).

Methods: We conducted a retrospective cohort study among 841adults living with HIV receiving ART between June 2014 and June 2020 at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia. Study participants were selected using a simple random sampling technique. Data from participants' medical records were extracted using a project-specific data extraction checklist. The Kaplan Meier survival curve estimated the OIs free survival time. The effects of undernutrition on time to develop OIs was estimated using inverse-probability weighting. Finally, regression coefficients with 95% confidence intervals (95% CIs) were reported, with a statistical significance of $p < 0.05$.

Results: Of 841 study participants, 262 (31.2%) developed OIs, and the overall incidence rate was 16.7 (95% CI: 14.8, 18.8) per 100 person-years. The incidence of OIs in undernourished participants (21/100 person-years, 95% CI: 17.8, 27.4) was higher than well-nourished participants (15.0/100 person-years, 95% CI: 12.9, 17.4). When everyone in the population of interest is well-nourished, average time to develop OIs is estimated as 26.5 (coefficient: 26.5, 95% CI: 20.6, 32.4, $p < 0.001$) months. When everyone in the population of interest is undernourished, average time to develop OIs is estimated as 17.7 (95% CI: 12.8, 22.6) months. However, when everyone is undernourished, average time to develop OIs decreases by 8.8 (coefficient: -8.8, 95% CI: -16.6, -1.0, $p =0.026$) months. Lastly, exposure to undernourishment (intervention) (ratio of average treatment effects to well-nourished potential outcome means in this study was a 32.5% reduction in OIs among adults living with HIV on ART.

Conclusion: We found that undernutrition significantly shortened time to develop OIs in adults living with HIV. This implies that the occurrence of OIs in this vulnerable population can be improved through different cost-effective nutritional interventions, such as routine nutritional assessments and education.

Keywords: Adults living with HIV, Ethiopia, ART, Opportunistic infections, Undernutrition

Introduction

Opportunistic infections (OIs) are illnesses frequently occurring in people with weakened immune systems, such as those infected with human immunodeficiency virus (HIV) (Centers for Disease Control and Prevention (CDC), 2019). Although OIs have reduced significantly with the introduction of antiretroviral therapy (ART), they remain the leading cause of hospitalization, morbidity, and mortality (94.1% of all deaths) in people living with HIV (PLHIV) (Ford et al., 2015; Weissberg et al., 2018). OIs reduce quality of life, accelerate progression from HIV to acquired immunodeficiency syndrome (AIDS)-defining conditions, increase healthcare system burden, and lead to treatment failure (Ghiasvand et al., 2019; Low et al., 2016; Mulisa et al., 2019). Occurrence/recurrence of OIs and disease progression from HIV to AIDS are strongly influenced by malnutrition (Alebel et al., 2021).

Although malnutrition includes both undernutrition and overnutrition, it commonly refers to undernutrition and related complications in low and middle-income countries (LMICs) (Saunders & Smith, 2010). Undernutrition is inadequate energy and nutrient intake to meet an individual's needs for maintaining health (Maleta, 2006). There is a complex relationship between malnutrition and HIV (Duggal et al., 2012). PLHIV are at higher risk of malnutrition due to reduced oral intake, increased metabolic requirements, and decreased absorption of nutrients (Ivers et al., 2009). Reduced oral intake may result from oral thrush, oesophageal candidiasis, depression, or anorexia (De Pee & Semba, 2010). Fever increases nutritional requirements as it increases the body's use of nutrients (Childs et al., 2019). Furthermore, HIV-associated intestinal mucosal damage and diarrhoea can decrease nutrient absorption (Sashindran & Thakur, 2020). The relationship between malnutrition and OIs in PLHIV is also bidirectional. Studies from LMICs found undernutrition significantly increases risk of developing OIs in PLHIV (Alebel et al., 2021; Moore et al., 2007; Nicholas et al., 2011). OIs can increase risk of malnutrition by reducing nutrient absorption (e.g., intestinal parasites), reducing food intake (oesophageal candidiasis; oral thrush), as well as causing anorexia or increasing nutritional requirements (tuberculosis) (Duggal et al., 2012; Ivers et al., 2009; Sashindran & Thakur, 2020).

Recent Ethiopian ART guidelines recommended interventions to prevent OIs, including exposure reduction (personal and environmental hygiene and safe sexual practices), provision

of chemoprophylaxis (co-trimoxazole preventive therapy (CPT) and isoniazid preventive therapy (IPT)), immunizations, and provision of highly active antiretroviral therapy (HAART) (Ministry of Health Ethiopia, 2017). Despite HAART is effective in reducing OIs in PLHIV, not all patients responded to the therapy equally (Low et al., 2016). Some patients experience a slow recovery of immune function, resulting in a continued high risk of OI-related morbidity and mortality. Inadequate immune response may be associated with malnutrition as the leading cause of immunodeficiency worldwide (Duggal et al., 2012).

Although there are several studies on the association between undernutrition and TB among this population in LMICs (Sabasaba et al., 2019; Tiruneh et al., 2019), to our knowledge, no study has examined the actual effect of undernutrition on OIs using a propensity score analysis. While randomized controlled trials (RCTs) are the gold standard for examining effects of treatment on outcomes, an RCT is not feasible on this topic due to ethical issues. In addition, we previously conducted a systematic review on this and found three significant gaps in the current body of literature (Alebel et al., 2021). Firstly, almost all studies included in our review on OIs focused on the association between undernutrition and TB, but little attention has been paid to the impact of undernutrition on other OIs. Secondly, most of the included studies used cox-regression to determine the association between undernutrition and TB instead of treatment effect analysis. Thirdly, although all studies attempted to control confounding variables using multivariable analysis, none of them used treatment effects analysis to show the actual effect of undernutrition on OIs. Thus, we conducted an observational study, examining effects of undernutrition on time to develop OIs using a propensity score analysis. Findings may assist clinicians in designing effective and efficient nutritional interventions to improve overall outcomes of PLHIV with malnutrition. Furthermore, findings provide insights to consider for a particular treatment option for managing OIs in malnourished adults living with HIV (ALHIV).

Methods

Study design, period, and setting

This institution-based retrospective cohort study used secondary data extracted from medical records of adult patients attending chronic HIV care at Debre Markos Comprehensive Specialized Hospital (DMSCH) between June 2014 and June 2020. DMCSH is the only referral hospital in East Gojjam Zone. The hospital started providing HIV care and ART services in

2005 with 1,209 PLHIV having ART initiated between June 2014 and June 2020 of which 1,177 (97.4%) were aged ≥ 15 years (adults).

HIV care provision in the ART clinic

Current Ethiopian ART guidelines state that all HIV-positive adults are eligible to start ART immediately, irrespective of WHO clinical disease staging and CD4 cell counts (Ministry of Health Ethiopia, 2017). Activities provided by a team of physicians and nurses on the initial visit include, as necessary and available, patient counselling, co-trimoxazole preventive therapy (CPT), treatment of OIs, management of co-morbidities and referrals, as well as continuation of ART for transfer-ins. Laboratory tests at initial visit include baseline CD4 counts, complete blood count, alanine transaminase, and creatinine, cryptococcal antigen, Gene Xpert test if presumptive TB, pregnancy test, and other indicated tests. Follow-up appointments were scheduled (two weeks post-first visit) and then every month for the next three months. After four months, patients attend every two months for the next two months (Ministry of Health Ethiopia, 2017). After six months, appointments at three-month intervals are scheduled for, as necessary, refilling ART and other mediations, managing drug toxicities, treating OIs, providing ART drug adherence support, referring to other services, and setting a next appointment.

Study population

All ALHIV who started ART at DMCSH within the study period and received ART for at least one month were eligible. ALHIV who had (I) transferred to DMCSH without baseline information, (II) unrecorded date of outcome of interest (OIs), and (III) pregnant women were excluded (as nutritional assessment differs from other ALHIV and their charts were not available) (Ververs et al., 2013).

Sample size estimation and sampling

The minimum required sample size was estimated using an independent cohort study formula and calculated using Open Epi Version 3 (Kelsey et al., 1996). Parameters used to estimate our sample size were α of 5%; power of 80%; $Z_{\alpha/2}$ of 1.96; P_0 of 19%; P_1 of 27%; and r of 1:1. The sample size of 802 was based on a previous Ethiopian study (Teshale et al., 2020), with an assumed 10% chart incompleteness yielding a final sample of 892. Through simple random sampling 892 records were selected from the eligible 1,177 ALHIV meeting inclusion criteria.

Of these, 51 were excluded because of transferred in without baseline information (n=21), pregnancy (n=20), and unrecorded outcome date (n=10). The final sample consisted of 841 records.

Data collection procedures

Project-specific standardized data extraction tools were based on current Ethiopian ART entry and follow-up forms to maintain data quality (Ministry of Health Ethiopia, 2017). These tools had three main components (i.e., sociodemographics, clinical and laboratory characteristics, and medications including ART). Sociodemographics included sex, age, educational level, residence, marital status, occupation, disclosure of HIV status, and family size. Clinical and laboratory characteristics included OIs, baseline weight and height, CD4 cell counts, WHO clinical disease staging, Hgb level, and functional status. Medication-related characteristics included baseline ART regimen, adherence, regimen changes, and treatment failure, taking CPT, and isoniazid preventive therapy (IPT). First month measurements post-ART initiation were considered baseline data. The nutritional status of study participants was assessed using body mass index (BMI). First, anthropometric measurements (height and weight) were extracted from patients' charts to determine their nutritional status (BMI). Second, BMI was calculated by dividing weight in kilograms by the height in meters squared (kg/m^2). Finally, the study participants were classified as undernourished and well-nourished. Two epidemiologists specialized in HIV who currently working at DMCSH were recruited as data collectors with a biostatistician providing data collection supervision.

Study variables

The dependent variable was time to develop new OIs after ART initiation. Participants either lost to follow-up, those who died or were still alive at the end of the follow-up, but did not develop OIs, were classified as censored. Follow-up time was calculated in months from the date of ART initiation until the date of events (OIs) or censoring (other than events). The exposure variable was nutritional status (undernourished vs well-nourished). Three main covariate (confounders) classifications were sociodemographic, clinical/laboratory, and ART and other medication-related variables (see data collection).

Operational definitions

According to the Ethiopian ART guidelines, the most common OIs are: herpes zoster, bacterial pneumonia, pulmonary and extra-pulmonary TB, oral and oesophageal candidiasis, mouth ulcer, diarrhoea, pneumocystis pneumonia, toxoplasmosis, cryptococcal meningitis, non-Hodgkin's lymphoma, Kaposi's sarcoma, cervical cancer, and others (Ministry of Health Ethiopia, 2017).

Undernutrition is defined as a BMI of less than 18.5 kg/m^2. The severity of undernutrition was classified as severe (BMI < 16 kg/m^2), moderate (BMI: 16-16.99 kg/m^2), and mild (BMI: 17-18.48 kg/m^2) (Purnell, 2018). Undernourished (BMI < 18.5 kg/m^2) participants were the exposed (treatment) group.

ART adherence was classified as good, fair, or poor, calculated from the total monthly dose of ART drugs (n=60). Good is compliance equal to or greater than 95% or ≤ 3 missed doses per month; fair 85-94% compliance or between 4 and 8 missing doses per month; and poor as less than 85% compliance or ≥ 9 missed doses per month (Ministry of Health Ethiopia, 2017).

The WHO divided adult immune status into four HIV-related immunodeficiency zones: no significant (CD4 > 500 cells/mm^3), mild (CD4: 350−499 cells/mm^3), advanced (CD4: 200−349 cells/mm^3), and severe (CD4<200 cells/mm^3) (Garcia & Guzman, 2020).

Loss to follow-up (LTFU) was defined as ALHIV missing an ART appointment for at least one month (Ministry of Health Ethiopia, 2017).

Missing data handling

One-quarter (24.4%, n=205) of CD4 cell counts and 5.9% (n=50) of haemoglobin (Hgb) levels were unavailable from records. Multiple imputation (MI) was used for these variables after checking the pattern and mechanisms of missing values. Little's MCAR test was conducted to check whether the values are missing at random or not (Little, 1988). The final imputation was performed using a multivariate normal imputation model. Variables included were sex, residence, WHO clinical disease staging, ART adherence, nutritional status, OIs, CPT, and IPT. Lastly, distributions in the observed, imputed, and completed data (multiple imputation diagnostic test) were assessed using the diagnostic plots for multiple imputation.

Statistical analysis

The Kaplan-Meier survival curve was constructed to estimate the OIs free survival time in undernourished (exposed) and well-nourished (non-exposed) participants. The survival curves were compared using a generalized log-rank test. As we used data from the observational study to determine treatment effects on outcomes, propensity scores were generated to reduce or eliminate confounding effects (Austin, 2011). The propensity scores were constructed and assessed in five steps, as presented below (Garrido et al., 2014).

Step 1: Covariate selection: Nine covariates (i.e., sex, residence, WHO clinical staging, CD4 cell count, Hgb, CPT, IPT, HIV status disclosure, and ART adherence) were identified from previous literature (Addis Alene et al., 2013; Dereje et al., 2019; Gupte et al., 2019; Liu et al., 2015; Solomon et al., 2018; Temesgen et al., 2019).

Step 2: Propensity score estimation: The propensity scores for all nine covariates were generated using a logistic regression model, in which nutritional status was regressed on these covariates. As our aim was estimating treatment effects using survival data, we employed the Log-normal model (with the least Akaike information criterion and Bayesian information criterion) for censoring time**.**

Step 3: Propensity score method selection: To adjust observed differences in baseline characteristics between exposed and non-exposed groups, we employed inverse-probability weighting (IPW) (Austin, 2011). This estimator was used for two reasons. Firstly, we intended to model treatment assignment (exposure) rather than the outcome. Secondly, our study had 579 (68.8%) censored observations. When there is censoring, IPW estimator calculated the weights from two models, one for censoring time and one for treatment assignment.

Step 4: Balance assessment: Common assumptions to use treatment-effects estimators (i.e., conditional independence, sufficient overlap, and correct adjustment for censoring) were assessed using overlap plots (positivity assumption) and covariate balance tests. The overlap assumption requires propensity score distribution for each treatment level greater than zero but less than one (Ali et al., 2019). Covariate balance was evaluated by comparing standardized differences and variance ratios before and after weighting. Weighted standardized differences close to zero indicate balanced data, as a high of 0.25 (25%). is acceptable (Stuart et al., 2013).

Rubin suggested covariates are considered balanced if weighted variance ratios are between 0.8 and 1.25 (Rubin, 2007).

Step 5: Treatment effects estimation: The average treatment effects (ATE) of undernutrition on time to develop OIs was estimated using an IPW. Regression coefficients with 95% confidence intervals (95% CIs) were reported, with a statistical significance of $p < 0.05$. All statistical analyses were performed using Stata™ Version 16.

Ethical considerations

Ethical approvals and permissions were granted from the DMCSH Medical Director's Office, the University of Technology Sydney Medical Research Ethics Committee (ETH20-5044), and the Amhara Regional Public Health Research Ethics Review Committee (Ref. no: 816). As the study was based on existing medical records of PLHIV, participants' verbal or written informed consent was not feasible, and a waiver of consent was granted. Data were completely de-identifiable to the authors, as the data abstraction tool did not include participants' unique ART numbers and names. The collected data was stored and locked in a separate room before data entry.

Results

Sociodemographic characteristics of the cohort

Of the 841 study participants, 21.6% (n=182) were from rural areas, and 59.0% (n=496) were female. More than half (n=467; 55.5%) of the participants were between 15 and 34 years old, with a median age of 32 years (IQR: 26-40). One-quarter (n=214; 25.5%) of participants were divorced, 69.6% (n=585) were able to read and write, and 21.4% (n=180) were employed. Almost one-third (n=276; 32.8%) did not disclose their HIV status to their sexual partners or family members and 55.4% (n=470) were from families with fewer than three people (see Table 10).

Table 10. Baseline sociodemographic characteristics of adults living with HIV on ART at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia (n=841)

Variables	Frequency (n)	Percentage (%)
Residence		
Urban	659	78.4

Rural	182	21.6
Age (years of age)		
15-34	467	55.5
≥35	374	44.5
Sex		
Male	345	41.0
Female	496	59.0
Marital status		
Single	153	18.2
Married	391	46.5
Divorced	214	25.5
Widowed	83	9.9
Level of education		
Unable to read and write	256	30.4
Able to read and write	585	69.6
Occupation		
Daily labourer	138	16.4
Merchant	167	19.9
Farmer	118	14.0
Employed	180	21.4
Student	47	5.6
Housewife	144	17.1
Others	47	5.6
HIV-status disclosure		
Disclosed	565	67.2
Not disclosed	276	32.8
Family size		
<3 individuals	470	55.4
≥3 individuals	387	44.6

Clinical characteristics of participants

At ART initiation, 39.7% (n=334) of participants presented with OIs, and 26.5% (n=223) were undernourished. Of these 223 undernourished participants, 116 (52%) had OIs. Only 16.5% (n=139) of participants were classified as bedridden or ambulatory functional status. Nearly one-third (n=271; 32.2%) of participants had severe immunodeficiency, with a median CD4 count of 324.3 (IQR=158-499) cells/mm^3 with 44.0% (n=370) classified as WHO clinical stage I. Forty-three (5.1%) participants had baseline anaemia, with mean Hgb of all participants at 13.8 (SD ±2.4) g/dl. More than half (n=464; 55.2%) of participants started ART through the test and treat approach, and most (n=757; 90.0%) began Efavirenz-based ART. Three-quarters (n=634; 75.4%) of participants showed good compliance with ART, while about one-third (31.5%; n=265) experienced a change in baseline ART regimen. Furthermore, 73.0% (n=614) and 62.8% (n=528) of the participants took CPT and IPT, respectively. ART treatment failure throughout follow-up was seen in 23 (2.7%) participants (see Table 11).

Table 11. Clinical characteristics of participants at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia (n=841)

Variables	Frequency (n)	Percentage (%)
Baseline OIs		
Yes	334	39.7
No	507	60.3
Baseline nutritional status		
Undernourished	223	26.5
Well-nourished	618	73.5
Functional status		
Working	702	83.5
Ambulatory/ bedridden	139	16.5
Immunodeficiency		
Not significant (CD4 ≥ 500 cells/mm^3)	210	25.0
Mild (CD4=350-499 cells/mm^3)	171	20.3
Advanced (CD4=200-349 cells/mm^3)	189	22.5
Severe (CD4 <200 cells/mm^3)	271	32.2
WHO clinical staging		

Stage I	370	44.0
Stage II	238	28.3
Stage III	187	22.2
Stage IV	46	5.5
Haemoglobin level		
Anaemic (<10 g/dl)	43	5.1
Non-anaemic (≥10 g/dl)	798	94.9
ART eligibility criteria		
Immunological/clinical	377	44.8
Test and treat	464	55.2
Baseline ART regimens		
Efavirenz (EFV)-based	757	90.0
Nevirapine (NVP)-based	22	2.6
Dolutegravir (DGT)-based	62	7.4
ART adherence		
Good	634	75.4
Fair	25	3.0
Poor	182	21.6
ART regimen change		
Yes	265	31.5
No	576	68.5
Taking IPT		
Yes	528	62.8
No	313	37.2
Taking CPT		
Yes	614	73.0
No	227	27.0
ART failure		
Yes	23	2.7
No	818	97.3

Incidence of opportunistic infections

Participants were followed retrospectively for between one month and 72 months, with total follow-up time being 18,855 person-months. At the end of follow-up, 262 (31.2%) participants developed OIs, and overall incidence rate was 16.7 (95% CI: 14.8, 18.8) per 100 person-years of observation. Of the OIs, tuberculosis (TB) (n=42; 15%), sexually transmitted infections (STIs) (n=39; 14.4%), and bacterial pneumonia (n=32; 11.8%) were most common (see Table 12). Approximately 160 (61.0%) cases of OIs occurred in the first year of follow-up. The incidence of OIs in undernourished (exposed) adults was 21 per 100 person-years (95% CI: 17.8, 27.4), while the incidence of OIs in well-nourished (non-exposed) adults was 15.0 per 100 person-years (95% CI: 12.9, 17.4). Undernourished participants' OIs-free survival time was significantly shorter than well-nourished participants (log-rank test, p = 0.004; see Figure 15).

Table 12. Common opportunistic infections during follow-up in adults living with HIV on ART at Debre Markos Comprehensive Specialized, Northwest Ethiopia, 2021

Common OIs	Frequency (n)	Percentage (%)
Tuberculosis	42	15.0
Sexual transmitted infections	39	14.4
Bacterial pneumonia	32	11.8
Diarrhea	30	11.1
Herpes zoster	30	11.1
Oral candidiasis	22	8.1
Meningitis	21	7.7
Upper respiratory infections	10	3.7
Cryptococcosis	8	3.0
Skin rash	7	2.6
Pneumocystis pneumonia	4	1.5
Others	26	9.6

Footnote: others included CNS toxoplasmosis, intestinal parasites, and urinary tract infections.

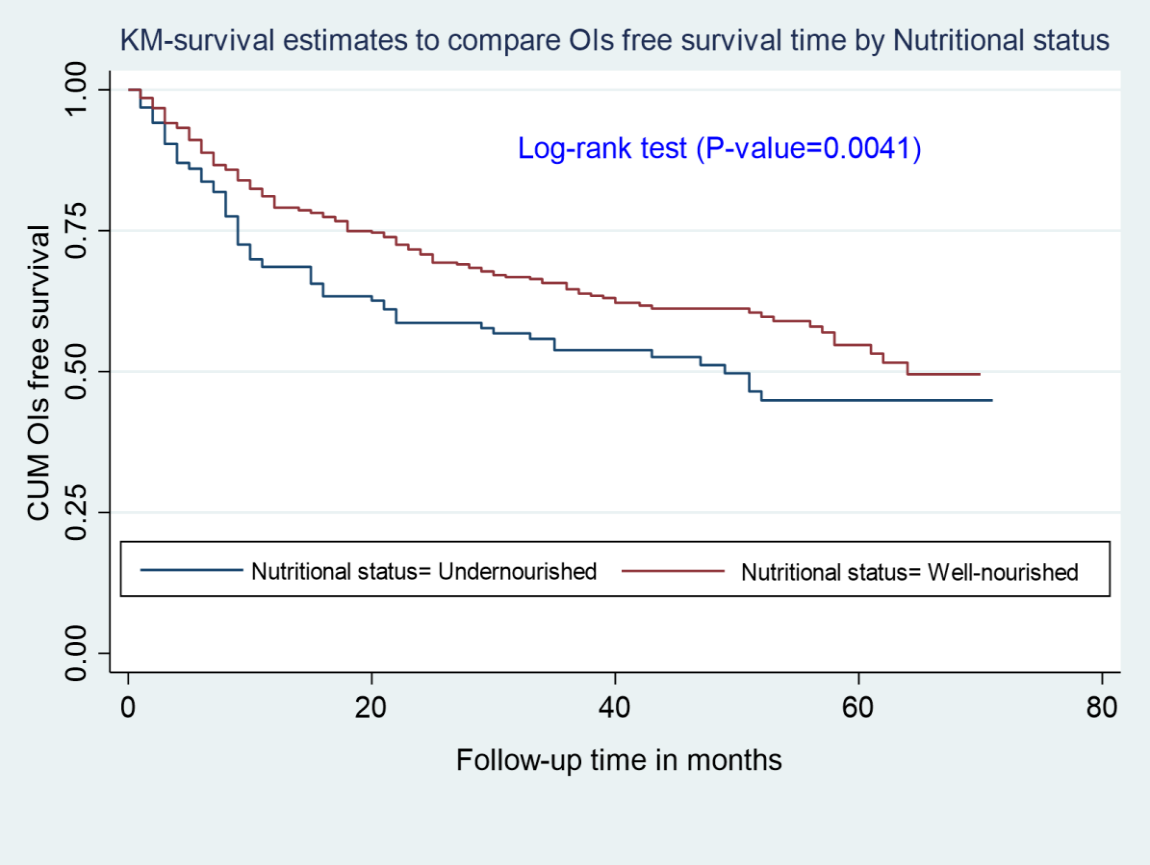

Figure 15. Kaplan-Meier survival curves to compare OIs free survival time between undernourished and well-nourished adults living with HIV on ART at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia, 2021.

