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Incidence and predictors of mortality among adolescents on antiretroviral therapy in Amhara Region, Ethiopia: A retrospective follow-up study

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Abstract

Objective: This study aimed to assess the incidence and predictors of mortality in adolescents receiving ART in Ethiopia's Amhara Region.

Design: We conducted an institution-based retrospective follow-up study.

Settings: The study was conducted at Amhara Region's comprehensive specialised hospitals in Ethiopia.

Participants: We included 961 randomly selected medical records of adolescents receiving ART between January 2005 and June 2020.

Primary and secondary outcomes: The primary outcome was the incidence of mortality since ART initiation, while the secondary outcome was to identify predictors of mortality. We assessed the association between mortality and predictors using cox-proportional hazard regression. Variables with p-values <0.05 in the multivariable analysis were considered statistically significant mortality predictors. AHR with 95%CI was used to measure the strength of association.

Results: More than half (n=496, 53.5%) of ALHIV in our sample were female. The follow-up time was 81,583 adolescents-months, with mortality rate of 0.015 (95%CI: 0.012, 0.018)per 100 person-years. Mortality was higher for ALHIV who had not received formal education (AHR=3.58), had changed their ART regimen (AHR=0.59), had widowed parents (AHR=1.73), received no social support (AHR=2.64). Adolescents who had opportunistic Infections at ART initiation (AHR=2.30), low Hgb levels (AHR=2.13), a bedridden functional status (AHR=3.13), stage IV clinical staging (AHR=2.40), and CD4 count 200-350 cells/mm^3 (AHR=2.10) had a higher risk of death. Not receiving CPT (AHR=1.85) and being only fairly adherent to medication (AHR=2.16) were associated with higher mortality risk.

Conclusions: Our study found a lower mortality rate for adolescents with HIV than previous Ethiopian studies, but our significant mortality predictors were similar to those found in earlier

studies of adults and adolescents. Our findings reveal a potential point for health service improvement in Ethiopia: incorporating monitoring of haemoglobin levels into patient follow-up care, supporting recommendations that clinicians emphasise managing OIs, and providing counseling services to improve adherence.

Study strengths and limitations

This study has several strengths and limitations

- Our analysis covers a wide geographic area of Ethiopia, unlike previous studies that usually focused on individual health facilities.
- We had a large sample from which we could collect a range of sociodemographic and clinical data.
- We used the Online Open Data collection Kit (ODK) application for data collection. This tool facilitates the online monitoring of data collection activities and provides immediate feedback to the data collectors, improving the reliability of data entry.

Our study also experienced the following limitations that the reader should consider when interpreting its findings.

- We used patient record data, and our analysis was constrained by the incompleteness or unavailability of important variables in these records, such as income and behavioural predictors, which might also influence mortality.
- We also did not assess health service quality, which affects HIV-related mortality.
- Our study only collected data at comprehensive specialised hospitals, which, we can assume, offer a higher standard of care than smaller facilities.

Background

Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) associated mortality is a significant contributor to global adolescent mortality [1] and the leading cause of death among adolescents aged 10 to 19 years in sub-Saharan Africa (SSA) [2]. The SSA region has the highest prevalence of HIV in the world [3, 4], with more than 39 million deaths resulting from HIV/AIDS and more than 36 million people currently living with HIV [3, 5]. Substantial progress has been made in responses to HIV/AIDS under the Millennium Development Goals framework [6]. However, adolescents and young people [7] are still heavily affected by the disease, accounting for 37% of all new global HIV infections in 2017 and 15% of all people living with HIV [1, 2]. Globally, in 2016 an estimated 2.1 million adolescents (age 10–19 years) were living with HIV [8]. In 2020 alone, 150,000 adolescents between the ages of 10 and 19 were newly infected with HIV, and 3200 estimated number of adolescents died of AIDS-related causes [9].

