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) [1]. The problem is more prominent in Ethiopia as a result of food insecurity and inadequate knowledge about healthy nutrition [2]. Approximately 26% of adults living with HIV in Ethiopia are

undernourished [3]; 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 [4].

Although antiretroviral therapy (ART) significantly improves PLHIV survival, early mortality from acquired immunodeficiency syndrome (AIDS)-related illness remains high, notably in SSA [5, 6]. 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 [7-10]. Studies frequently cited that low BMI at ART initiation is an independent predictor of mortality in adults living with HIV [1, 7, 11, 12], while normal BMI is significantly associated with adequate CD4 cell count response to ART and lower risk of loss to follow-up [13].

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 [14-16]. 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 [17]. 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 [13, 18, 19].

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 [20], 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 [21]. 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 [22], 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 [20]. 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

146 extensive experience in secondary data collection closely supervised the entire data collection
147 process.

148 ## *Study variables and measurements*

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

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

163 ## *Data management and statistical analyses*

164 **Missing data**

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

imputation [23]. 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 1 for detailed participant sociodemographic characteristics.

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 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 (Supplementary Material). The overall smoothed mean profile plot showed a linear increase in average BMI (see Figure 1).

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 2).

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 4).

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 5).

Discussion

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 [24-26]. This strong association could result from the recovery in adaptive and innate immunity elements after ART initiation [27]. Evidence furthermore suggests that a higher BMI is associated with higher CD4 cell counts at baseline and after six months [28]. 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 [29].

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

[30, 31]. 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 [32]. Another possible explanation is that integrase strand transfer inhibitors (INSTIs) may affect the gut microbiota of patients living with HIV [33]. 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 [34].

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 [34, 35]. 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 [30], reflecting effects of ART, as it significantly reduces the occurrence and recurrence of OIs and improves gastrointestinal function, appetite, and nutrient absorption [30]. 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 [24, 36]. 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) [37]. 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 [38], which could be due to dietary changes from a traditional diet to high-energy processed foods, fats, animal-derived foods, sugar, and sweet beverages [39]. This pattern of dietary change is more evident in urban residents than rural residents due to higher incomes and greater availability of processed foods [38].

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 [40, 41]. Underweight patients may have gained more weight due to increased food intake, reduced metabolic demand, and improved nutritional absorption after ART initiation [42]. 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 [43]. Lastly, continuous nutritional education given by health professionals as recommended by the Ethiopian ART guidelines or dietary supplements may promote healthier diets [20].

The mechanism of weight gain or loss is too complex, and observational studies like ours may not address such research questions because it needs molecular studies. However, as our study suggests that patients who failed to gain weight had a higher risk of death, discussing the possible reasons for failure to gain weight in this population is essential to make recommendations. We understand possible explanations for the weight gain in our study might be speculative but very important.

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 [44-46]. Patients with advanced disease stages are at higher risk of developing serious and life-threatening OIs, such as TB, cryptococcal meningitis, and toxoplasmosis [47]. Patients co-infected with TB are more likely to die in the early phase of ART due to the immune reconstitution inflammatory syndrome [48].

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 [49, 50]. 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 [51].

Similar to findings of previous LMICs-based studies [16, 52-56], 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.

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