Checking balance on propensity scores

After generating prosperity scores for nine covariates, overlap plots were used to evaluate the hypothesis of sufficient overlap (see Figure 16). Although there is no specific statistical test to verify the overlap assumption, predicted treatment probabilities were summarised, with the minimum and maximum predicted propensity scores for undernourished participants being 0.13 and 0.7, respectively. There is no evidence that the overlap assumption is violated.

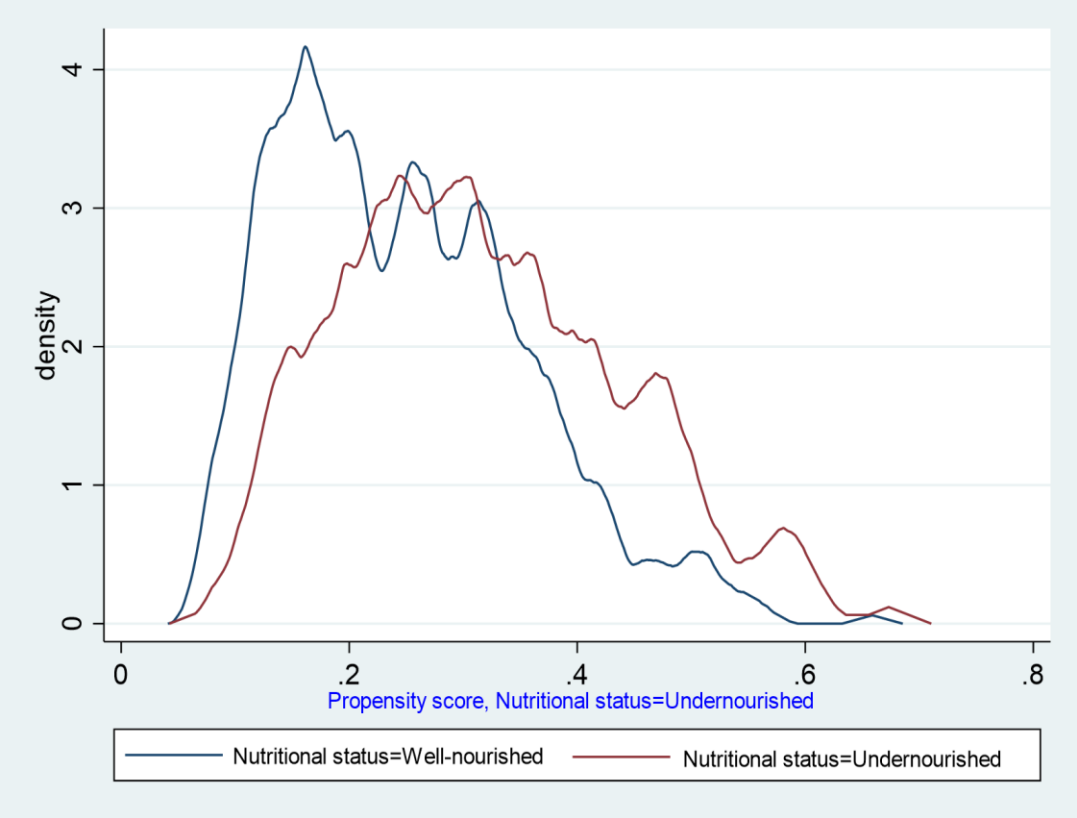

Figure 16. Propensity score distribution for overlap assumption among adults living with HIV on ART at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia, 2021.

Checking balance on covariates

The standardized differences of covariates ranged from 1.0% to 46.2% before weighting and 0.1% to 2.9% after weighting. Variance ratios of covariates ranged from 0.7 to 2.7 before weighting and ranged from 0.9 to 1.0 after weighting. An overidentification test was conducted for further verification. The test results ($\chi 2 = 11.6$, $p = 0.313$) confirmed there is no evidence to reject the null hypothesis (H_0 = covariates are balanced), implying the specified treatment model balanced the covariates.

Effect of undernutrition on opportunistic infections

When everyone in the population of interest is well-nourished, average time to develop OIs is estimated as 26.5 (95% CI: 20.6, 32.4) months. When everyone in the population of interest is undernourished, average time to develop OIs is estimated as 17.7 (95% CI: 12.8, 22.6) months. When everyone is undernourished, average time to develop OIs decreases by 8.8 (95% CI: -16.6, -1.0) months (see Table 13). Lastly, effectiveness of exposure to undernourishment

(intervention) (ratio of ATE to well-nourished potential outcome means [POM]) in this study was a 32.5% reduction in OIs (see Table 13).

Table 13. The effect of undernutrition on the time to develop OIs in adults living with HIV on ART at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia

Parameters	Treatment variable	OIs status		Coefficient (95% CI)	p-value
		Event	Censored		
	Nutritional status				
POMs	Undernourished	82	141	17.7 (12.8, 22.6)	<0.001
	Well-nourished	180	438	26.5 (20.6, 32.4)	<0.001
ATE				-8.8 (-16.6, -1.0)	0.026

POMs: potential outcome means

ATE: average treatment effects

Discussion

Although OIs have significantly reduced since the introduction of HAART, they remain the leading cause of premature deaths, especially in undernourished PLHIV (Low et al., 2016; Nicholas et al., 2011). This institution-based retrospective cohort study examined effects of undernutrition on OIs in ALHIV receiving ART. To the best of our knowledge, this is the first study investigating the effects of undernutrition on OIs in this population using a propensity score analysis for time-to-event data. During follow-up, nearly a third (31.2%) of participants developed OIs and TB at 15% was the most common. Besides, the incidence of OIs in undernourished (21 per 100 person-years: 95% CI: 17.8, 27.4) ALHIV on ART is higher than their well-nourished counterparts (15.0 per 100 person-years: 95% CI: 12.9, 17.4). This study also found that undernutrition significantly shortened time to develop OIs in ALHIV receiving ART. When everyone is undernourished, the average time to develop OIs decreases by 8.8 months.

Although we did not find similar studies that used propensity score analysis to examine the effects of undernutrition on OIs, we compared our findings with studies reporting the association between undernutrition and OIs. Our finding is consistent with a meta-analysis in sub-Saharan Africa conducted by our team, which found that the risk of developing TB in undernourished ALHIV is twice that of well-nourished ALHIV (Alebel et al., 2021).

Additionally, this result is comparable to a cross-sectional study conducted in Ethiopia that reported a significant association between undernutrition and parasitic infections (Gedle et al., 2017). Furthermore, a Zambian prospective cohort has also documented that the occurrence of AIDS-defining illness was strongly associated with moderate wasting (Chen et al., 2019).

The causal relationship between malnutrition and OIs can be explained in different ways, as malnutrition is one of the main causes of immunodeficiency worldwide (Duggal et al., 2012). For example, it causes nutritional-acquired immune dysfunction and increases host susceptibility to infection (Katona & Katona-Apte, 2008). Undernutrition also weakens the immune system through atrophy of the thymus, spleen, lymph nodes, and reduced cell-mediated immunity (Bourke et al., 2016). An essential amino acid deficiency also impairs the synthesis of proteins responsible for producing cytokines secreted by lymphocytes, macrophages, and other cells of the body during the acute inflammatory response(Wan et al., 1989). These collectively impair the patient's ability to fight and recover from infections.

The indirect effects of undernutrition on the occurrence of OIs can be explained in various mechanisms. In this regard, there is some evidence that malnutrition is significantly associated with poor adherence to ART (Berhe et al., 2013; Young et al., 2014). It is well known that although ART dramatically reduces the occurrence and recurrence of OIs, it is only effective if the patient takes its medication regularly (Ministry of Health Ethiopia, 2017). Alternatively, our finding could be justified by the impact of undernutrition on treatment failure, as undernutrition is a strong predictor of treatment failure (Ahmed et al., 2019; Babo et al., 2017; Enderis et al., 2019). Lastly, poor nutritional status was also cited as a common reason for the discontinuation of ART and loss to follow-up (Bernard et al., 2018; Hønge et al., 2013; Kalinjuma et al., 2020; Mekonnen et al., 2019; Teshome et al., 2015; Tweya et al., 2018). One qualitative study showed patients believe that ART without adequate food might be ineffective or even harmful, explaining poor ART adherence (Tiruneh et al., 2016). Lastly, patients may forget or are unable to take ART while working or searching for food (Weiser et al., 2010).

During follow-up, almost one-third (31.2%) of participants had OIs, with an incidence of 16.7 (95% CI: 14.8, 18.8) per 100 person-years of observation. This finding is higher than a Ugandan study (5.9 per 100 person-years of observation) (Weissberg et al., 2018). The variation could be due to the difference in follow-up period. We followed participants retrospectively for almost six years, while the follow-up period for the Ugandan study was ten years. As length of follow-up increased, the number of years of follow-up for each person also

increased. This can increase the denominator and decrease the overall incidence. In our study, approximately 61.0% of OIs occurred within the first year, which is similar to the same period in the Ugandan study at 74.1%. This reflects the shorter the follow-up period, the higher the incidence rate.

Regarding OI patterns, TB (15.5%), STIs (14.4%), bacterial pneumonia (11.8%), and diarrhoea (11.1%) were the most common. This finding is in line with a systematic review conducted in LMICs, which found oral candidiasis (19.1%), herpes zoster (9.4%), pulmonary TB (9.0%), and bacterial pneumonia (6.1%) are the most common OIs in ART-naïve people (Low et al., 2016). A similar pattern from a Ugandan study reported oral candidiasis (43.6%), tuberculosis (21.6%), herpes zoster (19.9%), and cryptococcal meningitis (4.6%) as the most common OIs (Weissberg et al., 2018). Ethiopia bears one of the highest countries of TB and TB/HIV co-infection rates globally (World Health Organization, 2021b). This trend is reflected in our study, where TB is the most common HIV-associated OI. The risk of developing TB in PLHIV is 20 times higher than in people without HIV (World Health Organisation, 2018).

Lastly, our study found that 61.0% of OIs occurred in the first year of follow-up. This finding is consistent with a study conducted in Uganda that showed 71.4% OIs happed in the first year (Weissberg et al., 2018). Immune reconstitution inflammatory syndrome is prevalent between the first and third months of ART. It strongly increases the protective responses of the immune system, leading to a typical inflammatory condition, which increases the risk of developing OIs, especially cryptococcal and TB meningitis (Bicanic et al., 2009; Boulware et al., 2014). This reflects patients must be closely monitored for the presence of OIs in the early phase of ART.

Strengths and limitations of the study

The strengths of this study are the longer follow-up period (6 years) and large sample size (n=841), increasing precision. The data recording system for HIV-positive patients is standardized across Ethiopia, providing an opportunity to obtain comparably high-quality data. However, this study has limitations that must be taken into account while interpreting the results. Since we used secondary data, important variables that are likely to influence OIs, such as viral load, income level, eating habits, substance use, and micronutrient deficiency were unavailable. Moreover, although OIs can recur, treatment effect analysis cannot handle recurrent events (multiple records). As a result, this study only estimated time to develop the

second OIs. The overall magnitude of OIs may be underestimated due to limited diagnostic options in resource-limited settings.

Conclusion

We found that undernutrition significantly shortened time to develop OIs in ALHIV. This implies that the occurrence of OIs in this vulnerable population can be improved through different cost-effective nutritional interventions, such as routine nutritional assessments and education. The finding also highlights the need for appropriate nutritional support and monitoring along with ART. There is a need to strengthen counselling and appropriate dietary support based on the nutritional assessment at each visit by ALHIV receiving ART. A comprehensive approach is needed to improve nutritional status of PLHIV. As TB remains the main OI in this population, detection and treatment in PLHIV still requires special attention. The results of this study are also helpful for clinicians to consider alternative nutritional treatment options or may inform revisions to existing guidelines such as other nutritional assessments, counselling, and supports targeting people living with HIV who have OIs. Further intervention studies may assess the impact of nutritional interventions on the occurrence of OIs in PLHIV.

List of abbreviations

AIDS: Acquired Immunodeficiency Syndrome, ALHIV: Adults living with HIV, ART: Antiretroviral Therapy, **BMI**: Body mass Index, **CI**: Confidence Interval, **CPT:** Cotrimoxazole Preventive Therapy**, DMCSH:** Debre Markos Comprehensive Specialized Hospital, **HAART**: Highly Active Antiretroviral Treatment, **HIV: Human Immunodeficiency Virus, IPT:** Isoniazid Preventive Therapy**, IPW:** Inverse-Probability Weighting**, LMICs**: Low and Middle-income Countries, **OIs**: Opportunistic Infections, **PLHIV**: People Living with Human Immunodeficiency Virus, **SSA**: Sub-Saharan Africa, **TB**: Tuberculosis, and **WHO**: World Health Organization

Declarations

Consent for publication

Not applicable

Availability of data and material

All relevant data are within the manuscript and its Supporting Information file.

Competing interests

All authors have declared that they have no competing interests.

Authors' contributions

AA: conception of the research idea, design, analysis, interpretation, and drafting the manuscript. **DD, PP**, and **DS**: Design, interpretation of results, reviewing and editing the manuscript. All authors have read and approved the final manuscript.

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6.3. Chapter summary

This chapter showed that among a cohort of 841 ALHIV on ART, 262 (31.1%) developed OIs during follow-up. The most common type of OIs was TB (n = 42; 15%), followed by sexually transmitted infections (n = 39; 14.4%). In addition, about 61.0% of OIs occurred during the first year of follow-up. Furthermore, the occurrence of OIs in undernourished participants was higher than in well-nourished participants. Lastly, undernutrition shortened the time to develop OIs in this population by almost nine months. The coming chapter presents findings from a longitudinal study examining weight change after ART initiation.

Chapter 7 │Weight change after ART initiation among ALHIV on in Ethiopia

7.1. Chapter introduction

This chapter discusses findings from a published study (Manuscript V) that assessed weight change after ART initiation. As mentioned in the literature gap (Chapter 2), evidence on weight gain after ART initiation, notably after introducing a new drug called DGT (often associated with weight gain), is lacking. Therefore, this literature gap is addressed through this study. The study followed 848 ALHIV for 24 months to examine weight changes over time and identify its determinants. The manuscript included in this chapter is presented in the following subheadings: abstract, strengths and limitations, introduction, methods, results, discussion, and conclusion. The manuscript has been published and is available in the *BMJ Open*.

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Authors' contributions for this manuscript

The candidate is the primary author of this study and was involved in the conception of the research idea, designing methodology, data analysis, interpretation of results, and drafting and editing the manuscript. The second, third, and fourth authors participated in developing research methods, interpreting results, and reviewing and editing the manuscript.

Weight change after antiretroviral therapy initiation among adults living with human immunodeficiency virus in Northwest Ethiopia: A longitudinal data analysis

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Abstract

Objectives: The first objective was to explore weight change in the first two years after antiretroviral therapy (ART) initiation in adults living with human immunodeficiency (HIV). The second objective was to identify the predictors of weight change over time among adults living with HIV on ART.

Design: An institution-based retrospective longitudinal study was conducted.

Setting: The study was conducted at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia.

Participants: The study included 848 randomly selected medical charts of adults living with HIV receiving ART between June 2014 and June 2020.

Primary and secondary outcomes: The primary outcome was weight change in the first two years after ART initiation. The secondary outcome was to identify predictors of weight change. Association between predictor variables and weight change was assessed using a linear mixed-effect model. Variables with p-values < 0.05 in the final model were considered as statistically significant predictors of weight change.

Results: Of 844 study participants, more than half (n=499; 58.8%) were female. Participants' mean weight increased from 54.2kg (SD± 9.6kg) at baseline to 59.5kg (SD± 10.7kg) at the end of follow-up. Duration of time on ART, sex, World Health Organization (WHO) clinical disease staging, functional status, nutritional status, and presence of opportunistic infections (OIs) were significant predictors of weight change at ART initiation. Significant interaction effects were observed between time and sex, WHO clinical disease staging, functional status, isoniazid preventive therapy (IPT), and nutritional status.

Conclusion: We found a linear increment of weight over 24 months of follow-up. Rate of weight gain over time was lower in patients with advanced disease stage and working functional status, whereas weight gain rate was higher in male and underweight patients.

Keywords: Adults living with HIV, ART, Ethiopia, weight change

Strengths and limitations of the study

- One of the strengths of this study is its large sample size (n=848), increasing precision.
- This study is the first of its kind to explore weight change in adults living with HIV in our study area.
- Longitudinal measurements on weight allowed us to thoroughly examine changes in weight over two years after ART initiation.
- Due to the retrospective nature of the study design, some important factors, such as dietary habits, physical activity, viral load (available only for 15% of all patients), and smoking status, were not available.
- We were unable to determine the anatomical distribution of weight gain, as data on body composition were not available.
- The generalizability of our results to other settings, particularly to developed countries, could be limited because we have defined adulthood as age ≥15 years.

Introduction

Human immunodeficiency virus (HIV)-associated weight loss and wasting syndrome are the most frequently occurring Acquired Immunodeficiency Syndrome (AIDS)-defining conditions and are associated with a higher risk of mortality and morbidity (Mangili et al., 2006; Tang et al., 2002; Wanke et al., 2000). Conversely, weight gain after antiretroviral therapy (ART) initiation is a good prognostic sign and associated with lower risk of mortality in underweight and normal-weight patients (Madec et al., 2009; Yuh et al., 2015). Though initiating highly active antiretroviral therapy (HAART) can significantly increase body weight and lean body mass (Achhra et al., 2016; Bakal et al., 2018; Koethe et al., 2016), particularly within the first year, the mechanisms are not fully understood (Lang et al., 2010; Rao et al., 2019). Weight gain after ART initiation could be due to the reversal of HIV-related catabolic effects (return-to-health). ART also reduces the occurrence and recurrence of opportunistic infections (OIs) and enhances gastrointestinal function, increasing appetite and nutrient absorption (Sax et al., 2020). It could also result from some antiretroviral regimens' side effects (Bhagwat et al., 2017; Taramasso et al., 2017).

Weight is one of the World Health Organization's (WHO) clinical staging parameters used to classify HIV-infected patients (Weinberg & Kovarik, 2010). Adult and adolescent patients with moderate unexplained weight loss (5-10%) are classified as stage II, patients with unexplained

severe weight loss (>10%) are classified as stage III, and those with HIV wasting syndrome are classified as stage IV (Ministry of Health Ethiopia, 2017). In developing countries, where monitoring the immunological and virological responses of patients is challenging (as routine viral load and CD4 cell count tests are expensive or simply unavailable) (Loveday et al., 2011), regular weight measurement is one of the most cost-effective tools used to monitor patients' clinical responses to ART (Colebunders et al., 2006).

Current Ethiopian ART treatment guidelines recommend that weight must be measured and recorded at each ART visit, demonstrating the importance of weight control (Ministry of Health Ethiopia, 2017). However, these guidelines do not discuss what constitutes an optimal weight gain after ART initiation in this population. Moreover, even if weight gain after ART initiation is common, not all patients gain weight and gains vary meaningfully across individuals (Sax et al., 2020; Tang et al., 2011; Weldesenbet et al., 2020). Longitudinal studies investigating weight change over time after initiating ART are essential to inform treatment guidelines. Additionally, identifying modifiable risk factors of weight gain in this population can help to improve the overall treatment outcomes. However, studies on longitudinal weight change after ART initiation among adults living with HIV in Ethiopia are scarce. Due to this, evidence-based weight management guidelines and recommendations are not available in this population in the context of Ethiopia, as mentioned above.

This study explored weight change in the first two years after ART initiation among adults living with HIV. The findings of this study will assist decision-makers, clinicians, and program planners to improve the quality of HIV patient care by enhancing the understanding of weight changes after initiating ART. Findings may also assist both adults living with HIV and clinicians in managing weight, particularly in resource-limited stings, including Ethiopia. In such settings, access to laboratory tests are limited; identifying simple and cost-effective tools to monitor disease progression such as weight measurement is imperative.

Methods

Study setting, design, and period

An institution-based retrospective longitudinal study was conducted among adults living with HIV receiving ART between June 2014 and June 2020 at Debre Markos Comprehensive Specialized Hospital (DMCSH), Northwest Ethiopia. DMCSH is located in the East Gojjam

administrative zone, Northwest Ethiopia, 300 km from Addis Ababa, the capital city of Ethiopia. It is currently the only referral hospital in East Gojjam Zone, with a catchment population of more than 3.5 million people. The total recorded number of PLHIV having ART initiated at DMCSH between June 2014 and June 2020 was 1,209, of which 1,177 (97.4%) were aged ≥ 15 years (adults). Despite ART care services are being uniform in all health facilities and provided by ART-trained persons, DMCSH hospital was selected because it provides ART follow-up and care services for a large proportion of HIV-positive patients (accounted for 36.6% (1,209) of all patients) in the East Gojjam Zone.

Study population

All adults living with HIV receiving ART between June 2014 and June 2020, who had at least two weight measurements (two visits) during ART follow-ups at DMCSH were eligible for inclusion. In this study, adulthood was defined as patients' ≥ 15 years of age since this population is considered and treated as adults in Ethiopia for treatment purposes. Patients transferred into DMCSH from other health institutions without baseline information and pregnant women were excluded. Pregnant women were excluded as pregnancy leads to weight gain, and nutritional assessment for pregnant women differs from other adults living with HIV (Ververs et al., 2013).

Sample size and sampling procedure

The sample size was determined using a formula for an independent cohort study, using Open Epi Version 3 (Kelsey et al., 1996) by considering the following parameters: α of 5%; power of 80%; $Z_{\alpha/2}$ of 1.96; P_0 of 19%; P_1 of 27%; and r of 1:1. The values of parameters to calculate sample size were taken from a previously conducted study in Ethiopia (Teshale et al., 2020). The calculated sample size was 802. After considering 10% chart incompleteness, the final sample size was 892. Then, the study participants were selected using a computer-generated simple random sampling technique. A list containing the medical registration number (MRN) of all adults living with HIV (n=1,177) who started ART between June 2014 and June 2020 was obtained from the health management information system unit of the DMCSH. A random number was generated for each patient using Microsoft™ Excel. These numbers were used to randomly select a sample of 892 participants from all adults living with HIV who started ART at DMCSH between June 2014 and June 2020.

Patient and public involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data collection procedures

Data abstraction tools were developed from the standard Ethiopian ART entry and follow-up forms currently used by Ethiopian hospitals to assure data quality (Ministry of Health Ethiopia, 2017). The tool included socio-demographic characteristics, clinical and immunological characteristics, follow-up characteristics, and longitudinal weight measurements. Laboratory tests and measurements recorded at ART initiation were the baseline values. Data were collected by two epidemiologists with Master-level qualifications currently employed by DMCSH and specialized in HIV. An experienced biostatistician in secondary data collection supervised the data collection process.

Variables of the study

This study's outcome (dependent) variable was weight change in the first two years after ART initiation among adults living with HIV who started ART for the first time (treatment naïve). Weight was measured in kilogram (kg) at ART initiation (baseline) and then measured repeatedly every three months for 24 months. The follow-up time was recorded in months from ART initiation until 24 months (early ART phase).

Predictor (independent) variables were socio-demographic variables, baseline immunological and clinical variables, and follow-up variables.

Socio-demographic variables included age, sex, level of education, residence, marital status, occupation, family size, and HIV-status disclosure. Baseline immunological and clinical variables included baseline OIs, CD4 cell counts, WHO clinical disease staging, Hgb level, nutritional status, functional status, ART eligibility criteria, and baseline ART regimen.

Follow-up variables were OIs during follow-up, ART adherence, history of ART regimen change, taking CPT, taking isoniazid preventive therapy (IPT), HIV treatment failure based on viral load, and length of time on ART.

Operational definitions

The WHO BMI classification for underweight was used, defined a body mass index (BMI) of less than 18.5 kg/m^2 as underweight (Weir & Jan, 2021).

ART adherence was classified as good, fair, or poor, according to the percentage of ART dosages taken, calculated from the total monthly dose of ART drugs (n=60). Good was defined as compliance equal to or greater than 95% or ≤ 3 missed doses per month; fair reflected 85-94% compliance or between 4 and 8 missing doses per month; and poor reflected less than 85% compliance or ≥ 9 missed doses per month (Ministry of Health Ethiopia, 2017).

HIV treatment failures was classified as clinical, immunological, and virological failure. Clinical failure is diagnosed when the patient developed new or recurrent clinical events indicating severe immunodeficiency (WHO clinical stage IV condition and certain WHO clinical stage III conditions such as pulmonary TB and severe bacterial infections) after six months of effective ART treatment. Immunological failure was diagnosed when a patient had a CD4 count at or below 250 cells/mm^3 following clinical failure or persistent CD4 levels below 100 cells/mm^3. Virological failure was diagnosed when the viral load was above or equal to 1000 copies/mL under ART based on two consecutive viral load measurements in three months apart, with adherence support following the first viral load test (Ministry of Health Ethiopia, 2017).

Functional status was classified as working, ambulatory, and bedridden. Working was defined as the capability of going out of home and participating in routine activities, including daily work. Ambulatory was defined as being capable of self-care and being able to use the toilet without support. Bedridden was defined as being unable to use the toilet without support (Ministry of Health Ethiopia, 2017).

Loss to follow-up (LTFU) is defined as adults living with HIV missing an ART appointment for at least one month (Ministry of Health Ethiopia, 2017).

According to WHO, anaemia is defined as haemoglobin levels less than 12 g/dl in males and < 13 g/dl in females (World Health Organization, 2011).

Statistical analyses

Exploratory data analysis, including individual profile plots of weight for 50 (for better visualization) randomly selected participants and the smoothed mean profile plot of all participants, were constructed. Since we used unbalanced data, a locally weighted scatterplot smoothing (LOWESS) mean was used. In addition, the mean and standard deviation of weight at each ART visit (every three months) were calculated. Normality assumption was checked using a Q-Q plot. The autoregressive (AR1) covariance structure was used in the final model. The two nested models (a model with only random intercept and a model with both random intercept and slope) were compared using the likelihood ratio (LR) test. Finally, a linear mixed-effect model (LMM) with random intercept and slope was applied to address the repeated measurements. The model goodness of fit was also assessed using a model diagnostic plot. Variables with $p \leq 0.25$ in the bivariate analysis were fitted into the multivariable analysis. For the LMM, statistical significance was set at $p < 0.05$. All statistical analyses were conducted using R Version 3.5.1 statistical software.

Results

Socio-demographic characteristics of participants

The final sample consisted of 848 adult records (see Figure 17). Of these, more than half (n=499; 58.8%) were female, and 45.3% (n=393) were married. More than three-quarters (n=665; 78.4%) of the study participants were from urban areas, and the median age of the study participants was 32 (IQR: 26-40) years. Nearly one-third (n=258; 30.4%) of the participants had no formal education. Furthermore, more than two-thirds (n=569; 67.1%) of the participants disclosed their HIV status (see Table 16).

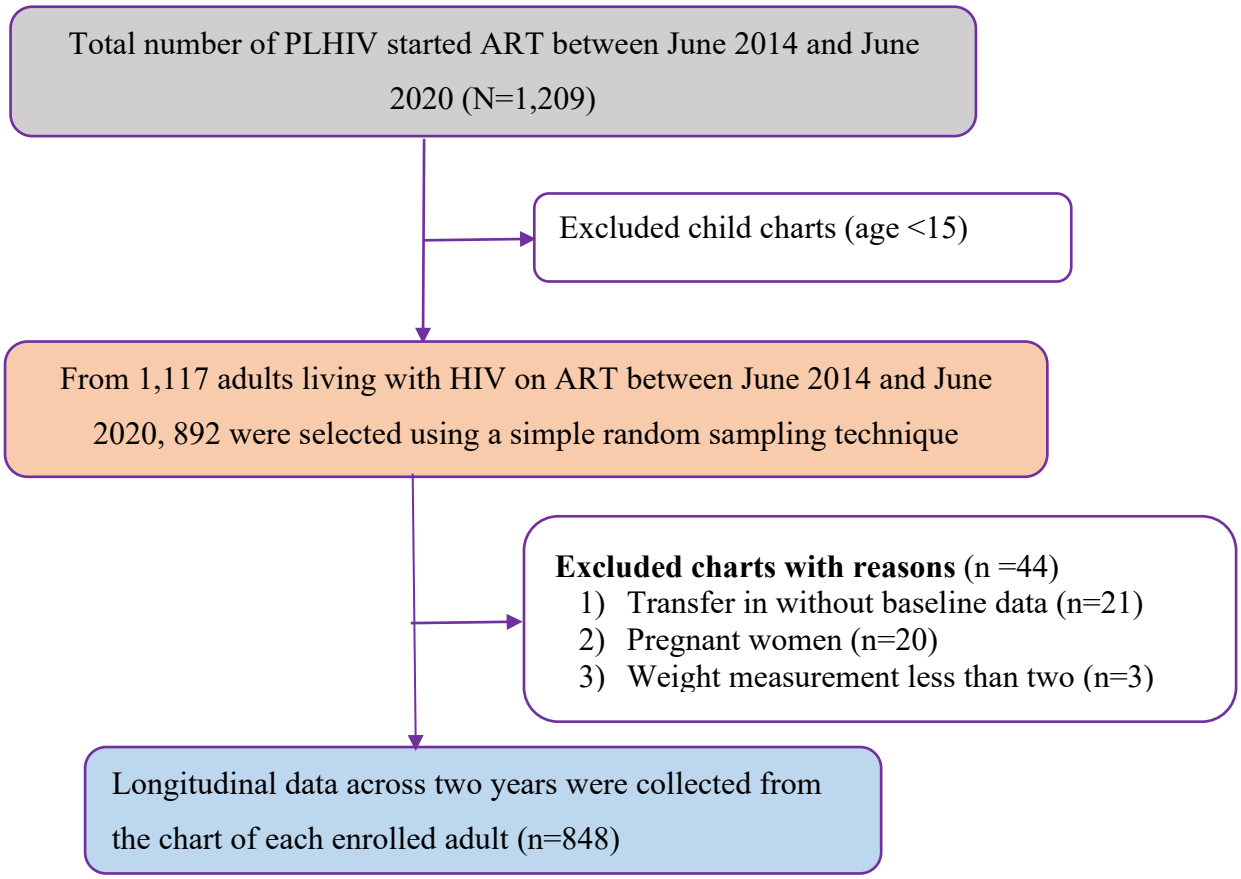

Figure 17. Flow chart showing the study participants recruitment process to assess weight change after ART initiation at Debre Markos Comprehensive Specialized Hospital in Northwest Ethiopia, between June 2014 and June 2020.

Table 14. Socio-demographic characteristics of adults living with HIV on ART at Debre-Markos Comprehensive Specialized Hospital, Northwest Ethiopia (n=848).

Variables	Frequency (N)	Percentage (%)
Residence		
Urban	665	78.4
Rural	183	21.6
Age (years of age)		
15-24	186	21.9
25-34	284	33.5
35-44	269	31.7
≥45	109	12.9
Sex		

Male	349	41.2
Female	499	58.8
Marital status		
Single	155	18.3
Married	393	45.3
Divorced	217	25.6
Widowed	83	9.8
Level of education		
No formal education	258	30.4
Primary	219	25.8
Secondary	224	26.4
Tertiary	147	17.3
Occupation		
Daily labourer	139	16.4
Merchant	168	19.8
Farmer	119	14.0
Employed	184	21.7
Student	47	5.5
Housewife	144	17.0
Others	47	5.5
HIV-status disclosure		
Disclosed	569	67.1
Not disclosed	279	32.9
Family size		
<3	470	55.4
≥3	387	44.6

Baseline clinical and immunological profile of participants

Approximately 40% (n=339) of the participants had baseline OIs (see Table 15), and more than a quarter (n=228; 26.9%) were underweight. The majority (n=707; 83.4%) were categorized as having a working functional status. Immunologically, 63.6% (n=406) of the participants had mild immunodeficiency (CD4 ≥200 cell/m^3). Clinically, 72.2% (n=612) of participants were classified as mild disease stage (WHO stage I and II). Majority (n=634; 79.4%) participants

were non-anaemic at ART initiation. More than half (n=470; 55.4%) of the study participants commenced ART through a test and treat approach.

Table 15. Baseline clinical and immunological profile of adults living with HIV on ART at Debre-Markos Comprehensive Specialized Hospital, Northwest Ethiopia (n=848).

Variables	Frequency (n)	Percentage (%)
Baseline OIs		
Yes	339	39.9
No	509	60.1
Baseline nutritional status		
Underweight	228	26.9
Normal-weight	620	73.1
Functional status		
Working	707	83.4
Ambulatory/ bedridden	141	16.6
CD4 Cell count		
Severe immunodeficiency (CD4 <200 cells/mm^3)	232	36.4
Mild immunodeficiency (CD4 ≥200 cells/mm^3)	406	63.6
WHO clinical staging		
Mild disease stage (Stage I&II)	612	72.2
Advanced disease stage (Stage III&IV)	236	27.8
Haemoglobin level		
Anaemic	164	20.6
Non-anaemic	634	79.4
ART eligibility criteria		
Immunological/clinical	378	44.6
Test and treat	470	55.4
Baseline ART regimens		
Efavirenz base	82	92.2
Nevirapine or Dolutegravir base	66	7.8

Follow-up characteristics of participants

The minimum and maximum length of time on ART for the study participants were six months (two visits) and 24 months, respectively. The median length of time on ART for the entire cohort was 12 months (IQR: 6-18). Almost one-third (n=269; 31.7%) of the participants developed OIs during the follow-up period. Three-quarters (n=637; 75.1%) of the participants had good adherence to their ART medication. Moreover, 62.5% (n=530) of the participants took prophylaxis for TB prevention (IPT). CPT was given to 73.2% (n=621) of the participants. Lastly, 2.7% (n=23) of participants had HIV treatment failure (see Table 16).

Table 16. Follow-up characteristics of adults living with HIV on ART at Debre-Markos Comprehensive Specialized Hospital, Northwest Ethiopia (n=848).

Variables	Frequency (n)	Percentage (%)
OIs during follow-up		
Yes	269	31.7
No	579	68.3
ART adherence		
Good	637	75.1
Fair/ poor	211	24.9
Regimen change		
Yes	266	31.4
No	582	68.6
Taking IPT		
Yes	530	62.5
No	318	37.5
Taking CPT		
Yes	621	73.2
No	227	26.8
HIV treatment failure		
Yes	23	2.7
No	825	97.3

Exploratory data analysis

The minimum and the maximum recorded weights throughout the follow-up period were 25kg and 98kg, respectively. Participants' mean weight increased from 54.2kg (SD± 9.6kg) at baseline to 59.5kg (SD± 10.7kg) at the end of follow-up. The average monthly weight gain was slightly higher (0.33kg/month) in the first year as compared to the second year (0.12kg/month) (see Table 17). The individual profile plots of 50 participants showed that considerable variability of weight change was observed between individuals (Appendix 7.1). Furthermore, the smoothed mean profile plot of all participants indicated a linear increment of weight over time (Appendix 7.2).

Table 17. Mean and standard deviation of weight at each visit among adults living with HIV on ART at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia.

Follow-up period (month)	(n)	Weight (in kg, mean ± SD))
Baseline	848	54.2 (± 9.6)
3rd month	848	55.7 (± 9.8)
6th month	779	56.7 (± 9.9)
9th month	649	57.6 (± 10.02)
12th month	590	58.1 (± 10.1)
15th month	543	58.4 (± 10.2)
18th month	509	58.7 (± 10.3)
21st month	484	58.9 (± 10.4)
24th month	445	59.5 (± 10.7)

Predictors of weight change

Initially, a bi-variable analysis was conducted, and variables with p-values ≤ 0.25 were included in the multivariable analysis. As presented in Table 18, the output from a multivariable LMM shows that duration of time on ART, sex, WHO clinical disease staging, functional status, nutritional status, and presence of OIs were factors significantly associated with weight change at ART initiation. Statistically significant interaction effects were observed between time and several variables, including sex, WHO clinical disease staging, functional status, IPT, and nutritional status. Specifically, with a one-month increase in ART treatment duration, mean body weight increased by 0.43kg (β=0.43, 95%CI: 0.35, 0.5). The mean weight

of male participants at ART initiation was 4.8kg higher than female participants (β=4.8, 95%CI: 3.5, 6.0), and the rate of weight gain over time in male participants was 0.07kg/month higher than female participants (β=0.07, 95%CI: 0.02, 0.11). The mean weight of patients with advanced disease stage was 2.6kg lower than patients with mild disease stage at ART initiation (β=-2.6, 95%CI: -4.2, -1.0), and the rate of weight gain was 0.08kg/month less in patients with advanced disease stage than those with mild disease stage (β=-0.08, 95%CI: -0.14, -0.02).

The average weight of participants presented with working functional status was 3.9kg higher than the average weight of participants presented with ambulatory/bedridden functional status (β=3.9, 95%CI: 2.2, 5.7) at ART initiation. However, over time, the monthly weight gain rate in participants with working functional status was 0.08kg/month less than participants with ambulatory/bedridden functional status (β=-0.08, 95%CI: -0.16, -0.01). The mean weight of normal weight participants was estimated to be 8.6kg higher than underweight (BMI< 18.5kg/m^2) participants at baseline (β=8.8, 95%CI: 7.1, 10.1). However, the rate of weight gain over time in normal-weight participants was 0.11kg/month less than their underweight counterparts (β=-0.11, 95%CI: -0.17, -0.06). At ART initiation, the average weight in patients presenting with OIs was 2.6kg less than the average weight of patients presenting without OIs (β=-2.6, 95%CI: -3.9, -1.3). However, no statistically significant difference was observed in the monthly weight gain rate over time between patients presenting with OIs and without OIs. There was no significant difference of mean weight between patients who took IPT and those who did not take IPT at baseline, but there was a higher rate of weight gain among participants who did not take IPT compared to those who took IPT (β=-0.05, 95%CI: -1.1, -0.001) (see Table 18).

Table 18. Multivariable linear mixed effect model to identify predictors of weight change among adults living with HIV on ART at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia.

Variables	Coefficient	95%CI	P-values
Intercept	46.2	(43.5, 48.8)	<0.001
Residence			
Urban	0.9	(-0.7, 2.5)	0.2747
Rural	Ref	—	—
Sex			

Male	4.8	(3.5, 6.0)	<0.001
Female	Ref	—	—
WHO clinical staging			
Mild disease stage	Ref	—	—
Advanced disease stage	-2.6	(-4.2, -1.0)	0.0012
Functional status			
Working	3.9	(2.2, 5.7)	<0.001
Ambulatory/bedridden	Ref	—	—
ART eligibility criteria			
Immunological/clinical	Ref	—	—
Test and treat	-1.1	(-2.4, 0.2)	0.0875
ART adherence			
Good	Ref	—	—
Fair/poor	-0.7	(-2.1, 0.7)	0.3250
Baseline nutritional status			
Underweight	Ref	—	—
Normal weight	8.6	(7.1, 10.1)	<0.001
Taking IPT			
Yes	-0.2	(-1.5, 1.2)	0.8002
No	Ref	—	—
Baseline OIs			
Yes	-2.6	(-3.9, -1.3)	0.0001
No	Ref	—	—
Time on ART	0.43	(0.35, 0.5)	<0.001
Sex*time			
Male*time	0.07	(0.02, 0.11)	0.0073
Female*time	Ref	—	—
WHO clinical staging*time			
Mild disease stage*time	Ref	—	—
Advanced disease stage*time	-0.08	(-0.14, -0.02)	0.0073
Functional status*time			
Working*time	-0.08	(-0.16, -0.01)	0.0192

Ambulatory/ bedridden*time	Ref	—	—
Baseline nutritional status*time			
Underweight*time	Ref	—	—
Normal*time	-0.11	(-0.17, -0.06)	0.0001
Taking IPT*time			
Yes*time	-0.05	(-1.1, -0.001)	0.0434
No*time	Ref	—	—
Variance component			
Standard deviation (Intercept)	6.3		
Standard deviation (Time)	0.13		
Standard deviation (Residual)	5.0		
Corr (intercept)	0.343		

Discussion

In this longitudinal study of 848 participants, we found a linear increment of weight over 24 months of follow-up, with a higher rate of weight gain in the first 12 months. This study also showed that the duration of time on ART has a positive association with weight gain. The mean weight at ART initiation and the rate of weight gain over time was higher in male participants than female participants. The mean weight at ART initiation and weight gain rate over time was lower in patients with advanced disease stage than in patients with mild disease stage. Normal-weight patients had a higher mean weight at ART initiation but less weight gain over time than underweight patients. In addition, patients with working functional status had a higher mean weight at ART initiation but a lower rate of weight gain over time, compared to participants with ambulatory or bedridden functional status. Furthermore, patients presenting with OIs had less mean weight at ART initiation than patients presenting without OIs. However, no statistically significant difference was observed over time in the monthly weight gain rate between patients presenting with and without OIs. Lastly, at ART initiation, there was no significant difference in mean body weight between patients who received IPT and those who did not. However, the rate of weight gain was higher in participants who did not take IPT than in those who took IPT.

In this study, patients experienced a slightly higher weight gain rate in the first year of ART than in the second year (0.33kg/month vs 0.12kg/month). Similar patterns of higher weight

gain in the first year of ART treatment were noted in previous studies conducted in similar low resource settings (Huisin ’t Veld et al., 2015), including Vietnam (Tang et al., 2011), and Cambodia and Kenya (Madec et al., 2009). Although the exact mechanisms of weight gain following ART remain unclear, reasons may include reversing HIV-related catabolic effects (return-to-health) and reducing the basal metabolic rate due to viral load suppression (Bourgi et al., 2020). ART also significantly reduces the occurrence and recurrence of OIs and enhances gastrointestinal function, increasing appetite and nutrient absorption (Sax et al., 2020). This study’s finding of a one-month mean body weight increase of 0.43kg during ART treatment is consistent with prior Ethiopian studies (Reda et al., 2013; Weldesenbet et al., 2020). This may be explained by patients on ART for a longer period demonstrating higher levels of healthy practices, including ART adherence and social support, thereby enhancing clinical outcomes (Siril et al., 2017).

Men had a higher mean weight at baseline and a higher rate of weight gain over time than women. While this finding is consistent with a previous Ethiopian study (Weldesenbet et al., 2020), it contradicts previous studies (Sax et al., 2020; Yuh et al., 2015) done elsewhere. Gender differences in weight gain might be associated with hormonal differences, and a higher likelihood of female patients living with HIV developing psychosocial issues such as anxiety and depression, negatively affecting body weight (Albert, 2015; Kuehner, 2017). In addition, a meta-analysis showed that the proportion of women reporting 90% adherence to prescribed ART was lower than that of their male counterparts (Ortego et al., 2012). Furthermore, lower weight gain in females might be due to higher levels of food insecurity among females in developing countries (Boneya et al., 2019; Jung et al., 2017). This implies that gender-specific interventions and close follow-up are needed to improve weight among patients living with HIV on ART.

The mean weight of normal-weight participants was higher than underweight participants at baseline. However, the rate of weight gain over time was higher in underweight participants compared to their normal-weight counterparts, consistent with findings in previous studies (Achhra et al., 2016; Crum-Cianflone et al., 2010; Koethe et al., 2010). This may be explained by underweight patients benefiting more directly from nutritional improvements resulting from ART initiation, such as increased nutritional intake and absorption by decreasing the occurrence and recurrence of OIs (Günthard et al., 2016). Moreover, underweight PLHIV are eligible for nutritional supplements (Mallewa et al., 2018), as nutritional supplements in this

population significantly increase weight (PrayGod et al., 2018). Thus, the weight of underweight patients can be further improved by providing appropriate nutritional education, as recommended by the Ethiopian ART guidelines (Ministry of Health Ethiopia, 2017).

This study also found that participants in advanced disease stages had a lower mean weight at baseline and gained less weight over time than participants presented with mild disease stage. This finding is supported by prior studies done in low-resource settings (Huisin ’t Veld et al., 2015; Reda et al., 2013). Poor weight gain in patients with advanced disease stages might be due to (undiagnosed) OIs, especially TB, or high-energy expenditure due to increased metabolic demand. Reported energy requirements for symptomatic adults living with HIV increased by 20-30% compared to a 10% increase in asymptomatic adults living with HIV (L. Kosmiski, 2011). Furthermore, the most common cause of swallowing difficulty, like oesophageal candidiasis, is a defining characteristic of stage IV, while unexplained chronic diarrhoea and pulmonary TB are the main clinical manifestation of stage III (Ministry of Health Ethiopia, 2017). These comorbidities indicate that weight management of HIV patients with advanced disease stages need special attention and can be addressed by preventing and treating OIs, improving ART adherence, and providing counselling to improve diet by consuming locally available foods.

At ART initiation, the mean weight was lower in patients presenting with OIs compared to patients without OIs, but no statistically significant difference was observed over time. OIs cause weight loss in PLHIV through impaired nutrient absorption due to chronic diarrhoea or intestinal tract damage, or reduced dietary intake due to oral thrush and oesophageal candidiasis (Evans et al., 2012). Moreover, patients presenting with OIs, especially tuberculosis, could have an inadequate response to ART due to common complications in people starting ART with co-infections and co-morbidities (World Health Organization, 2016a). Our results suggested that if clinicians are proactive in prevention and treatment of OIs as early as possible, they could significantly improve the weight trajectory of HIV-infected patients on ART.

The average weight of participants with working functional status was higher than participants with ambulatory or bedridden functional status at ART initiation. However, the weight gain rate over time in participants with working functional status was less than participants with ambulatory or bedridden functional status. This finding is consistent with studies conducted elsewhere (Baraki et al., 2019; Weldesenbet et al., 2020) and likely reflects HIV disease severity before ART initiation and the return to health in patients with more advanced disease.

Lastly, there is a higher rate of weight gain among participants who did not take IPT compared to those who took IPT. This finding is directly associated with disease progression, as IPT is indicated for HIV-positive patients with advanced disease but has no confirmed TB infection (Ministry of Health Ethiopia, 2017; World Health Organization, 2016b). In addition, it may be directly related to the side effects of IPT, such as vomiting, loss of appetite, and nausea which are the most common side effects of IPT (Denholm et al., 2014).

Conclusion

In this study, we found a linear increment of weight over 24 months of follow-up, with a higher rate of weight gain in the first 12 months. Over time, the rate of weight gain was lower in patients with advanced disease stage, who took IPT and working functional status. However, male and underweight patients had a higher rate of weight gain. The clinical implication is that health professionals must continuously monitor and assess patients' weight with poor clinical conditions (i.e., patients presented with advanced disease stage and OIs) to find potential reasons for failure to gain weight. Further studies examining the effects of weight gain on treatment outcomes by incorporating some variables, such as dietary and exercise habits, are needed.

List of abbreviations

AIDS: Acquired Immune Deficiency Syndrome, **ART**: Antiretroviral Therapy, **BMI:** Body Mass Index, **CPT**: Co-trimoxazole Preventive Therapy, **DMCSH:** Debre Markos Comprehensive Specialized Hospital, **HAART**: Highly Active Antiretroviral Therapy, **Hgb**: Hemoglobin, **HIV**: Human Immunodeficiency Virus, **IPT:** Isoniazid Preventive Therapy, **IQR:** Interquartile Range, **Kg**: Kilogram, **LMM:** Linear Mixed Model, **OIs:** Opportunistic Infections, **PLHIV**: People Living with Human Immunodeficiency Virus, **SD:** Standard Deviation, **TB**: Tuberculosis, and **WHO**: World Health Organization.

Declarations

Ethics approval and consent to participate

Ethical approvals and permissions were granted from the DMCSH Medical Director Office, the University of Technology Sydney Medical Research Ethics Committee (ETH20-5044), and the Amhara Regional Public Health Research Ethics Review Committee (Ref. no: 816). As the

study was based on existing medical records of PLHIV, informed verbal or written consent from participants was not feasible. However, the data was entirely de-identifiable to authors since the participants' unique ART numbers and names were not included in the data abstraction tool.

Consent for publication: Not applicable

Availability of data and material: Data used for this study will be available upon reasonable request to the corresponding author.

Authors' contributions: AA: conception of the research idea, design, analysis, interpretation, and drafting the manuscript. **DD, PP**, and **DS**: Design, interpretation of results, reviewing and editing the manuscript. All authors have read and approved the final manuscript.

Competing interests: Authors have declared that they have no competing interests.

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7.3. Chapter summary

This chapter found that a linear increment of weight over 24 months of follow-up, with a more substantial weight gain in the first 12 months. Duration of time on ART, sex, WHO clinical disease staging, functional status, nutritional status, and presence of OIs were identified as significant predictors of weight change. Significant interaction effects were observed between time and some variables, including sex, WHO clinical disease staging, functional status, IPT, and nutritional status. The upcoming chapter describes findings from a longitudinal study that examines the association between BMI variation and early mortality among ALHIV on ART in Northwest Ethiopia.

Chapter 8 │Association between body mass index variation and early mortality among ALHIV on ART in Ethiopia

8.1. Chapter introduction

This chapter presents the results of a published retrospective longitudinal study (Manuscript VI) that examined the association between longitudinal changes in BMI and mortality after ART initiation in ALHIV. The manuscript addressed the fifth objective using the records of 834 ALHIV receiving ART at DMCSH in Northwest Ethiopia between June 2014 and June 2020. This manuscript has been published and is available online in *Infectious Diseases and Therapy*.

8.2. Publication (Published in *Infectious Diseases and Therapy)*

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Authors' contributions for this manuscript

The candidate is the primary author of this study and was involved in the conception of the research idea, designing methodology, data analysis, interpretation of results, and drafting and editing the manuscript. The second and fourth authors participated in designing the research method, interpreting of results, and reviewing and editing the manuscript. The third author interpreted the results, reviewed, and edited the manuscript.

Association between body mass index variation and early mortality among 834 Ethiopian adults living with HIV on ART: A joint modelling approach

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Abstract

Introduction: Body mass index (BMI) is a simple and cost-effective tool for monitoring the clinical responses of patients living with human immunodeficiency virus (HIV) after antiretroviral therapy (ART) initiation, especially in resource-limited settings where access to laboratory tests are limited. Current evidence on the association between longitudinal BMI variation and clinical outcomes among adults living with HIV receiving ART is essential to inform clinical guidelines. Therefore, this study examines the association between BMI variation and premature mortality in adults living with HIV on ART.

Methods: An institution-based retrospective cohort study was conducted among 834 adults living with HIV receiving ART from June 2014 to June 2020 at Debre Markos Comprehensive Specialized Hospital in Northwest Ethiopia. We first identified predictors of mortality and BMI variation using proportional hazards regression and linear mixed models, respectively. Then, the two models were combined to form an advanced joint model to examine the effect of longitudinal BMI variation on mortality.

Results: Of the 834 participants, 49 (5.9%) died, with a mortality rate of 4.1 (95% CI: 3.1, 5.4) per 100 person-years. A unit increase in BMI after ART initiation corresponded to an 18% reduction in mortality risk. Patients taking tuberculosis preventive therapy (TPT), mild clinical disease stage, and changing ART regimens were at lower risk of death. However, patients with ambulatory/bedridden functional status were at higher risk of death. Regarding BMI variation over time, patients presenting with opportunistic infections (OIs), underweight patients, patients who started a Dolutegravir (DGT)-based ART regimen and those with severe immunodeficiency had a higher BMI increase over time. However, patients from rural areas and overweight/obese patients experienced a lower BMI increase over time.

Conclusion: BMI improvement after ART initiation was strongly associated with a lower mortality risk, regardless of BMI category. This finding implies that BMI may be used as a better predictor tool for death risk in adults living with HIV in Ethiopia. Additionally, patients who took a DGT-based ART regimen had a higher BMI increase rate over time, which aligns with possible positive effects, such as weight gain, of the DGT-based ART regimen in developing countries.

Keywords: Adults living with HIV, ART, body mass index, Ethiopia, mortality

Key summary points

Why carry out this study?

- Current studies on the association between BMI variation and clinical outcomes in adults living with HIV receiving ART is essential to inform clinical guidelines.
- Therefore, this study examines the association between BMI variation and premature mortality in adults living with HIV on ART.

What was learnt from this study?

- This study found that an increase in BMI after ART initiation was strongly associated with a lower risk of mortality in adults living with HIV.
- Patients who took a DGT-based ART regimen had a higher BMI increase rate over time, which aligns with possible positive effects, such as weight gain, of the DGT-based ART regimen in developing countries.

Introduction

Undernutrition (body mass index (BMI) < 18.5kg/m^2) is a common problem among people living with human immunodeficiency virus (PLHIV) in sub-Saharan Africa (SSA) (Alebel et al., 2021). The problem is more prominent in Ethiopia as a result of food insecurity and inadequate knowledge about healthy nutrition (The World Bank, 2022). Approximately 26% of adults living with HIV in Ethiopia are undernourished (Alebel et al., 2020); as HIV increases nutritional requirements and reduces food intake due to mouth and throat sores, loss of appetite, medication side effects, or household food insecurity. Furthermore, it decreases nutrient absorption due to HIV infection of intestinal cells, diarrhoea, and vomiting (Enwereji et al., 2019).

Although antiretroviral therapy (ART) significantly improves PLHIV survival, early mortality from acquired immunodeficiency syndrome (AIDS)-related illness remains high, notably in SSA (Braitstein et al., 2006; Grinsztejn et al., 2009). Common factors associated with high premature death in PLHIV are low CD4 cell counts, male gender, advanced clinical disease stage, anaemia, tuberculosis (TB), and low BMI (Gupta et al., 2011; Leite et al., 2022; Saavedra et al., 2017; Zachariah et al., 2006). Studies frequently cited that low BMI at ART initiation is an independent predictor of mortality in adults living with HIV (Alebel et al., 2021;

Johannessen et al., 2008; Zachariah et al., 2006; Zhang et al., 2016), while normal BMI is significantly associated with adequate CD4 cell count response to ART and lower risk of loss to follow-up (Evans et al., 2012).

The association between BMI and mortality in adults living with HIV is well documented, but most of these studies used baseline BMI only which is limiting (Damtew et al., 2015; Dao et al., 2011; Tesfamariam et al., 2016). A single measurement does not adequately capture body weight variances over time, which limits association with mortality. Furthermore, the association between a single BMI measurement and mortality may be confounded by underlying diseases and health conditions that may cause weight loss (Robins, 2008). Despite joint modelling being highly recommended to examine the association between time-varying covariates (i.e., BMI) and mortality, previous studies have used standard statistical models (i.e., Cox regression) to assess the association between BMI and mortality (Evans et al., 2012; Naidoo et al., 2018; Otwombe et al., 2014).

Viral load and CD4 cell count measurements for monitoring patient response after ART initiation are often expensive or unavailable in developing countries, including Ethiopia. Therefore, understanding and developing easy and cost-effective alternative measurements, such as BMI, is critical. Although current Ethiopian ART guidelines include BMI as a clinical indicator for patients living with HIV (Ministry of Health Ethiopia, 2017), these guidelines are not evidence-informed due to lack of longitudinal studies examining the association between BMI variation and early mortality among adults living with HIV.

This study aimed to assess the impact of BMI variation on early mortality among adults living with HIV receiving ART in Northwest Ethiopia. The findings may assist healthcare professionals and policymakers design evidence-based interventions to improve BMI, eventually reducing nutrition-related mortality. Our findings can inform future Ethiopian ART guidelines.

Methods

Study design, period, and area

This institution-based retrospective cohort study used de-identified data extracted from the medical records of adults living with HIV who received ART between June 2014 and June 2020 at Debre Markos Comprehensive Specialized Hospital (DMCSH) in Northwest Ethiopia.

The DMCSH is located 300 km from Addis Ababa, the capital of Ethiopia, and 265 km from Bahir-Dar, the main city of the Amhara Region. It is the only referral hospital in the East Gojjam Zone and serves more than 3.5 million people in its catchment area. The hospital has been providing HIV care and antiretroviral treatment to people living with HIV since 2005. Of the 1,209 people living with HIV who received ART at DMCSH between June 2014 and June 2020, 1,177 (97.4%) were 15 years of age or older (defined as adults).

Study participants

Study participants include all adults living with HIV who received ART between June 2014 and June 2020 at DMCSH for at least one month and who had at least two BMI measurements. Patients, who transferred to DMCSH without baseline information, pregnant, or did not have the date of the event (death) recorded, were excluded.

Sample size and sampling

The minimum sample size required for this study was estimated based on the formula for an independent cohort study, using the Open Epi Version 3.01 (Kelsey et al., 1996). The following assumptions were made: α of 5%; power of 80%; $Z_{\alpha/2}$ of 1.96; P_0 of 19%; P_1 of 27%; and r of 1:1. The value of each parameter was obtained from a previous study conducted in Ethiopia (Teshale et al., 2020), resulting in a required sample size of 802. Assuming 10% chart incompleteness, the final required sample was estimated to be 892. There were 1,117 adults living with HIV on ART at DMCSH between June 2014 and June 2020. The medical records of 892 study participants were selected using a simple random sampling technique. We obtained the medical registration numbers (MRNs) for all adults living with HIV on ART at DMCSH between June 2014 and June 2020.

Data collection procedures

To maintain data quality, a standardized data extraction checklist was used, adapted from the national ART entry and follow-up forms currently employed by Ethiopian hospitals (Ministry of Health Ethiopia, 2017). The data extraction checklist included sociodemographic, clinical, and treatment-related variables. Sociodemographic variables were age, sex, level of education, residence, marital status, occupation, family size, and HIV-status disclosure. Clinical variables included baseline opportunistic infections (OIs), CD4 cell counts, World Health Organization (WHO) clinical disease staging, haemoglobin (Hgb) levels, nutritional status, functional status,

and ART eligibility criteria. Treatment-related variables consisted of ART adherence, change in ART regimen, taking co-trimoxazole preventive therapy (CPT), taking tuberculosis preventive therapy (TPT), HIV treatment failure based on viral load, and length of time on ART. Laboratory results and measurements recorded during ART initiation were taken as baseline values. All necessary data were extracted manually from patient charts. Two epidemiologists currently working at the study hospital, both with postgraduate qualifications who are specialized in HIV care, were employed as data collectors. Additionally, a biostatistician with extensive experience in secondary data collection closely supervised the entire data collection process.

Study variables and measurements

This study had two outcome variables. The primary outcome was survival, determined as the length of time (in months) after ART initiation until a patient died, lost to follow-up, transfer out to another health facility, or end of follow-up. Death was ascertained by reviewing the patient medical record written by a managing physician. Study participants were classified as event (death) or censoring (other than event). Early mortality was considered when patients died from any cause within the first 24 months of starting ART. The secondary outcome was the BMI variation in the first two years after ART initiation. Body weight was measured in kilogram (kg) at baseline (ART initiation) and then every three months for two years (24 months) with the corresponding BMI for each visit calculated by dividing weight in kilograms by the height in meters squared (kg/m^2).

Explanatory (independent) variables included sociodemographic, clinical, and treatment-related variables (as described in the data collection section). Detailed information, including classification and operational definitions of the explanatory variables were available as supplementary material (Appendix 8.1).

Data management and statistical analyses

Missing data

The values for some variables were not available due to incomplete medical records. For example, 202 (24%) CD4 counts and 48 (5.7%) haemoglobin levels were not recorded in medical records. Missing values for CD4 counts and haemoglobin levels were accounted for using a multiple imputation method. Little's missing completely at random test was applied to

verify whether the values were missing at random or not before performing the actual multiple imputation (Little, 1988). A multivariate normal imputation model was employed for the final imputation. Covariates included in the imputation model were sex, residence, WHO clinical disease staging, ART adherence, nutritional status, baseline OIs, CPT, and TPT.

Longitudinal model to assess variations in BMI over time

Individual profile plots were used to assess variation in BMI within and between subjects, and a smoothed mean profile plot was used to visualize the average evolution over time. A locally weighted scatterplot smoothing (LOWESS) mean was used because BMI contained unbalanced data. The mean and standard deviation of BMI every three months were calculated. The normality assumption was assessed using a Q-Q plot, and model comparison was done using a likelihood ratio (LR) test. A linear mixed model (LMM) with random intercept and slope was used as the final model. Variables with $p \leq 0.25$ in the bivariate analysis were included in the multivariable analysis. The model goodness of fit was assessed using a model diagnostic plot.

Survival model

The survival time of study participants was examined using the Kaplan-Meier survival curve. Both bivariable and multivariable proportional hazards regression models were fitted to identify predictors of mortality. Only variables with $p \leq 0.25$ in the bivariable analysis were included in the multivariable models. The proportionality assumption of the Cox-proportional hazards regression model was assessed using the Schoenfeld residual test. Adjusted hazard ratios (AHRs) with 95% confidence intervals (CIs) and p-values were used to assess significant predictors of mortality.

Survival and longitudinal joint modelling

Association between BMI variation and early mortality was assessed using joint modelling. We compared various specifications of the baseline risk function for the survival sub-model using the *Akaike information and Bayesian information criteria.* Lastly, a linear mixed-effects model and a relative risk model with a piecewise-constant baseline risk function (piecewise PH-GH) were used. For all models, statistical significance was set at $p < 0.05$. All statistical analyses were performed using Stata 16 and R version 4.1.2 statistical software.

Compliance with Ethics Guidelines

Ethical approvals and permissions were granted from the DMCSH Medical Director's Office, the University of Technology Sydney Health and Medical Research Ethics Committee (ETH20-5044), and the Amhara Regional Public Health Research Ethics Review Committee (Ref. no: 816). As the study was based on existing medical records of PLHIV, obtaining participants' verbal or written informed consent was not feasible, and a waiver of consent was granted. Data were completely de-identifiable to the authors, as the data abstraction tool did not include participants' unique ART numbers and names.

Results

Sociodemographic characteristics

Of the 892 sampled patient charts, 58 records were excluded for the following reasons: transferred to DMCSH without baseline information (n=21), pregnant women (n=20), weight measured only once (n=3), the treatment outcome date was not recorded (n=10), and height recorded only once (n=4). In total, 834 adult records were included in the final analysis. About one-fifth (21.8%, n=182) were from rural areas and 41.6% (n=347) were male. The median age of participants at ART initiation was 32 years (interquartilerange (IQR): 14 years). One quarter (25.7%; n=214) of participants were divorced and almost one-third had no formal education (30.3%; n=253). More than two-thirds (67.2%; n=560) of participants disclosed their HIV status and more than half (55.2%; n=460) came from families with less than three family members. See Table 19 for detailed participant sociodemographic characteristics.

Table 19. Sociodemographic characteristics of adults living with HIV receiving ART at DMCSH between Jane 2014 and June 2020 (n=834).

Variables	Frequency (N)	Percentage (%)
Residence		
Urban	652	78.2
Rural	182	21.8
Age (years of age)		
15-24	182	21.8
25-34	279	33.5

35-44	264	31.7
≥45	109	13.0
Sex		
Male	347	41.6
Female	487	58.4
Marital status		
Single	151	18.1
Married	387	46.4
Divorced	214	25.7
Widowed	82	9.8
Level of education		
No formal education	253	30.3
Primary	214	25.7
Secondary	221	26.5
Tertiary	146	17.5
Occupation		
Daily labourer	137	16.4
Merchant	166	19.9
Farmer	119	14.3
Employed	181	21.7
Student	46	5.5
Housewife	139	16.7
Others	46	5.5
HIV-status disclosure		
Disclosed	560	67.2
Not disclosed	274	32.8
Family size		
<3	460	55.2
≥3	374	44.8

Clinical and treatment-related characteristics

Three hundred and thirty-six (40.3%) patients presented with OIs at ART initiation with 83.1% (n=693) classified as working functional status. One-third (33.0%; n=275) were severely

immunocompromised, and 28.3% (n=236) were classified as having advanced disease. More than half (55.2%; n=460) initiated ART through test and treat strategy. One-fifth (20.5%, n= 171) of participants were anaemic, with mean haemoglobin level and the median CD4 count at ART initiation being 13.8 g/dl (SD ±2.3 g/dl) and 318.9 cell/m^3 (IQR: 344 cell/m^3), respectively. Most participants (87.2%; n=727) started on the Efavirenz-based ART regimen and three-quarters (74.9%; n=625) demonstrated good adherence to ART. About one-third (31.8%; n=265) changed from their initial ART regimen during the study, with the availability of new drugs being the most common reason for regimen change (n=228, 84.1%). Most patients underwent TPT and CPT with 62.8% (n=524) and 73.6% (n=614), respectively. ART treatment failure occurred in 23 individuals (2.7%) (See Table 20).

Table 20. Clinical and treatment related characteristics of adults living with HIV receiving ART at DMCSH between June 2014 and June 2020 (n=834).

Variables	Frequency (n)	Percentage (%)
Baseline OIs		
Yes	336	40.3
No	498	59.7
Functional status		
Working	693	83.1
Ambulatory/ bedridden	141	16.9
Immunodeficiency		
Severe (CD4 <200 cells/mm^3)	275	33.0
Mild (≥200 cells/mm^3)	559	67.0
WHO clinical disease staging		
Mild **(**Stage I and II)	598	71.7
Advanced **(**Stage III and IV)	236	28.3
Haemoglobin level		
Anaemic	171	20.5
Non-anaemic	663	79.5
ART eligibility criteria		
Immunological/clinical	374	44.8
Test and treat	460	55.2
Baseline ART regimens		

Efavirenz (EFV)-based	727	87.2
Dolutegravir (DGT)-based	61	7.3
Others	46	5.5
ART adherence		
Good	625	74.9
Fair/ poor	209	25.1
Baseline nutritional status		
Underweight	223	26.7
Normal-weight	543	65.1
Overweight/obesity	68	8.2
ART regimen change		
Yes	265	31.8
No	569	68.2
Taking IPT		
Yes	524	62.8
No	310	37.2
Taking CPT		
Yes	614	73.6
No	220	26.4
ART failure		
Yes	23	2.8
No	811	97.2

Exploratory data analysis of body mass index variation over time

At ART initiation, 223 (26.7%) participants had BMI < 18.5 kg/m^2 (underweight), with minimum and maximum BMI recorded during the 24 months of follow-up being 12.9 kg/m^2 and 33.6 kg/m^2, respectively. The minimum and maximum BMI recorded during the 24 months of follow-up were 12.9 kg/m^2 and 33.6 kg/m^2, respectively. The participants' mean BMI at baseline was 20.5 kg/m^2 (SD± 3.1 kg/m^2), and at termination was 22.6 kg/m^2 (SD± 3.3 kg/m2). On average, participants' mean BMI increased by 0.14 kg/m^2 per month in the first 12 months and increased by 0.03 kg/m^2 in the second year (see Table 3). Individual profile plots of 50 randomly selected patients showed that BMI varied significantly between individuals at ART initiation and during follow-up. However, less variability was observed within individuals

(Appendix 8.2). The overall smoothed mean profile plot showed a linear increase in average BMI (see Figure 18).

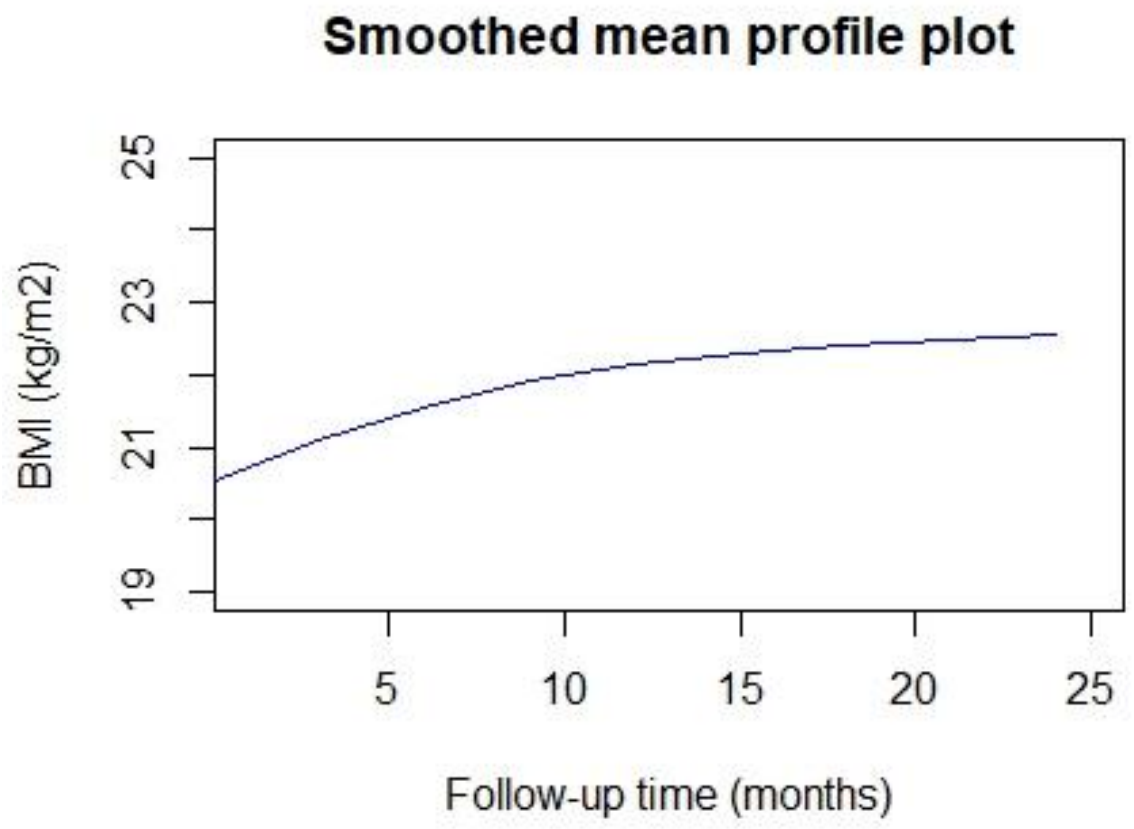

Figure 18. The smoothed mean profile plot of body mass index among adults living with HIV receiving ART at DMCSH, Northwest Ethiopia.

Table 21. Mean and standard deviation of BMI every three months in adults living with HIV receiving ART at DMCSH, Northwest Ethiopia.

Follow-up time (month)	(n)	BMI (in kg/m^2, mean ± SD))
Baseline	834	20.5 (± 3.09)
3rd month	834	21.1 (± 3.08)
6th month	770	21.5 (± 3.1)
9th month	635	21.9 (± 3.13)
12th month	577	22.2 (± 3.16)
15th month	530	22.3 (± 3.19)
18th month	596	22.4 (± 3.21)
21st month	471	22.4 (± 3.26)

24th month	433	22.6 (± 3.32)

Incidence of early mortality during ART follow-up

Participants were followed for a minimum of three months and a maximum of 24 months, contributing to 14,277 person-months. Two-year follow-up showed 49 (5.9%) participants died resulting in a mortality rate of 4.1 (95% CI: 3.1, 5.4) per 100 person-years. Of these deaths, 49% (n=24), 75.5% (n=37), and 79.6% (n=39) happened within the first six, 12 months, and 18 months of ART follow-up, respectively. The cumulative survival probability at the end of 24 months was 0.92 (95% CI: 0.89, 0.94). The mean survival time for the entire cohort was 23 months (95% CI: 22.7, 23.3 months) (see Figure 19).

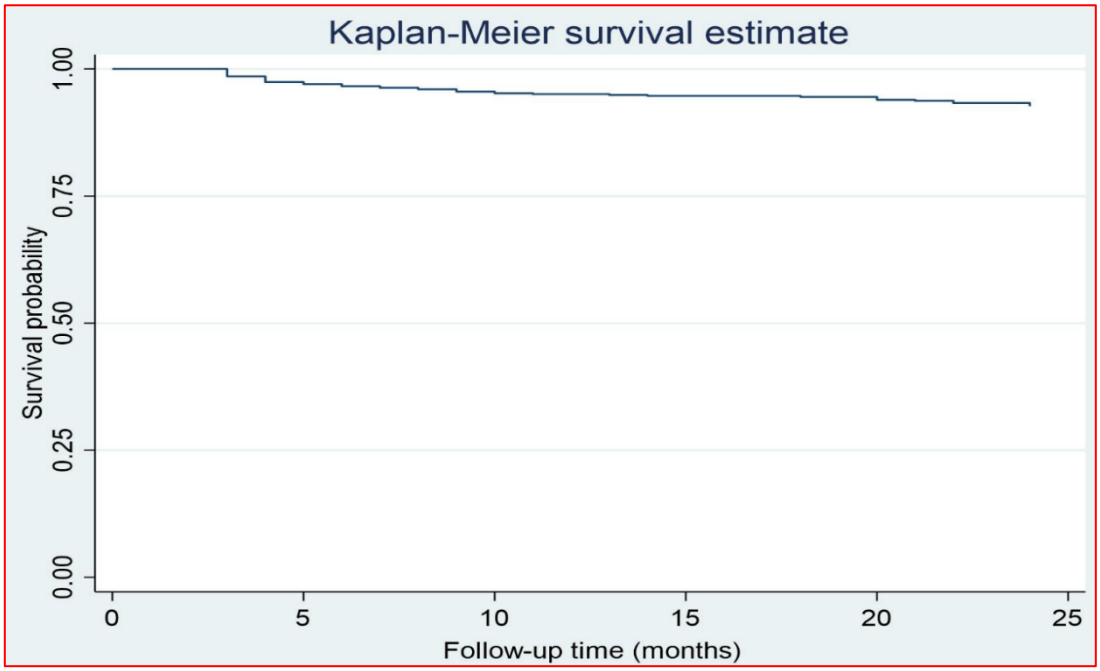

Figure 19. The overall Kaplan-Meier survival showing the survival time of adults living with HIV receiving ART at DMCSH, Northwest Ethiopia

Longitudinal sub-model

Results from the longitudinal sub-model revealed no significant difference in mean BMI between urban and rural residents at baseline; however, patients from rural areas had a lower BMI increase over time than urban patients (β=-0.08; 95%CI: (-0.1, -0.02). As the ART treatment duration increased by one month, mean BMI increased by 0.2kg/m^2 (β=0.2; 95%CI: 0.1, 0.3). Female participants had lower mean BMI at ART initiation (β=-0.3; 95% CI: (-0.6, -

0.1), but this difference was not statistically significant over time. Anaemic participants presented with lower mean BMI at ART initiation (β=-0.4; 95%CI: -0.7, -0.1), but BMI evolution over time was not significantly different, resulting in the interaction between anaemia and time was excluded from the final model. Mean BMI of ambulatory/bedridden functional status participants was 0.9 kg/m^2 lower than working functional status participants (β=-0.5; 95% CI: -0.8, -0.1) at ART initiation, although the BMI variation over time was not significantly different between groups so this interaction was excluded from the final model.

Participants, who had OIs at ART initiation, presented with lower mean BMI (β=-0.3; 95% CI: -0.6, -0.1) but had a higher rate of BMI increase (β=0.1, 95% CI: 0.03, 0.13) over time compared to non-OIs affected participants. The mean BMI difference between participants who had severe or mild immunodeficiency at baseline was not statistically significant but increase over time was higher in participants with severe immunodeficiency than their mild affected counterparts (β=0.1; 95%CI: 0.07, 0.2). Those who started Dolutegravir (DGT)-based ART regimen had lower mean BMI at ART initiation (β=-1.1; 95% CI: (-1.9, -0.5), but had a higher rate of mean BMI increase over time (β=0.2, 95% CI: 0.01, 0.4) as compared to participants started other ART regimens.

Patients receiving TPT had higher mean BMI than those not taking TPT at ART initiation (β =0.5; 95% CI: 0.2, 0.8), but this difference was not statistically significant during follow-up. Underweight patients presented with lower mean BMI at ART initiation (β=-3.7; 95% CI: 4.0, -3.5) but experienced higher BMI increases over time than normal-weight patients (β=0.1; 95% CI: 0.07, 0.2). On the contrary, overweight/obese patients presented with higher mean BMI at baseline (β= 5.3; 95% CI: 4.9, 5.7) but had lower BMI increase over time than normal-weight patients (β=-0.1; 95% CI: -0.2, -0.03) (see Table 22).

Table 22. Longitudinal process estimates from the joint model to identify predictors of BMI variation in adults living with HIV on ART at DMCSH, Northwest Ethiopia.

Variables	Coefficient	95%CI	p-value
Intercept	22.0	(21.4, 22.6)	<0.001
Residence			
Rural	-0.3	(-0.6, 0.001)	0.051
Urban	Ref	—	—
Sex			

Female	-0.3	(-0.6, -0.1)	0.012
Male	Ref	—	—
WHO clinical staging			
Mild disease stage	-0.1	(-0.4, 0.3)	0.763
Advanced disease stage	Ref	—	—
Haemoglobin level			
Anaemic	-0.4	(-0.7, -0.1)	0.004
Non-anaemic	Ref	—	—
Functional status			
Ambulatory/bedridden	-0.5	(-0.8, -0.1)	0.013
Working	Ref	—	—
ART adherence			
Fair/poor	-0.1	(-0.4, 0.2)	0.584
Good	Ref	—	—
Baseline nutritional status			
Underweight	-3.7	(-4.0, -3.5)	<0.001
Normal-weight	Ref	—	—
Overweight/obese	5.3	(4.9, 5.7)	<0.001
Baseline OIs			
Yes	-0.3	(-0.6, -0.1)	0.014
No	Ref	—	—
Immunodeficiency			
Severe	0.2	(-0.1, 0.5)	0.172
Mild	Ref	—	—
Taking IPT			
Yes	0.5	(0.2, 0.8)	<0.001
No	Ref	—	—
Baseline ART regimens			
Efavirenz (EFV)-based	-0.3	(-0.8, 0.2)	0.288
Dolutegravir (DGT)-based	-1.2	(-1.9, -0.5)	<0.001
Others	Ref	—	—
Time on ART	0.2	(0.1, 0.3)	<0.001

Baseline nutritional status			
Underweight*time	0.1	(0.07, 0.2)	<0.001
Normal-weight*time	Ref	—	—
Overweight/obesity*time	-0.1	(-0.2, -0.03)	0.007
Baseline OIs *time			
Yes*time	0.1	(0.03, 0.13)	0.004
No*time	Ref	—	—
Residence *time			
Rural*time	-0.08	(-0.1, -0.02)	0.008
Urban *time	Ref	—	—
Immunodeficiency*time			
Severe*time	0.1	(0.07, 0.2)	<0.001
Mild*time	Ref	—	—
Baseline ART regimens*time			
Efavirenz (EFV)-based *time	-0.1	(-0.2, 0.04)	0.185
Dolutegravir (DGT)-based *time	0.2	(0.01, 0.4)	0.035
Others*time	Ref	—	—
Variance component			
Standard deviation (Intercept)	1.6		
Standard deviation (Time)	0.3		
Standard deviation (Residual)	0.8		
Corr (intercept)	0.03		

Survival sub-model

Significant predictors of mortality from the survival sub-model were WHO clinical disease stage, ART regimen change, taking TPT, and functional status. Participants with a mild disease stage had a 60% lower risk of death than severe disease stage individuals (AHR: 0.4; 95% CI: 0.2, 0.9). Participants who changed their initial regimen had an 80% lower risk of death than participants who did not (AHR: 0.2; 95% CI: 0.1, 0.5). Participants who took TPT had a 77% lower risk of death compared to participants who did not take TPT (AHR: 0.23; 95% CI: 0.1, 0.5). Risk of death was 2.7 times higher in patients presenting with ambulatory/bedridden functional status as compared to those presenting with working functional status (AHR: 2.7; 95% CI: 1.3, 5.4) (see Table 5).

Joint models

The joint model showed a strong association between longitudinal BMI variation and early mortality with one unit increase in BMI corresponding to an 18% reduction in mortality risk (AHR: 0.82; 95% CI: 0.75, 0.9) (see Table 23).

Table 23. Event process estimates from the joint model to identify to identify predictors of mortality among adults living with HIV on ART at DMCSH, Northwest Ethiopia

Variables	Survival status		AHR	95%CI	p-value
	Event	Censored			
Residence					
Rural	18	164	1.3	(0.7, 2.6)	0.412
Urban	31	621	Ref	—	—
Sex					
Female	25	462	0.8	(0.5, 1.6)	0. 580
Male	24	323	Ref	—	—
WHO clinical staging					
Mild disease stage	19	579	0.4	(0.2, 0.9)	0.020
Advanced disease stage	30	206	Ref	—	—
Haemoglobin level					
Anaemic	21	150	1.4	(0.7, 2.6)	0.374
Non-anaemic	28	635	Ref	—	—
ART regimen change					
Yes	5	260	0.2	(0.1, 0.5)	0.001
No	44	525	Ref	—	—
IPT					
Yes	11	513	0.23	(0.1, 0.5)	<0.001
No	38	272	Ref	—	—
Baseline OIs					
Yes	31	305	1.1	(0.5, 2.2)	0.807
No	18	480	Ref	—	—
ART adherence					
Fair/poor	25	184	1.7	(0.9, 3.2)	0.112

Good	24	601	Ref	—	—
Baseline nutritional status					
Normal/overweight/obese	23	588	1.1	(0.6, 2.0)	0.862
Underweight	26	197	Ref	—	—
Immunodeficiency					
Mild	25	534	1.0	(0.5, 1.9)	0.918
Severe	24	251	Ref	—	—
Functional status					
Ambulatory/ bedridden	26	115	2.7	(1.3, 5.4)	0.005
Working	23	670	Ref	—	—
Baseline ART regimens					
Efavirenz (EFV)-based	38	689	0.9	(0.3, 2.9)	0.829
Dolutegravir (DGT)-based	8	53	2.3	(0.6, 8.5)	0.209
Others	3	43	Ref	—	—
Association			0.82	(0.75, 0.9)	<0.001

Discussion

This institution-based retrospective cohort study used separate models to identify mortality and This institution-based retrospective cohort study used separate models to identify mortality and BMI variation predictors in Ethiopian adults living with HIV on ART. A joint model approach examined the association between longitudinal BMI variation and early mortality. Our survival analyses identified that patients who changed their initial ART regimen, took TPT, and had mild clinical disease stage were at lower risk of death. However, patients with ambulatory/bedridden functional status were at higher risk of death. Our longitudinal sub-model also showed that patients presenting with OIs, underweight patients, patients who started a DGT-based ART regimen and those with severe immunodeficiency had a higher BMI increase over time. However, patients from rural areas and overweight/obese patients experienced a lower BMI increase over time.

Nutritional status was not significantly associated with mortality at ART initiation. However, a unit increase in BMI corresponding to an 18% reduction in mortality risk after ART initiation. This demonstrates the time-dependent nature of BMI, which is consistent with our hypothesis. The association between BMI change and mortality was expected and consistent with previous

studies (Madec et al., 2009; Sudfeld et al., 2013; Yuh et al., 2015). This strong association could result from the recovery in adaptive and innate immunity elements after ART initiation (Hughes & Kelly, 2006). Evidence furthermore suggests that a higher BMI is associated with higher CD4 cell counts at baseline and after six months (Bleasel et al., 2020). The association between BMI improvement and early mortality could also reflect a negative association between BMI on OIs since OIs are the leading cause of mortality and morbidity among PLHIV (Alebel et al., 2022a).

Our study also found that patients who took a DGT-based ART regimen had lower mean BMI at ART initiation, but a higher BMI increase over time than those receiving other ART regimens. This finding is in line with a previous clinical trial conducted in developing countries (Sax et al., 2020; Thivalapill et al., 2021). Although the mechanism of DGT-associated weight gain is not fully understood, it could have resulted from its higher tolerability compared to other regimens. Furthermore, patients treated with DGT were found to achieve significant viral suppression and increased CD4 counts (Nickel et al., 2021). Another possible explanation is that integrase strand transfer inhibitors (INSTIs) may affect the gut microbiota of patients living with HIV (Moure et al., 2016). Evidence suggested that a marker of gut integrity, such as fatty acid-binding protein level, is an independent predictor of weight gain and visceral fat gain in patients living with HIV (El Kamari et al., 2019).

In this study, patients who experienced OIs had a lower mean BMI at ART initiation but higher BMI increase over time, which aligns with previous studies (Alebel et al., 2022b; El Kamari et al., 2019). Higher BMI increase over time in patients with OIs could be the restoration of healthy pre-infection weight, known as the "return-to-health" phenomenon (Sax et al., 2020), reflecting effects of ART, as it significantly reduces the occurrence and recurrence of OIs and improves gastrointestinal function, appetite, and nutrient absorption (Sax et al., 2020). Differentiating healthy from unhealthy weight gain is not easy; however, our results suggest that patients with OIs, severe immunodeficiency, and underweight had a higher BMI increase after ART initiation. This indicates that the weight gain seen in this study is more likely due to "returning to health".

A higher rate of BMI increase was observed during follow-up in participants with severe immunodeficiency, aligning with previous research (Tang et al., 2011; Yuh et al., 2015). Patients with severe immunodeficiency (CD4 cell counts <200 cell/mm^3) are at higher risk of developing life-threatening OIs such as oesophageal candidiasis (which compromises oral

intake) (Ratnam et al., 2018). As a result, the rapid weight gain in severely immunocompromised patients in our study may directly result from the beneficial effects of ART. Another reason could be that recovering from OIs can reduce metabolic demands and contribute to weight gain after starting ART. Of note, this study did not consider the time-dependent nature of CD4 cell measurements as routine CD4 cell count measurements to initiate ART were no longer required after 2016.

Patients from rural areas had a lower BMI increase over time than urban patients. A general population study also found that overweight and obesity are more prevalent in urban areas than rural areas (Ajayi et al., 2016), which could be due to dietary changes from a traditional diet to high-energy processed foods, fats, animal-derived foods, sugar, and sweet beverages (Sola et al., 2011). This pattern of dietary change is more evident in urban residents than rural residents due to higher incomes and greater availability of processed foods (Ajayi et al., 2016).

This study also found a higher BMI increase over time in underweight patients compared to normal-weight patients. However, overweight/obese had a lower rate of BMI increase over time compared to normal-weight patients, which is in line with previous studies conducted in Zambia and the United States (Crum-Cianflone et al., 2010; Koethe et al., 2010). Underweight patients may have gained more weight due to increased food intake, reduced metabolic demand, and improved nutritional absorption after ART initiation (Günthard et al., 2016). A higher weight gain in underweight patients could also result from their desire not to look too thin, leading others to suspect their HIV status (Crum-Cianflone et al., 2008). Lastly, continuous nutritional education given by health professionals as recommended by the Ethiopian ART guidelines or dietary supplements may promote healthier diets (Ministry of Health Ethiopia, 2017).

Our survival analysis found that patients with mild disease stage had a lower risk of death compared to patients with advanced disease stage, which is consistent with previous studies (Kouanda et al., 2012; Palombi et al., 2009; Workie et al., 2021). Patients with advanced disease stages are at higher risk of developing serious and life-threatening OIs, such as TB, cryptococcal meningitis, and toxoplasmosis (Melkamu et al., 2020). Patients co-infected with TB are more likely to die in the early phase of ART due to the immune reconstitution inflammatory syndrome (Müller et al., 2010).

Participants who took TB prophylaxis had a lower risk of death compared to participants who did not take TB prophylaxis in our study, similar to previous studies (Atey et al., 2020; Badje et al., 2017). This study also found that participants who changed their initial ART regimen had an 80% lower risk of death than those who did not. Due to incomplete data, we could not conclude which specific regimens are associated with lower mortality risk. The most (84%) common documented reason for regimen change in our study was the availability of new drugs. Hence, improved survival may be due to the availability of a more effective ART drug, such as DTG. However, we believe that based on the data available in our study, this would be too speculative, and further studies are needed. In response to the WHO's recommendation, 82 low-and middle-income countries (LMICs), including Ethiopia, reported switching to a DTG-based HIV regimen in 2019 (World Health Organization, 2019b).

Similar to findings of previous LMICs-based studies (Bajpai et al., 2016; Biadgilign et al., 2012; Damtew et al., 2015; Gesesew et al., 2018; Kebede et al., 2020; Muhula et al., 2015), we found the risk of death among patients classified as ambulatory/bedridden functional status was much higher than those classified as working functional status. At ART initiation, bedridden functional status (i.e., remain in bed and physically inactive) patients are in an advanced disease stage and severely immunocompromised at ART initiation.

Strengths and limitations

The large sample size (i.e., increased statistical power) and advanced statistical analyses, including missing value handling, are some of the strengths of this study. In addition, as we used longitudinal measurements of BMI, it may reflect the actual relationship between BMI (nutrition) and mortality. However, this study has some limitations that must be considered when interpreting the results. The values for some important nutritional status and mortality determinants, such as micronutrient deficiency, dietary diversity, and viral load, were unavailable from the routinely collected patient records. Furthermore, cause-specific mortality was not determined, as the specific causes of deaths in PLHIV were not recorded. The long-term effects of weight gain on chronic disease were not reflected in this study because of the short follow-up period (two years). Lastly, cases of patients who died at home may not be reported to HIV clinics due to a passive reporting system, thereby potentially underestimating the mortality rate.

Conclusion

This study found that BMI improvement after ART initiation was strongly associated with lower mortality risk, regardless of BMI category. This implies that clinicians can predict patients' prognosis (poor or good) by looking at their BMI evolution after ART initiation. Therefore, patients whose BMI does not improve after ART initiation need special attention and close follow-up because they are at higher risk of early mortality. The longitudinal finding of this study also showed that patients who took a DGT-based ART regimen had a higher BMI increase over time. This finding confirms the possible positive benefits of the DGT-based ART regimen in developing countries, such as weight gain. The study also found that patient with poor clinical conditions (i.e., presence of OIs, underweight and severe immunodeficiency) had higher BMI increase over time. Moreover, the provision of TB prophylaxis should be strengthened based on patients' eligibility. Further prospective follow-up studies are needed to examine the effects of diet, income, nutritional knowledge, exercise, social and cultural influences on BMI improvement and their association with treatment outcomes. Lastly, the long-term effects of weight gain on chronic comorbidities such as cardiovascular diseases, diabetes, and metabolic syndrome and their association with mortality need to be investigated.

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Author Contributions

Animut Alebel: Conception of the research idea, design, analysis, interpretation, drafting and reviewing of the manuscript. David Sibbritt and Daniel Demant**:** Design, interpret results, review, and edit the manuscript. Pammla Petrucka**:** interpretation of results, reviewing and editing the manuscript. All authors have read and approved the final manuscript.

Disclosures

Animut Alebel, David Sibbritt, Pammla Petrucka, and Daniel Demant declare that they have no conflicts of interest in this research.

Compliance with Ethics Guidelines

Ethical approvals and permissions were granted from the DMCSH Medical Director's Office, the University of Technology Sydney Health and Medical Research Ethics Committee (ETH20-5044), and the Amhara Regional Public Health Research Ethics Review Committee (Ref. no: 816). As the study was based on existing medical records of PLHIV, obtaining participants' verbal or written informed consent was not feasible, and a waiver of consent was granted. Data were completely de-identifiable to the authors, as the data abstraction tool did not include participants' unique ART numbers and names.

Data availability

The data sets used and/or analysed for this study are available from the corresponding author on reasonable request.

8.3. Chapter summary

In this chapter, the records of 834 ALHIV receiving ART between June 2014 and June 2020 at DMCSH in Northwest Ethiopia were analysed using a joint modelling approach. At the end of follow-up, 49 (5.9%) died, with a mortality rate of 4.1 per 100 person-years (95% CI: 3.1, 5.4). A unit increase in BMI after ART initiation corresponded to an 18% reduction in mortality risk. Patients taking TPT, mild clinical disease stage, and changing ART regimens were at lower risk of death. However, patients with ambulatory/bedridden functional status were at higher risk of death. Regarding BMI variation over time, patients presenting with opportunistic infections (OIs), underweight patients, patients who started a DGT-based ART regimen and those with severe immunodeficiency had a higher BMI increase over time. However, patients from rural areas and overweight/obese patients experienced a lower BMI increase over time. The next chapter focuses on the general discussion of the thesis.

Chapter 9 │General discussion

The main aim of this thesis is to assess the effects of undernutrition on the overall treatment outcomes among ALHIV receiving ART in Northwest Ethiopia. This aim is addressed through five sequential and interrelated objectives:

- First, a systematic review and meta-analysis was conducted to estimate the effects of undernutrition on mortality and morbidity among ALHIV on ART in the context of SSA (Chapter 4).
- Second, the effect of undernutrition on LTFU in ALHIV receiving ART in northwest Ethiopia was estimated (Chapter 5).
- Third, the effects of undernutrition on the occurrence of OIs in ALHIV on ART in Northwest Ethiopia was examined using treatment effects analysis (Chapter 6).
- Fourth, the longitudinal weight change after initiation of ART among ALHIV in Northwest Ethiopia was evaluated for two years (Chapter 7).
- Finally, the association between BMI (nutritional) variation and early mortality in ALHIV receiving ART in Northwest Ethiopia was examined (Chapter 8).

9.1. Discussion of main findings

The main findings of this thesis are summarised into three themes: 1) effects of undernutrition on mortality and morbidity in ALHIV; 2) effects of undernutrition on LTFU in ALHIV; and 3) predictors of nutritional change (weight and BMI) after ART initiation in ALHIV.

9.1.1. Effects of undernutrition on mortality and morbidity in ALHIV

Results from Chapters four, six, and eight are discussed under this theme. As presented in Chapter four, undernutrition significantly increased the risk of mortality and morbidity among ALHIV in SSA. The risk of death in undernourished ALHIV was two times higher than in their well-nourished counterparts. The study also found that, as the degree of undernutrition became more severe, mortality rate also increased. This finding implies that early screening and management of malnutrition in this population is key to achieving the optimal treatment outcomes from ART. Regarding the current practices of managing malnutrition in this population, the WHO ART guidelines recommend that nutritional supplements for malnourished ALHIV are necessary and should be provided (World Health Organization,

2021a). Despite this recommendation, two recent randomized controlled trials reported that the provision of nutritional supplements for the treatment of malnutrition in African ALHIV did not reduce mortality (Filteau et al., 2015; Mallewa et al., 2018). Conversely, a Lancet HIV commentary paper argued that providing nutritional supplements to undernourished patients receiving ART is still essential, although it is ineffective in reducing mortality. The author's justification for this recommendation was that nutritional supplements could increase body weight, speed up physical and functional recovery, and improve work capacity and quality of life (PrayGod et al., 2018). On this issue, further studies are needed to evaluate the effectiveness of the management of malnutrition in this population. Regular nutritional counselling based on anthropometric measurements at every ART visit is recommended in the current Ethiopian ART treatment guidelines (Ministry of Health Ethiopia, 2017). However, this practice is limited in the clinical settings due to the sensitive nature of the disease (social stigma). In Ethiopia, given the extent and severity of the problem, preventive interventions, such as health promotion about healthy food through regular counselling and health education by Health Extension Workers, are needed beyond the clinical management of malnutrition in this population. However, as HIV is a sensitive disease (social stigma), PLHIV may not be comfortable disclosing their HIV status to Health Extension Workers. Therefore, the acceptability and feasibility of this intervention requires further qualitative study to determine the preferred ways forward.

Undernutrition can increase the risk of death in PLHIV either directly or indirectly. Its effects on the immune system could explain a direct impact of undernutrition on mortality, as nutritional deficiencies significantly impair the immune system. Nutritional deficiencies lead to atrophy of lymphoid organs (i.e., thymus gland and peripheral lymphoid tissue), impaired antibody production, and reduced delayed hypersensitivity reactions (Maggini et al., 2018). It also causes changes in T-cells and T-cell subsets (helper cells, suppressor–cytotoxic cells, and natural ‘killer’ cells) and reduces interleukin (IL)-2 receptors and cytokine production, leading to dysregulation of the equilibrium host response (Childs et al., 2019). As a result, undernutrition-associated mortality in PLHIV could be due to worsening of immunodeficiency (Maggini et al., 2018). Thus, a patient`s ability to fight infection can be severely compromised due to malnutrition-induced immunodeficiency, leading to premature death before full response to ART.

The indirect association between undernutrition and mortality in this population can also be mediated by ART adherence and treatment failure. Studies conducted in SSA have shown that undernutrition negatively affects ART adherence (Berhe et al., 2013; Nigusso & Mavhandu-Mudzusi, 2020). Similarly, different studies have demonstrated that adherence to ART is a proximal risk factor for death (Birhanu et al., 2021; Joseph et al., 2019; Rai et al., 2013). ART must be taken daily to be effective, as it is a lifelong medication. Evidence also showed that undernutrition significantly increases the risk of treatment failure (Ahmed et al., 2019; Zenu et al., 2021). The association between treatment failure and mortality is well documented.

As discussed in Chapter two, most of the previous studies reported the impact of malnutrition on mortality using baseline nutritional data. Therefore, this thesis addressed this knowledge gap by investigating the association between longitudinal BMI variation and mortality. The finding suggested that BMI (nutritional) improvement after ART initiation was strongly associated with lower mortality risk, regardless of BMI category. One unit increase in BMI corresponded to an 18% reduction in mortality risk. The impact of weight gain on reduced mortality risk after initiation of ART in low- and normal-weight patients has also been documented in previous studies conducted elsewhere (Madec et al., 2009; Sudfeld et al., 2013; Yuh et al., 2015). The clinical importance of this finding is that BMI change after ART initiation can be used as the best clinical parameter for monitoring patient response, as laboratory tests, including viral load and CD4 counts, are expensive and scarce in resource-limited countries, including Ethiopia. In addition, BMI measurement is easy to perform and does not need a specialized person. In this study, BMI increase is still an excellent prognostic factor due to the context of the study area (low-income country) and short follow-up. However, its long-term impacts need further investigation as excess weight gain in this population can increase the risk of chronic diseases, such as cardiovascular diseases and diabetes mellitus (Achhra et al., 2016; Kumar & Samaras, 2018; McCann et al., 2021). Based on the current findings, health provider engagement is essential in providing adequate information about the benefit of mild to moderate weight gain after ART initiation and encourage them to have a healthy body weight. Furthermore, assessing for the presence of ART side effects, loss of appetite, food insecurity, OIs, and ART discontinuation is crucial for those who failed to gain weight after ART initiation.

Another finding from Chapter four showed that undernutrition increased the risk of co-morbidities such as AIDS-defining conditions and OIs. This association was particularly

notable with TB; undernourished patients were two times at higher risk of developing TB than well-nourished patients. Chapter six also demonstrated that the incidence of OIs in undernourished participants was higher than in well-nourished participants. Further, when population of interest members are well nourished, the average time to develop OIs is estimated to be 26.5 months, but when undernourished this interval is shortened to 17.7 months. This implies that if undernutrition in ALHIV is prevented, the onset of OIs can be delayed by almost nine months. The negative impacts of malnutrition on OIs in this population has also been documented in the previous studies (Llf Putri et al., 2018; Tewachew et al., 2021). Undernutrition and OIs have a bidirectional relationship. Poor nutrition increases the risk of infection. Similarly, OIs increase the risk of malnutrition due to increased nutrient requirements, decreased food intake (i.e., anorexia and dysphagia), and decreased nutrient absorption (França et al., 2009; Walson & Berkley, 2018). Hence, in addition to providing chemoprophylaxis (CPT and IPT) for OIs prevention, consideration of good nutrition as a feasible and cost-effective means of preventing OIs is important. Lastly, assessing and managing malnutrition should be a priority for those who developed OIs.

9.1.2. The effect of undernutrition on LTFU in ALHIV

A study incorporated in Chapter five showed that the incidence of LTFU in undernourished participants (8.2 per 100 person-years) was higher compared to well-nourished participants (4.3 per 100 person-years). The adjusted risk of LTFU was two times higher in undernourished participants compared to their well-nourished counterparts. The significant association between undernutrition and higher risk of LTFU was also documented in other SSA countries (Evans et al., 2012; Kalinjuma et al., 2020; Kiwanuka et al., 2020). The public health implication of this finding is that improving nutritional status could significantly contribute to retention in ART care. As the nutritional status of PLHIV is affected by many factors, the problem needs multisector collaborations. The potential masking effect of ART on the actual impact of undernutrition on LTFU did not have any influence on this study's findings and conclusions. This is because both the exposed and unexposed groups were receiving ART, with the only difference being their nutritional status.

The impact of undernutrition on LTFU among PLHIV in SSA is often related to food insecurity (Benzekri et al., 2021). ART medications are freely available in Ethiopia, but PLHIV often face financial challenges associated with accessing healthcare and treatments, such as transportation costs. Qualitative studies reported from SSA have shown that economic factors,

particularly the high cost of transportation, also pose a significant challenge to sustaining successful treatment (Tuller et al., 2010; Weiser et al., 2010). Patients may possibly prioritise using their limited financial resources to buy food rather than paying for transportation to access healthcare based on their perception of imminent need. Alternatively, they may spend their time at work to earn money rather than going to the clinic and waiting for medical appointments (Benzekri et al., 2021) often simply forgetting or neglecting to take ART while working or searching for food (Weiser et al., 2010). In addition, patients in rural areas of SSA are particularly likely to miss their appointments, especially during harvesting and planting sessions, as agriculture is the main source of income for these patients (Nagata et al., 2012). In this regard, clinicians in Ethiopia often try to schedule ART appointments considering religious holidays. These activities should be reinforced to ensure that patients attend their regular appointments. Lastly, ART drugs can increase appetite and hunger or have side effects that may worsen without food. In these cases, patients sometimes rationalize that they should skip doses or not initiate ART if they cannot afford the additional nutritional burden (Weiser et al., 2010). Nurses and physicians should regularly assess patients' level of understanding and inform them not to skip or stop their medications when there are misunderstandings. In addition, patients should be regularly advised to consider locally available foods.

As presented in Chapter six, undernutrition also significantly increases the risk of OIs. Therefore, undernutrition could indirectly contribute to a higher risk of LTFU by increasing disease progression from HIV to AIDS in PLHIV (Chen et al., 2019). A systematic review and meta-analysis from LMICs found that advanced WHO clinical disease staging was significantly associated with higher risk of LTFU (Frijters et al., 2020). Advanced WHO clinical disease stage increases the risk of LTFU in various ways. Patients with WHO stage III or IV are more likely to have OIs and are bedridden most of the time, which can make it difficult for them to stay engaged in HIV care. In addition, HIV patients with advanced disease stage are at higher risk of premature death from severe OIs, especially during the first year. As result, these patients may have died at home but were not reported due to a passive surveillance system. When the above information is considered, in addition to providing ART, financial issues, such as transportation costs and food shortage shall be assessed, particularly for those who missed their appointments. Therefore, healthcare professionals should look at the causes of LTFU in PLHIV from different perspectives. More importantly, health professionals (nurses and physicians) should continuously monitor food availability, accessibility, and utilisation at each ART visit, particularly for patients traced after LTFU.

9.1.3. Predictors of nutritional change after ART initiation in ALHIV

This section includes the results of chapters seven and eight. Findings suggested that weight and BMI increased linearly during the two years of ART follow-up, with more increases in the first year than in the second year. Previous studies have shown that weight gain is typical after ART initiation, especially in the first year of follow-up (Madec et al., 2009; Sax et al., 2020; Tang et al., 2011; Weldesenbet et al., 2020). Weight gain after initiation of ART is considered a marker of improvement and is associated with low risk of death who are underweight or normal-weight (Yuh et al., 2015). The mortality preventive effect of BMI increase is also demonstrated in Chapter eight. In addition to its mortality preventive effect, weight gain after ART initiation could also have a psychological benefit, particularly in severely wasted patients. This benefit was reported in a qualitative study in Uganda, which found that patients wanted to gain moderate to high-level weight to improve their body image and mask their HIV status, as most people think that HIV is a disease of thin people, particularly in developing countries (Alhassan et al., 2022).

Weight gain after starting ART is often the result of a return-to-health phenomena due to viral load suppression (Bourgi et al., 2020). Differentiating healthy weight gain from unhealthy weight gain is not straightforward. However, results from this thesis reported in Chapter eight showed that patients with OIs, severe immunodeficiency, and underweight had a higher rate of BMI increase after ART initiation. This finding indicates that weight gain is more likely due to 'returning to health'. Return-to-health (pre-illness weight) is not fully understood and is influenced by many factors, such as HIV metabolism, immune response, ART combination, and sociodemographic characteristics (Bailin et al., 2020; Sax et al., 2020). The most common postulated reason for return-to-health is that prior to ART initiations PLHIV often have high metabolic requirements due to AIDS-related illness, which at initiation, sees the reversal of this metabolic state and improvement of appetite and nutrient absorption (Kumar & Samaras, 2018; Sax et al., 2020).

As described in Chapter seven, duration on ART was positively associated with weight gain. Previous studies have also reported a positive correlation between duration of ART use and weight gain (Reda et al., 2013; Weldesenbet et al., 2020). Indeed, as patients stay in HIV care

longer, they are more likely to have frequent contacts with health professionals and receive advice on the importance of nutrition, self-care, and drug adherence. The impact of regular counselling on favourable treatment outcomes in patients living with HIV is well documented (Mbuagbaw et al., 2015; Uusküla et al., 2018). However, the positive correlation between ART duration and weight gain should be interpreted cautiously, as it is likely temporary and needs further study.

Another finding from Chapter seven is that undernourished patients had higher rates of weight gain over time than well-nourished patients. This finding aligns with Chapter eight, which showed a higher rate of BMI increase among undernourished patients. Conversely, a lower BMI increase was seen in normal-weight patients than in overweight/obese patients. Previous studies also found greater weight gain in undernourished patients after ART initiation (Crum-Cianflone et al., 2010; Koethe et al., 2010). A higher weight gain in undernourished patients after initiation of ART may be due to a direct effect of ART on viral suppression or nutritional supplementation (Kanters et al., 2022; Mallewa et al., 2018; Ndekha et al., 2009; Olsen et al., 2014). The clinical implication is that undernourished patients benefited more from ART, which ultimately improved their survival.

As described in Chapter eight, patients with poor clinical status (i.e., severe immunodeficiency and OIs) had higher BMI increase over time compared with patients with good clinical status. Furthermore, the results in Chapter seven suggested that patients with bedridden or ambulatory functional status gained more weight over time than patients with working functional status. Conversely, Chapter seven also found that patients with advanced disease stages were found to gain less weight over time than those with mild disease stages. Clinical disease staging or CD4 cell count can be used to assess the severity of HIV infection, but CD4 cell count reflects patients' immunological profile and is more reliable in predicting patient outcomes (Mermin et al., 2011). Thus, the discussion in this thesis focused on the results based on CD4 cell count. Consistent with these findings, previous studies also suggested that more significant weight gain was seen in individuals with poor clinical status (i.e., low CD4 count and high viral load) at baseline (Bakal et al., 2018; Kanters et al., 2022; Sax et al., 2020; Yuh et al., 2015). While this effect may be desirable for some patients, it may sometimes lead to unhealthy weight gain in patients with early HIV infection and those who are already overweight or obese. Therefore, health professionals must provide regular and frequent advice about healthy body weight at each ART visit.

As presented in Chapter eight, patients who took a DGT-based ART regimen had a higher BMI increase over time than those receiving other ART regimens. Our findings confirm the existing literature showing that DGT is associated with significant weight gain (Kanters et al., 2022; Sax et al., 2020; Thivalapill et al., 2021). DGT-related weight gain has been widely reported, but the question is whether this is directly due to DGT itself or to other factors. This insight is important to advise patients about their ART preferences. The mechanism of weight gain in INSTIs, such as DGT, may differ from what was previously thought to be a direct effect of INSTIs. For example, older drugs, such as TDF and EFV, seem to cause weight loss (Wood & Huhn, 2021). Thus, weight gain in patients switching to a DGT-based ART regimen may be due to the discontinuation of these weight suppressors and not the new drug, as ART is a combination of drugs.

DGT-related weight gain could be considered a positive benefit of the drug in resource-limited settings, including Ethiopia, as most patients in developing countries have experienced significant weight loss at ART initiation. Besides, evidence, including the current study, suggests that weight gain after ART initiation is significantly associated with lower mortality risk (Madec et al., 2009; Sudfeld et al., 2013; Yuh et al., 2015). Apart from these benefits, there are growing concerns that unexpected excess weight gain following ART initiation in the long term may increase the risk of cardiovascular disease and metabolic complications (Galdamez et al., 2019; McCann et al., 2021; Rebeiro et al., 2021). Hence, clinicians should encourage healthy weight gain and provide advice based on continuous weight measurements.

A study incorporated in Chapter eight showed that a greater increase in BMI was observed among patients living in urban areas than in rural areas. The urban-rural disparities reflected in this study are consistent with studies conducted on the general population in developing countries (Ajayi et al., 2016; Dagnew & Asresie, 2021). This finding is in contrast to studies conducted in developed countries which showed that rural residents are more obese than urban residents (Gurka et al., 2018; Keramat et al., 2021; Pouliou & Elliott, 2009). The causes of obesity are complex and multifactorial, generally including genetic, environmental, dietary, and exercise factors (National Heart, 2021). In the context of Ethiopia, many factors are associated with rural residents being less likely to be obese or overweight. For example, rural residents in Ethiopia are often engaged in agricultural activities, mainly physical work, as well as concomitantly traveling long distances on foot, being more physically active, and being less likely to consume packaged, high fat, high-energy food (Yeshaw et al., 2020).

Furthermore, less weight gain in rural-dwelling HIV patients could relate to their propensity towards poor ART adherence (Fite, 2021). Therefore, targeted interventions are needed to improve healthy weight gain by engaging rural populations through health education.

Further findings from Chapter eight demonstrated that patients who received IPT had a lower risk of death, while Chapter seven found that patients who received IPT gained less weight than patients who received IPT. Hence, together these findings suggest that IPT is beneficial for preventing mortality but not weight gain. Although the primary goal of IPT is to prevent TB, its clinical benefit in preventing mortality has also been documented in previous studies (Atey et al., 2020; Badje et al., 2017). As there is insufficient evidence as to why patients receiving IPT do not gain weight, further studies are needed. The possible reason could be related to the side effects of IPT, such as vomiting, loss of appetite, and nausea which are the most common side effects of IPT (Denholm et al., 2014).

As described in Chapter seven, male participants gained more weight their female counterparts. While this finding is consistent with a study done in Ethiopia (Weldesenbet et al., 2020), it differs from most studies done elsewhere (Bares et al., 2018; Bourgi et al., 2020; Kanters et al., 2022; Sax et al., 2020; Yuh et al., 2015). The reasons for gender differences in weight gain are generally not fully understood. However, it might be due to hormonal differences and a higher likelihood of female patients living with HIV developing psychosocial issues, such as anxiety and depression, negatively affecting body weight (Albert, 2015; Kuehner, 2017). In addition, a meta-analysis showed that the proportion of women reporting 90% adherence to prescribed ART was lower than that of their male counterparts (Ortego et al., 2012). Furthermore, lower weight gain in females might be due to higher levels of food insecurity among females in developing countries (Boneya et al., 2019; Jung et al., 2017). Thus, gender-specific interventions and close follow-up are needed to improve weight among patients living with HIV on ART.

9.2. Strengths and limitations

Since specific strengths and limitations have been described in each chapter, only significant limitations and strengths are included in this section. In terms of significant strengths, this thesis is the first program of research that examined the overall effects of undernutrition on treatment outcomes in ALHIV in the context of developing countries, specifically Ethiopia. This study included a relatively large sample size, increasing the precision and generalisability

of findings. The thesis also employed advanced statistical analyses, such as meta-analysis, treatment effects analysis (causal inference), survival analysis, longitudinal data analysis, and joint modelling of survival and longitudinal data, allowing for adjustment for potential confounders. For example, this study determined the actual effects of undernutrition on OIs using treatment effects analysis based on observational data, as clinical trials are impossible due to ethical reasons. The thesis also addressed the time variant nature of nutritional status using a longitudinal data analysis. Moreover, this research applied a joint modelling approach to examine the association between BMI variation and early mortality, whereas the previous studies used baseline nutritional status. The registration system for HIV-positive patients is standardized throughout Ethiopia, resulting in comparably good-quality data, collected by qualified individuals. Furthermore, studies included in Chapters seven and eight used repeated measurements of weight and BMI. These approaches may better reflect the actual relationship between BMI (nutrition) and mortality, as BMI and weight vary over time. Lastly, this is the first study evaluating the impact of the new ART drug (DGT) on weight gain in Ethiopia.

Despite the above strengths, this thesis has some limitations that need to be considered. Due to the retrospective nature of the study, several important variables that could influence nutritional status were not available in the records, including smoking status, physical activity, income, dietary habits, and micronutrient deficiencies. As mentioned in Chapter eight, short-term weight gain was protective against mortality, but its long-term effects on the chronic disease was not addressed due to the short follow-up period. This study also used BMI to assess the nutritional status of participants. Although BMI is the cheapest and easiest way to determine the nutritional status of HIV-infected people, it does not reflect the location or amount of body fat. Another limitation noted in Chapter six is that, while OIs may occur more than once, the treatment effects model does not consider repeated events. Therefore, our study focused on the occurrence of OIs for the second time. Moreover, the exact cause of death in HIV-positive patients was not documented; consequently, cause-specific mortality was not determined. Finally, patients who died at home may not be reported to HIV clinics due to a passive reporting system, potentially underestimating the mortality rate in this study. At the same time, LTFU could be overestimated because some patients classified as LTFU may have died or have started ART in other health care facilities without correct recording.

9.3. Implications

9.3.1. Policy

Adherence support through phone calls is the primary strategy currently implemented across Ethiopian health facilities to trace patients lost from ART care. However, in addition to tracing through phone calls, adherence supporters, and HIV case managers, designing interventions that aim at enhancing the nutritional status of ALHIV should be incorporated based on patients' need assessment to improve ART retention for *patients who missed their appointments. In addition, designing strategies that can provide financial relief, such as job opportunities, could be vital in improving the success of ART care, as the condition by itself affects productivity and cause financial stress. As discussed in Chapter six, undernutrition reduces the time to develop OIs in HIV-positive patients on ART by nine months. This finding indicates that OIs may be prevented in this population by enhancing their nutritional status. Therefore, besides providing CPT and IPT, nutritional supplements could be cost-effective in OIs prevention. Moreover, the development of specific guidelines for preventing and early detection of OIs in undernourished HIV infected population should be considered, as they are highly vulnerable.*

The current Ethiopian ART guidelines recommend that weight must be measured and recorded at each ART visit. However, these guidelines do not provide sufficient information about healthy and unhealthy weight gain and its benefits and potential harms; particularly what specific actions should be taken when patients gain more weight than expected. Specifically, the guidelines recommend seeking clinical treatment if the patient experiences unintended weight loss exceeding six kg within two to three months. However, these guidelines did not mention specific recommendations for patients with unhealthy weight gain. Apart from experts' opinions, organized clinical guidelines regarding weight management in this population have not been available from a formal organization such as WHO. As a result, developing a clear and particular approach for managing weight after ART initiation is necessary.

This research found that good nutrition is associated with better survival and a lower risk of LTFU and OIs. Policymakers should therefore consider designing well-organised and regular nutrition education by nurses and physicians in ART clinics. This This approach potentially reduces OIs-associated treatment costs and LTFU-associated treatment failure. This intervention can also improve the patient`s overall quality of life. Moreover, community

education about nutrition by health extensions workers should be considered as an alternative strategy. Lastly, according to the current Ethiopian ART guidelines, DGT is recommended as the first-line ART drug for all patients. This research found that DGT is associated with higher weight gain. At the same time, short-term weight gain is associated with a better survival rate, but its long-term consequences are not yet investigated. This drug may cause unhealthy weight gain, particularly for those already overweight at baseline. Therefore, the Ethiopian ART guidelines should consider risks for overweight patients when advising DGT as a first-line treatment.

9.3.2. Clinical practice

The Ethiopian ART guidelines currently focus on the clinical management of malnutrition and its complications in PLHIV by providing nutritional supplements, such as ready-to-use therapeutic foods. However, more emphasis should be given to the preventive aspects of malnutrition in this population, as a more cost-effective and feasible means of intervention in developing countries such as Ethiopia. Clinicians should carefully assess the nutritional status of HIV-positive patients from various perspectives, such as financial shortage, nutritional knowledge, and possible ART side effects and recommend appropriate interventions based on assessment results. Moreover, assessing the possible presence of OIs among undernourished HIV-positive patients needs particular emphasis. Healthcare professionals must encourage patients to gain healthy weight, which is a sign of good improvement after ART initiation. In addition, clinicians must continuously monitor a patient`s weight to uncover potential reasons why a patient is not able to gain weight. Clinicians should also give special attention and closely monitor those patients whose BMI does not improve after ART initiation because they are at higher risk of premature death. At the same time, clinicians must be vigilant if patients gain excessive weight, especially those on DGT-based ART regimens. Finally, physicians must consider of the possibility of more frequent follow-up visits for those who do not gain or lose weight after initiating ART, as this is a warning sign of poor prognosis.

9.3.3. Future research

Future research directions are suggested based on the knowledge gaps identified in this research. These directions will help to understand more about the impact of undernutrition on treatment outcomes of ALHIV in Ethiopia. First, prospective follow-up studies that examine the effects of BMI improvement on treatment outcomes by incorporating dietary habits,

income, nutritional knowledge, exercise, and social and cultural influences are needed. Previous studies suggested that uncontrolled weight gain following ART initiation in the long term increases risks for cardiovascular diseases and metabolic complications (Galdamez et al., 2019; McCann et al., 2021; Rebeiro et al., 2021). Hence, the long-term effects of weight gain on chronic comorbidities, such as cardiovascular diseases, diabetes, and metabolic syndrome and their association with mortalities, need to be investigated, mainly related the emergent DGT protocols. As this study used BMI to assess the nutritional status of patients, further prospective studies addressing different methods of nutritional assessments, such as dietary diversity score and micronutrient deficiencies, are needed. Lastly, qualitative studies explore possible nutritional-related barriers, such as food security, affecting overall success of ART, are needed.

9.4. Conclusions

This thesis employed different quantitative research methods and identified vital findings that could improve undernutrition-related morbidity and mortality, thereby improving the overall care of HIV patients in the context of resource-constrained countries. Five key findings emerged from this novel research thesis, as follows: Firstly, it was found that undernutrition significantly increased the risk of mortality and morbidity among ALHIV. Moreover, the risk of mortality was found to be more severe among severely undernourished patients. Secondly, undernutrition was identified as an important contributing factor to the elevated risk of LTFU) in this population. Specifically, undernourished ALHIV were found to be at two-fold higher risk of LTFU compared to their counterparts. Thirdly, the thesis concluded that undernutrition shortened the time to develop opportunistic infections in ALHIV by nearly nine months. Fourthly, a consistent linear pattern of weight gain was observed throughout the follow-up period, with a higher rate of increase noted during the initial year. Several factors were identified as significant determinants of weight change, including gender, nutritional status, and functional status, WHO disease stage, and IPT. Finally, the fifth objective revealed a strong association between improved nutrition (measured by BMI) after initiating ART and reduced mortality risk, regardless of the initial BMI category. Patients taking DGT-based ART regimens and those with poor clinical conditions (such as the presence of opportunistic infections, being underweight, and severe immunodeficiency) exhibited higher BMI increases over time.

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List of appendices

Appendices for Chapter 3

Appendix 3.1: Data abstraction tool

This tool was designed to extract data from the medical charts of adults living with HIV receiving ART at Debre Markos Comprehensive Specialized Hospital, Ethiopia. The study aimed to examine the effects of undernutrition on the overall treatment outcomes (OIs, LTFU, and weight gain) of adults living with HIV.

Date -------- ----------month----------Year----------

Name of data collector----------signature----------

Name of supervisor----------signature----------

MRN----------

Part I: Sociodemographic characteristics			
S. No	Variables	Response (s)	Skip
101	Age at ART initiation	---------- years	
102	Sex	0. Male 1. Female	
103	Marital status	0. Single 1. Married 2. Divorced 3. Widowed	
104	Level of education	0. No formal education 1.Primary 2.Secondary 3. Tertiary	
105	Occupation	0. Sex worker 5. Gov't employee 1. Driver 6. Private employee 2. Daily labourer 7. Student 3. Merchant 8. Housewife 4. Farmer 9. Others (specify)----------	
106	Residence	Urban 1. Rural	
107	HIV-disclosure	0. Disclosed 1. Not disclosed	
108	Family Size	---------- individuals	

Part II Baseline clinical, laboratory and ART information			
201	Baseline OIs	0. No 1. Yes	If no, to 203
202	If yes, the type of OIs	0. Herpes zoster 1. Candidiasis 2. Cryptococcus 3. Meningitis 4. B. Pneumonia 5. PTB 6. Diarrhea 7. PCP 8. Others (specify)----------	
203	Weight at baseline	(----------) kg	
204	Height at baseline	(----------) cm	
205	Baseline Functional status	0. Working 1. Ambulatory 2.Bedridden	
206	Baseline CD4 cell count	---------- Cell/mm^3	
207	Baseline WHO clinical staging	0. Stage I 1. Stage II 2. Stage III 3. Stage IV	

208	Baseline haemoglobin (Hgb) level	----------g/dl	

Part III: Data on treatment outcomes and ART and other drugs			
301	HIV+ confirmation date	dd/mm/yy----------/----------/----------E.C	
302	ART started date	dd/mm/yy----------/----------/----------E.C	
303	Eligibility criteria	0. CD4 cell count 1. WHO staging 2. Test and treat	
304	Baseline ART regimens	0.1a=d4t-3TC-NVP 1.1e=TDF-3TC-EFV 2. 1b=d4t-3TC-EFV 3.1f=TDF+3TC+NVP 4. 1c=AZT-3TC-NVP 5.1g=ABC+3TC+EFV 6. 1d=AZT-3TC-EFV 7. 1h=ABC+3TC+NVP 8. 1j=TDF+3TC+DTG 9. other (specify)----------	
305	OIs during follow-up time	0. No 1. Yes	If no, to 308
306	If yes, date	dd/mm/yy----------/----------/----------E.C	
307	If yes, type (s) of OIs	0. Herpes zoster 1. Candidiasis 2. Cryptococcus 3. Meningitis 4. B. Pneumonia 5. PTB 6. Diarrhea 7. PCP 8. Others (specify)----------	
308	ART adherence in the last three months of follow-up	0. Good 1. Fair 2. Poor	
309	Any regimen change?	0. No 1. Yes	If no, to 314
310	If yes, when?	dd/mm/yy---------/----------/----------E.C	
311	If yes, for how many times?	0. Once 1. Twice 2. More than twice	
312	If yes, reasons for change	0. Side effects 1. New drug available 2. New TB 3. Drug stock out 4. Treatment failure 5. Others(specify)----------	
313	Regimen change category	0. First line 1. Second line	
314	Ever taken IPT	0. No 1. Yes	
315	Ever taken CPT	0. No 1. Yes	
316	ART treatment failure	0. No 1. Yes	If no, to 319
317	If yes, the type of failure	0. Clinical failure 1. Immunologic failure 2. Virology failure	
318	If yes, date of treatment failure	dd/mm/yy----------/----------/----------E.C	
319	Patient outcomes at the end of follow-up	0. Alive 1.Died 2. Lost to follow-up 3. Transfer out	
320	If died, date of death (dd/mm/yy)	----------/----------/----------E.C	

321	If lost, date of lost (dd/mm/yy)	----------/----------/----------E.C	
322	Last date of ART visit (dd/mm/yy)	----------/----------/----------E.C	

Part IV: Follow-up data in the first two years (24 months) of ART initiation												
Follow up time In months	Follow up date (dd/mm/yy E.C)				**Follow-up data**							
		Months on ART	Weight (kg)	BMI(kg/m^2)	Functional status	WHO stage	CD4 counts	OIs	ART adherence	Regimen (code)	ART side effects	Viral load
Initial visit												
3												
6												
9												
12												
15												
18												
21												
24												

Appendix 3.2: Ethical supportive letter from DMCSH, Ethiopia

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Debremarkos Referal Hospital

Amhara National Regional State
Health Bureau
Deber Markos Referral Hospital
No 1

ቁጥር 2741/22-217/12
No
ቀን 16/7/2012
Date

To: University of Technology Sydney, Australia

Subject: Evidence of permission for Animut Alebel Ayalew

Dear sir/Madam,

Mr. Animut Alebel Ayalew a PhD student at University of Technology Sydney, Australia, informed our office that he is going to conduct his PhD project entitled "**Effects of undernutrition on treatment outcomes among adults living with HIV at Debre Markos referral hospital, Ethiopia: A longitudinal study**" in our hospital. He requested our office for permission to conduct his PhD project. Therefore, based on his request, we are writing this letter to provide evidence of permission for his request. We would like to confirm that our office will permit and cooperate with Mr. Animut to conduct his research project in our hospital after he gets ethical clearance and permission from the University of Technology Sydney.

With kind regards,

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ዶ/ር አብዩ ዘለቀ
Dr Ablyie Zeleke
ደ/ማርቆስ ሪፈራል ሆስፒታል
ሜዲካል ዳይሬክተር
Debere Markos
Referral Hospital
Chief Clinical officer/cco

Amhara National Regional State Health Bureau Deber Markos Referral Hospital No 1

ስልክ ቁ.
Tell. 058-771-2250 (CEO)
058 771-1013 (HRM)
058-771-28 52 (CCO)
058-771-22-46 (ግ/ፋ/ን/አስ/ደ/የሥራ ሂደት)
058 77115-87 (አድሚሽን ቢሮ)
058 1780150 /ፕላንና ፕሮግራም
E-mail .....

ፋክስ Fax. 058-771-2739
ፖ.ሣ.ቁ
P.O.Box. 37

B.L

Appendix 3.3: Ethical approval from the Amhara Public Health institute, Ethiopia

በአማራ ብሔራዊ ክልላዊ መንግስት ጤና ጥበቃ ቢሮ

Amhara National Regional State Health Bureau
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Amhara Public Health Institute (APHI)
ባህር ዳር : Bahir Dar

Ref.no. RTTD/ / -------
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date 25/06/2020 G.C
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Amhara Public Health Institute Research Ethics Review Committee Response Form

To፡ - Animut Alebel Ayalew

Subject: Health Ethical Clearance

You have submitted a project proposal **"Effects of under nutrition on treatment outcomes among adults living with HIV on ART at Debremarkose referral Hospitals, North west Ethiopia A longitudinal study "** to Amhara public health institute. The Regional public Health Research Ethics Review Committee /RERC/ has reviewed the submitted project proposal critically. We are writing to advise you that the RERC has granted approval for a period of **one year from June 25, 2020 to June 20, 2021.** All your recently submitted documents have been approved for use in this study. The study should comply with the standard international and national scientific and ethical guideline. Any change to the approved protocol or consent material must be reviewed and approved through the amendment process prior to its implementation. In addition, any adverse or unanticipated events should be reported within 24-48 hours to RERC. Please ensure that you submit progressive report prior the expiry date of the project.

We, therefore, request your esteemed organization to ensure the commencement and conduct of the study accordingly and wish for the successful completion of the project.

With regards

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Taye Zeru Tadege
Public Health Research and Technology Transfer Directorate Director

Appendices for Chapter 4

Appendix 4.1: PRISMA 2009 checklist for Manuscript I

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	On title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	02-03
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	03-05
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	07
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Registered (**ID: CRD42020161822**)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	07-08
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	05
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Additional file 2

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	07-08
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	09
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	08
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	08-09
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10-11

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10-11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12-13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	37-40
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15.17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15-17

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	41
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 4.1: Searching strategy from four databases for Manuscript I

1. PubMed search history

Search	Query	Items found
#8	#4 AND #3 AND #2 AND #1 Filters: Publication date from 2002/01/01 to 2019/11/19; Humans; English	970
#7	#4 AND #3 AND #2 AND #1 Filters: Humans; English	1097
#6	#4 AND #3 AND #2 AND #1 Filters: Humans	1137
#5	#4 AND #3 AND #2 AND #1	1297
#4	Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Republic of the Congo OR Democratic Republic of the Congo OR Cote d'Ivoire OR Djibouti OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR The Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome and Principe OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR South Sudan OR Sudan OR Swaziland OR Tanzania OR Togo OR Uganda OR Zambia OR Zimbabwe	529753
#3	HIV Infections[MH] OR hiv[tw] OR hiv-1[tw] OR hiv-2[tw] OR hiv-infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus [tw] OR human immune-deficiency virus[tw] OR acquired immunodeficiency syndrome [tw] OR acquired immunedeficiency syndrome[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR "Sexually Transmitted Diseases, Viral"[MeSH:NoExp]	402058
#2	Mortality[MH] OR Mortalit*[TIAB] OR incidence [TIAB] OR survival [TIAB] OR death rate[TIAB] OR risk factors[TIAB] OR time to death[TIAB] OR Case fatality rate[TIAB] OR determinates[TIAB] OR Mortality rate[TIAB] OR predictors[TIAB] OR Opportunistic Infections [MH] OR AIDS Related opportunistic Infections[MH] OR morbidit*[TIAB] OR opportunistic infect*[TIAB] OR hospital admissions[TIAB] OR hospitalization[TIAB] OR herpes zoster[TIAB] OR bacterial pneumonia[TIAB] OR pulmonary TB[TIAB] OR extra-pulmonary TB[TIAB] OR tuberculosis[TIAB] OR TB[TIAB] OR oral candidiasis[TIAB] OR oesophageal candidiasis[TIAB] OR mouth ulcer[TIAB] OR diarrh*[TIAB] OR pneumocystis pneumonia[TIAB] OR central nervous system toxoplasmosis[TIAB] OR toxoplasmosis[TIAB] OR cryptococcal meningitis[TIAB] OR non-Hodgkins lymphoma[TIAB] OR Kaposi's sarcoma[TIAB] OR cervical cancer[TIAB] OR herpes simplex[TIAB] OR cytomegalovirus[TIAB] OR AIDS defining disease[TIAB]	3250509
#1	Malnutrition[MH] OR Body Mass Index[tw] OR Malnourishm*[tw] OR undernutrition[tw] OR Nutritional deficienc*[tw] OR Nutritional status[tw] OR BMI[tw] OR underweight[tw] OR stunting[tw] OR wasting[tw] OR micronutrient deficienc*[tw]	451855

2. EMBASE search history (Elsevier)

No	Query	Results
#8	#7 AND 'human'/de	1,302
#7	#5 AND (2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py) AND [english]/lim	1,337

#6	#5 AND (2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py)	1,365
#5	#1 AND #2 AND #3 AND #4	1,500
#4	'angola' OR 'benin' OR 'botswana' OR 'burkina faso' OR 'burundi' OR 'cameroon' OR 'cape verde' OR 'central african republic' OR 'chad' OR 'comoros' OR 'republic of the congo' OR 'democratic republic of the congo' OR 'cote d ivoire' OR 'djibouti' OR 'equatorial guinea' OR 'eritrea' OR 'ethiopia' OR 'gabon' OR 'the gambia' OR 'ghana' OR 'guinea' OR 'guinea-bissau' OR 'kenya' OR 'liberia' OR 'madagascar' OR 'malawi' OR 'mali' OR 'mauritania' OR 'mauritius' OR 'mozambique' OR 'namibia' OR 'niger' OR 'nigeria' OR 'rwanda' OR 'sao tome and principe' OR 'senegal' OR 'seychelles' OR 'sierra leone' OR 'somalia' OR 'south africa' OR 'south sudan' OR 'sudan' OR 'swaziland' OR 'tanzania' OR 'togo' OR 'uganda' OR 'zambia' OR 'zimbabwe'	713,318
#3	'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus' OR hiv:ti,ab OR 'hiv-1':ti,ab OR 'hiv-2':ti,ab OR 'human immunodeficiency virus':ti,ab OR 'human immuno-deficiency virus':ti,ab OR 'human immunedeficiency virus':ti,ab OR 'human immune-deficiency virus':ti,ab OR 'acquired immune-deficiency syndrome':ti,ab OR 'acquired immunedeficiency syndrome':ti,ab OR 'acquired immunodeficiency syndrome':ti,ab OR 'acquired immuno-deficiency syndrome':ti,ab	533,865
#2	('mortality'/exp OR 'mortality':ti,ab OR 'survival':ti,ab OR 'time to death' OR 'risk factors of mortality' OR 'predictors of mortality' OR 'mortality rate':ti,ab OR 'mortality rates':ti,ab OR 'death rate' OR 'case fatality rate' OR 'mortality determinates' OR 'mortality predictors' OR 'morbidity' OR 'morbidities') AND 'opportunistic infection'/exp OR 'opportunistic infection' OR 'opportunistic infections' OR 'aids related opportunistic infection' OR 'hospital admissions' OR 'hospitalization' OR 'herpes zoster' OR 'bacterial pneumonia' OR 'pulmonary tb' OR 'extra-pulmonary tb' OR 'tuberculosis' OR 'tb' OR 'oral candidiasis' OR 'oesophageal candidiasis' OR 'mouth ulcer' OR 'diarrhoea' OR 'diarrhea' OR 'pneumocystis pneumonia' OR 'central nervous system toxoplasmosis' OR 'cryptococcal meningitis' OR 'non-hodgkins lymphoma' OR 'kaposis sarcoma' OR 'cervical cancer' OR 'herpes simplex' OR 'cytomegalovirus' OR 'aids defining disease'	1,333,445
#1	'malnutrition'/exp OR 'malnutrition':ti,ab OR 'body mass':ti,ab OR 'body mass index':ti,ab OR 'nutritional deficiency':ti,ab OR 'bmi':ti,ab OR 'underweight'/exp OR 'underweight':ti,ab OR 'thinness':ti,ab OR 'stunting':ti,ab OR 'wasting' OR 'wasting syndrome':ti,ab OR 'micronutrient deficiency':ti,ab OR 'nutritional status':ti,ab OR 'deficient nutrition':ti,ab OR 'malnourishment':ti,ab OR 'severe acute malnutrition':ti,ab OR 'underfeeding':ti,ab OR 'undernourishment':ti,ab OR 'undernutrition':ti,ab	679,986

3. Scopus search history

No	Query	Results
#7	("malnutrition" OR "undernutrition" OR "malnourishmt*" OR "nutritional deficienc*" OR "nutritional status" OR "Body Mass Index" OR "BMI" OR "micronutrient deficienc*" OR "stunting" "wasting" OR "underweight") AND ("Mortalit*" OR "opportunistic infection*" OR "AIDS Related opportunistic infection*" OR "survival status" OR "death rate" OR "case fatality rate" OR "mortality determina*" OR "mortality rat*" OR "mortality predict*" OR "risk of mortality" OR "morbidit*" OR "hospital admissions" OR "hospitalization" OR "herpes zoster" OR "bacterial pneumonia" OR "pulmonary TB" OR "extra-pulmonary TB" OR "oral candidiasis" OR "oesophageal candidiasis" OR "mouth ulcer" OR "diarrhoea" OR "pneumocystis pneumonia" OR "central nervous system toxoplasmosis" OR "cryptococcal meningitis" OR "non-Hodgkins lymphoma" OR "Kaposi's sarcoma" OR "cervical cancer" OR "herpes simplex" OR "cytomegalovirus") AND ("HIV infect*" OR "hiv" OR "human immunodeficiency virus" OR "human immunedeficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immunedeficiency	1,917 document results

	syndrome" OR "acquired immunodeficiency syndrome" OR "acquired immune-deficiency syndrome" OR "hiv-positive" OR "sexually transmitted diseases") AND ("Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cameroon" OR "Cape Verde" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Republic of the Congo" OR "Democratic Republic of the Congo" OR "Cote d'Ivoire" OR Djibouti OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "The Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Liberia" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome and Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "Tanzania" OR "Togo" OR "Uganda" OR "Zambia" OR "Zimbabwe") AND (LIMIT-TO (PUBYEAR,2019) OR LIMIT-TO (PUBYEAR,2018) OR LIMIT-TO (PUBYEAR,2017) OR LIMIT-TO (PUBYEAR,2016) OR LIMIT-TO (PUBYEAR,2015) OR LIMIT-TO (PUBYEAR,2014) OR LIMIT-TO (PUBYEAR,2013) OR LIMIT-TO (PUBYEAR,2012) OR LIMIT-TO (PUBYEAR,2011) OR LIMIT-TO (PUBYEAR,2010) OR LIMIT-TO (PUBYEAR,2009) OR LIMIT-TO (PUBYEAR,2008) OR LIMIT-TO (PUBYEAR,2007) OR LIMIT-TO (PUBYEAR,2006) OR LIMIT-TO (PUBYEAR,2005) OR LIMIT-TO (PUBYEAR,2004) OR LIMIT-TO (PUBYEAR,2003) OR LIMIT-TO (PUBYEAR,2002)) AND (LIMIT-TO (LANGUAGE,"English"))	
#6	("malnutrition" OR "undernutrition" OR "malnourishmt*" OR "nutritional deficienc*" OR "nutritional status" OR "Body Mass Index" OR "BMI" OR "micronutrient deficienc*" OR "stunting" "wasting" OR "underweight") AND ("Mortalit*" OR "opportunistic infection*" OR "AIDS Related opportunistic infection*" OR "survival status" OR "death rate" OR "case fatality rate" OR "mortality determina*" OR "mortality rat*" OR "mortality predict*" OR "risk of mortality" OR "morbidit*" OR "hospital admissions" OR "hospitalization" OR "herpes zoster" OR "bacterial pneumonia" OR "pulmonary TB" OR "extra-pulmonary TB" OR "oral candidiasis" OR "oesophageal candidiasis" OR "mouth ulcer" OR "diarrhoea" OR "pneumocystis pneumonia" OR "central nervous system toxoplasmosis" OR "cryptococcal meningitis" OR "non-Hodgkins lymphoma" OR "Kaposi's sarcoma" OR "cervical cancer" OR "herpes simplex" OR "cytomegalovirus") AND ("HIV infect*" OR "hiv" OR "human immunodeficiency virus" OR "human immunedeficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immunodeficiency syndrome" OR "acquired immune-deficiency syndrome" OR "hiv-positive" OR "sexually transmitted diseases") AND ("Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cameroon" OR "Cape Verde" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Republic of the Congo" OR "Democratic Republic of the Congo" OR "Cote d'Ivoire" OR Djibouti OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "The Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Liberia" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome and Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "Tanzania" OR "Togo" OR "Uganda" OR "Zambia" OR "Zimbabwe") AND (LIMIT-TO (PUBYEAR,2019) OR LIMIT-TO (PUBYEAR,2018) OR LIMIT-TO (PUBYEAR,2017) OR LIMIT-TO (PUBYEAR,2016) OR LIMIT-TO (PUBYEAR,2015) OR LIMIT-TO (PUBYEAR,2014) OR LIMIT-TO (PUBYEAR,2013) OR LIMIT-TO (PUBYEAR,2012) OR LIMIT-TO (PUBYEAR,2011) OR LIMIT-TO (PUBYEAR,2010) OR LIMIT-TO (PUBYEAR,2009) OR LIMIT-TO (PUBYEAR,2008) OR LIMIT-TO (PUBYEAR,2007) OR LIMIT-TO (PUBYEAR,2006) OR LIMIT-TO (PUBYEAR,2005) OR LIMIT-TO (PUBYEAR,2004) OR LIMIT-TO (PUBYEAR,2003) OR LIMIT-TO (PUBYEAR,2002))	1,931 document results

#5	#1 AND #2 AND #3 AND #4	2,112 document results
#4	"Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cameroon" OR "Cape Verde" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Republic of the Congo" OR "Democratic Republic of the Congo" OR "Cote d'Ivoire" OR Djibouti OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "The Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Liberia" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome and Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "Tanzania" OR "Togo" OR "Uganda" OR "Zambia" OR "Zimbabwe"	3,020,727 document results
#3	"HIV infect*" OR "hiv" OR "human immunodeficiency virus" OR "human immunedeficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immunodeficiency syndrome" OR "acquired immune-deficiency syndrome" OR "hiv-positive" OR "sexually transmitted diseases"	1,289,262 document results
#2	"Mortalit*" OR "opportunistic infection*" OR "AIDS Related opportunistic infection*" OR "survival status" OR "death rate" OR "case fatality rate" OR "mortality determina*" OR "mortality rat*" OR "mortality predict*" OR "risk of mortality" OR "morbidit*" OR "hospital admissions" OR "hospitalization" OR "herpes zoster" OR "bacterial pneumonia" OR "pulmonary TB" OR "extra-pulmonary TB" OR "oral candidiasis" OR "oesophageal candidiasis" OR "mouth ulcer" OR "diarrhoea" OR "pneumocystis pneumonia" OR "central nervous system toxoplasmosis" OR "cryptococcal meningitis" OR "non-Hodgkins lymphoma" OR "Kaposi's sarcoma" OR "cervical cancer" OR "herpes simplex" OR "cytomegalovirus"	4,791,117 document results
#1	"malnutrition" OR "undernutrition" OR "malnourishmt*" OR "nutritional deficienc*" OR "nutritional status" OR "Body Mass Index" OR "BMI" OR "micronutrient deficienc*" OR "stunting" "wasting" OR "underweight"	40,633 document results

4. Search from CINHAL

Search ID#	Search Terms	Results
S6	Limiters - Published Date: 20020101-20191231	120
S5	S1 AND S2 AND S3 AND S4	124
S4	"Angola" OR "Benin" OR "Botswana" OR "Burkina Faso" OR "Burundi" OR "Cameroon" OR "Cape Verde" OR "Central African Republic" OR "Chad" OR "Comoros" OR "Republic of the Congo" OR "Democratic Republic of the Congo" OR "Cote d'Ivoire" OR Djibouti OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Gabon" OR "The Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Kenya" OR "Liberia" OR "Madagascar" OR "Malawi" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Mozambique" OR "Namibia" OR "Niger" OR "Nigeria" OR "Rwanda" OR "Sao Tome and Principe" OR "Senegal" OR "Seychelles" OR "Sierra Leone" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sudan" OR "Swaziland" OR "Tanzania" OR "Togo" OR "Uganda" OR "Zambia" OR "Zimbabwe"	69,581
S3	(MH "Human Immunodeficiency Virus") OR "HIV infect*" OR "hiv" OR "human immunedeficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immunodeficiency syndrome" OR "acquired immune-deficiency syndrome" OR "hiv-positive" OR "sexually transmitted diseases"	117,637

S2	(MH “mortality”) OR (MH “morbidity”) OR (MH "AIDS-Related Opportunistic Infections") OR “opportunistic infection*” OR OR “survival status” OR “death rate” OR “case fatality rate” OR “mortality determina*” OR “mortality rat*” OR “mortality predict*” OR “risk of mortality” OR “morbidit*” OR “hospital admissions” OR “hospitalization” OR “herpes zoster” OR “bacterial pneumonia” OR “pulmonary TB” OR “extra-pulmonary TB” OR “oral candidiasis” OR “oesophageal candidiasis” OR “mouth ulcer” OR “diarrhoea” OR “pneumocystis pneumonia” OR “central nervous system toxoplasmosis” OR “cryptococcal meningitis” OR “non-Hodgkins lymphoma” OR “Kaposi’s sarcoma” OR “cervical cancer” OR “herpes simplex” OR “cytomegalovirus”	226,082
S1	(MH "Malnutrition") OR (MH “Body Mass Index”) OR “undernutrition” OR “malnourishmt*” OR “nutritional deficienc*” OR “nutritional status” OR “BMI” OR “micronutrient deficienc*” OR “stunting” “wasting” OR “underweight”	117,352

Appendices for Chapter 5

Appendix 5.1: Reporting checklist for protocol of a systematic review for Manuscript II

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	Title Page
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	N/A
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title Page
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state	6

		plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	N/A
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
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	6-7
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	6
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	Additional file 2
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Study records - 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)	6-7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done	7

		independently, in duplicate), any processes for obtaining and confirming data from investigators	
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	7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
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	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8-9
Data synthesis	#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 I2, Kendall's τ)	8-9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9-10
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

Appendix 5.2: Searching strategy from PubMed for Manuscript II

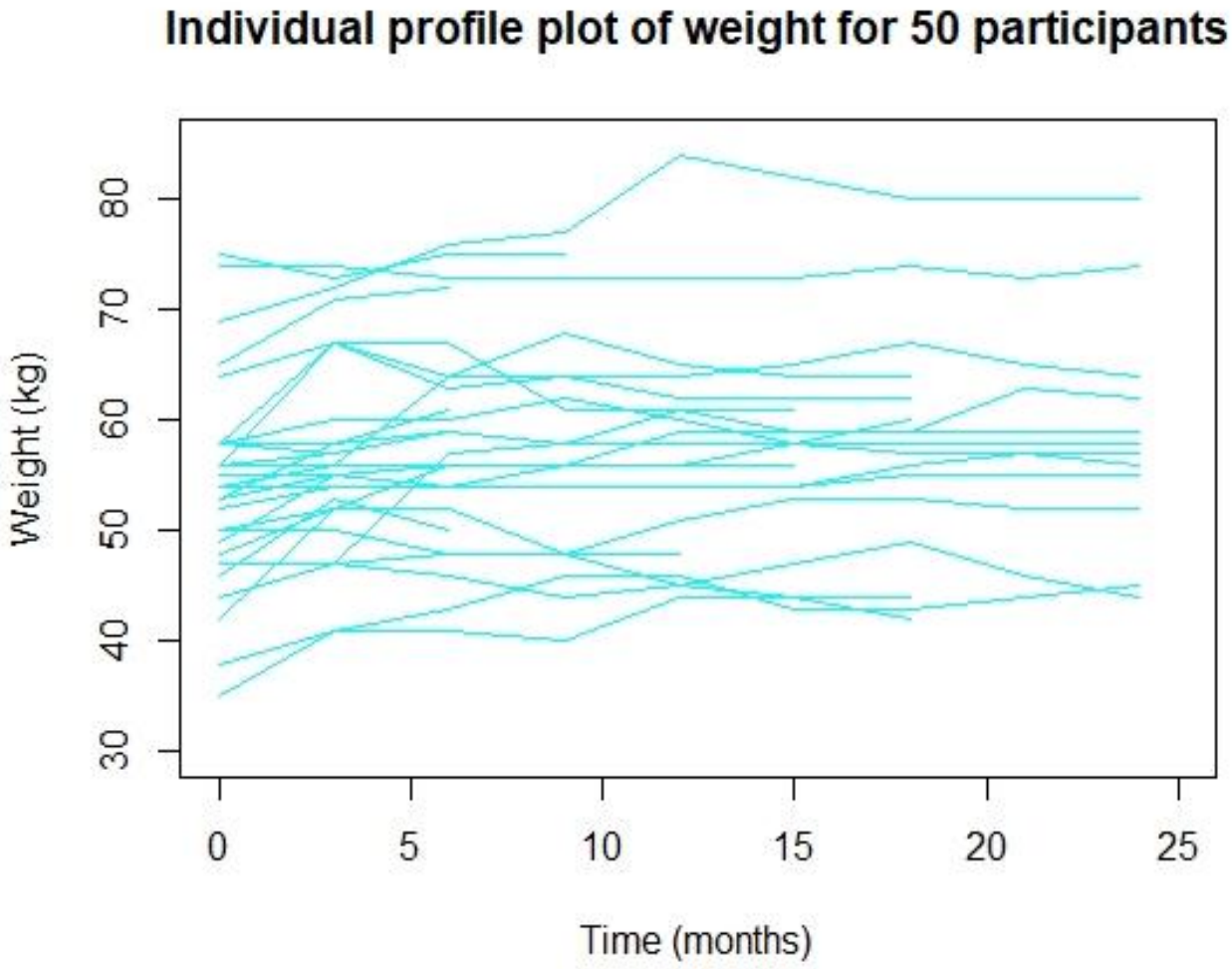
Electronic search strategy conducted in **PubMed.**

Search	Query
#9	**#3 AND #6 AND #9 AND #10** Filters: **English, Humans, from 2005 – 2021**
#11	**#3 AND #6 AND #9 AND #10**
#10	"Angola"[Title/Abstract] OR Benin*[Title/Abstract] OR Botswana*[Title/Abstract] OR "Burkina Faso"[Title/Abstract] OR Burundi*[Title/Abstract] OR Cameroon*[Title/Abstract] OR "Cape Verde"[Title/Abstract] OR "Central African Republic"[Title/Abstract] OR Chad*[Title/Abstract] OR Comoros*[Title/Abstract] OR "Republic of the Congo"[Title/Abstract] OR "Democratic Republic of the Congo"[Title/Abstract] OR "Cote d'Ivoire"[Title/Abstract] OR "Djibouti"[Title/Abstract] OR "Equatorial Guinea"[Title/Abstract] OR Eritrea*[Title/Abstract] OR Ethiopia*[Title/Abstract] OR Gabon*[Title/Abstract] OR The Gambia*[Title/Abstract] OR Ghana*[Title/Abstract] OR Guinea*[Title/Abstract] OR Guinea-Bissau*[Title/Abstract] OR Kenya*[Title/Abstract] OR Liberia[Title/Abstract] OR Madagascar*[Title/Abstract] OR Malawi*[Title/Abstract] OR Mali*[Title/Abstract] OR Mauritania[Title/Abstract] OR Mauritius[Title/Abstract] OR Mozambique[Title/Abstract] OR Namibia[Title/Abstract] OR Niger*[Title/Abstract] OR Nigeria*[Title/Abstract] OR Rwanda[Title/Abstract] OR Sao Tome and Principe[Title/Abstract] OR Senegal[Title/Abstract] OR Seychelles[Title/Abstract] OR Sierra Leone[Title/Abstract] OR Somalia*[Title/Abstract] OR "South Africa"[Title/Abstract] OR South Sudan*[Title/Abstract] OR Sudan*[Title/Abstract] OR Swaziland*[Title/Abstract] OR Tanzania*[Title/Abstract] OR Togo*[Title/Abstract] OR Uganda*[Title/Abstract] OR Zambia*[Title/Abstract] OR Zimbabwe*[Title/Abstract] OR West Africa[Title/Abstract] OR East Africa [Title/Abstract] OR Southern Africa [Title/Abstract] OR sub-Saharan Africa [Title/Abstract] OR WHO Africa region Cambria
#9	**#7 OR #8**
#8	LTFU[Title/Abstract] OR LTU[Title/Abstract] OR LFU[Title/Abstract] OR "loss to follow-up"[Title/Abstract] OR "lost to follow-up"[Title/Abstract] OR "loss to follow up"[Title/Abstract] OR "lost to follow up"[Title/Abstract] OR "loss to care"[Title/Abstract] OR "lost to care"[Title/Abstract] OR "loss to program"[Title/Abstract] OR "lost to program"[Title/Abstract] OR "loss to programme"[Title/Abstract] OR

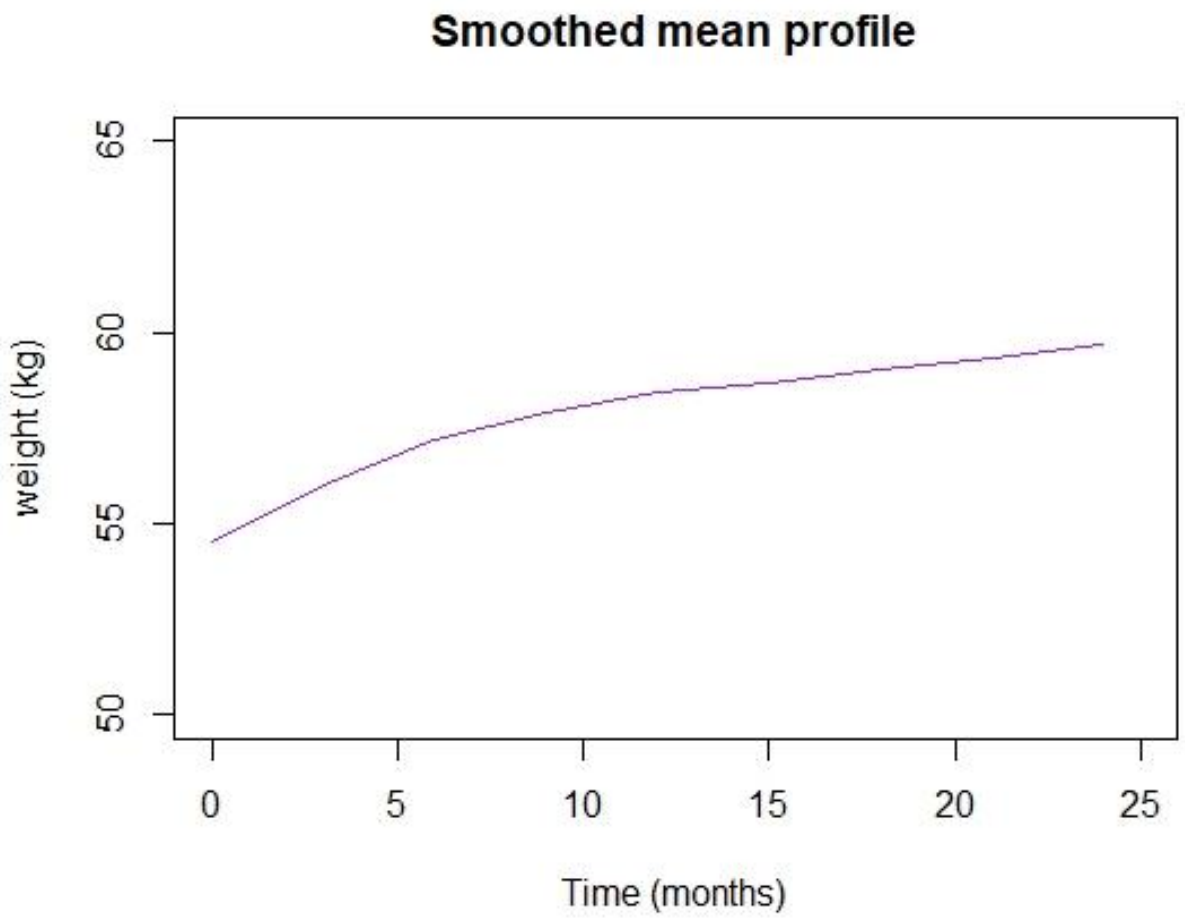
	retention[Title/Abstract] OR attrition[Title/Abstract] OR retain*[Title/Abstract] OR default*[Title/Abstract] OR transfer*[Title/Abstract] OR “drop-out”[Title/Abstract] OR "drop out"[Title/Abstract]
#7	"Lost to Follow-Up"[MeSH Terms] OR "Patient Transfer"[MeSH Terms]
#6	**#4 OR #5**
#5	“HIV”[Title/Abstract] OR “HIV-1”[Title/Abstract] OR “HIV-2”[Title/Abstract] OR “HIV-infect*”[Title/Abstract] OR “human immunodeficiency virus”[Title/Abstract] OR “human immunedeficiency virus”[Title/Abstract] OR “human immuno-deficiency virus” [Title/Abstract] OR “human immune-deficiency virus”[Title/Abstract] OR “acquired immunodeficiency syndrome”[Title/Abstract] OR “acquired immunedeficiency syndrome”[Title/Abstract] OR “acquired immunodeficiency syndrome”[Title/Abstract] OR “acquired immune-deficiency syndrome”[Title/Abstract] OR “Sexually Transmitted Diseases, Viral”[MeSH:NoExp]
#4	"HIV"[MeSH Terms] OR "HIV Infections"[MeSH Terms] OR "Acquired Immunodeficiency Syndrome"[MeSH Terms]
#3	**#1 OR #2**
#2	Malnutrition[MeSH Terms] OR Body Mass Index [MeSH Terms] OR Thinness ([MeSH Terms]
#1	Body Mass Index[tw] OR Malnourishm*[tw] OR undernutrition[tw] OR Nutritional deficienc*[tw] OR Nutritional status[tw] OR BMI[tw] OR underweight[tw] OR stunting[tw] OR wasting[tw] OR micronutrient deficienc*[tw]

Appendices for Chapter 7

Appendix 7.1: Individual profile plots of weight for 50 study participants for Manuscript V.



Appendix 7.2: The smoothed mean profile plot of weight for all percipients for Manuscript V



Appendices for Chapter 8

Appendix 8.1: Classification and definitions of explanatory variables for Manuscript VI

Supplementary table. Classification and operational definitions of explanatory variables.

Variables	Classification/definition
Early mortality	In this study, early mortality was defined as the death of patients from any cause within the first 24 months of starting ART.
Loss to follow-up (LTFU)	LTFU was recorded when patients missed their ART appointment for at least one month.
ART Adherence	Patients' adherence to ART was categorized into three categories: good, fair, and poor. Good ART adherence was recorded when patients took ≥ 95% of the monthly dose or missed ≤ three pills per month. Fair ART adherence was considered when patients took 85-94% of the monthly dose or missed four to eight pills per month. Poor was recorded when patients took less than 85% of their monthly dose or missed ≥ nine pills per month.
Anaemia	Anaemia was diagnosed when the haemoglobin level was below 12 g/dl for men and below 13 g/dl for women.
Functional status	Functional status included three categories (working, ambulatory, and bedridden). Patients are classified as working functional status if they can go out of home and do routine activities, including daily work. Patients are classified as ambulatory functional status if they are capable of self-care and use the toilet without support. Finally, patients are classified under bedridden functional status if they are incapable of essential self-care (i.e., not able to use the toilet without support).
Degree of immunodeficiency	The WHO staging of HIV has four levels to determine the degree of immunodeficiency based on CD4 cell count: no significant immunosuppression (CD4 > 500 cells/mm^3), mild immunosuppression (CD4: 350−499 cells/mm^3), advanced immunosuppression (CD4: 200−349 cells/mm^3), and severe immunosuppression (CD4<200 cells/mm^3).
Nutritional status	Undernutrition is defined as a BMI of less than 18.5 kg/m^2.

Appendix 8.2: Individual profile plots of BMI for 50 study participants for Manuscript VI