HIV prevalence in Ethiopia has been declining at a moderate rate, reducing from 2.4 % in 2001 to 0.9 % in 2020 among adults [10]. According to the 2018 Ethiopia HIV statistics, 690,000 people in Ethiopia live with HIV [11], and in 2016, nearly 20,000 HIV-related deaths occurred [12]. There are no recent data on the number of ALHIV in Ethiopia, but as of 2021, approximately 140,000 (88%) of the global ALHIV population were from SSA [13], growing in proportion to the global ALHIV population [14]. The United Nations Children's Fund suggests that turning the tide against AIDS requires a stronger focus on adolescents [15], and policymakers agree that a critical factor contributing to gaps in HIV/AIDS service uptake among adolescents is the limited provision of adolescent-friendly services [16].

Despite the growing number of adolescents in Ethiopia and the high number of HIV infections among adolescents, Ethiopian HIV/AIDS policies do not currently pay sufficient attention to the unique needs of adolescents [17-20]. Current HIV care and treatment guidelines in Ethiopia focus

only on adults and children, with ART guidance for treating ALHIV split between tools for paediatric patients (0-14 years old) and adult patients (age 15 and above). There are a lack of adolescent-specific treatment literacy and adherence counselling tools [21].

The lack of attention to ALHIV in Ethiopia is in keeping with findings from high-, middle- and low-income countries that show services for adolescents are often highly fragmented and poorly coordinated [16, 22]. Pockets of excellence in adolescent services exist, but, overall, studies suggest that services need significant improvement and should be brought into conformity with global best-practice guidelines [16, 22]. Failure to consider the unique needs of ALHIV may not only lead to inappropriate or unresponsive care, but it may also lead to a lack of services that are important for adolescents. These might include screening for mental health disorders, substance use disorder counselling, reproductive health counselling, screening for potential interactions between specific antiretroviral medications and hormonal contraceptives, and counselling on the transition to adult care settings [23]. Failure to consider such services could result in poor treatment adherence, viral suppression, and increased mortality [23, 24].

The first step in designing such interventions is understanding the current experiences and health outcomes of ALHIV in countries like Ethiopia. Research on this topic is, however, relatively sparse. The present study is part of a more extensive mixed-methods study that begins to address this gap. The current study focuses on assessing the mortality rates and identifying potential predictors of mortality among ALHIV in Ethiopia's Amhara Region who are receiving antiretroviral therapy (ART). Survival chances for ALHIV vary significantly across the world [16], and few rigorous studies of mortality among ALHIV have been conducted in Ethiopia. By providing baseline mortality estimates from one of Ethiopia's most populous regions, our project will assist policymakers, program implementers, and non-governmental organisations in Ethiopia and similar settings to plan, monitor, evaluate, and take evidence-based actions to improve ALHIV health outcomes.

Methods

Study setting and period

We conducted an institution-based retrospective cohort study among all adolescents living with HIV who initiated ART between January 2005 and June 2020 at specialised comprehensive hospitals in Ethiopia's Amhara Region. At the time of data collection, the Amhara Region had five specialised comprehensive hospitals: Felege Hiwot, Gondar, Dessie, Debre Berhan, and Debre Markos. Each hospital had a catchment area of more than five million people and provided a range of HIV/AIDS services, including ART in outpatient and inpatient care. All adolescents living with HIV who initiated ART between 2005 to 2020 were considered for inclusion.

Inclusion and Exclusion

The study population comprised all ALHIV aged 10-19 years old who initiated ART between January 2005 and June 2020. This included adolescents who transferred into study facilities from elsewhere. Adolescents with at least one viral load test record were included. Charts with incomplete medical records for essential variables such as treatment outcome, age, CD4, and viral load were excluded. In addition, patients who transferred out of care to a non-study facility during the study period were excluded from the study. The outcome of this study was death due to HIV while taking ART.

Sample size determination

The minimum required sample size was determined using Stata statistical software Version 16 based on a survival analysis sample size determination formula. Sample size calculations were based on four predictors of mortality previously identified in the literature [25]: age (15-19 years old), residence (rural setting), CD4 count at ART initiation (<200cells/mm3), and Hgb at ART initiation (<10g/dl). Identical assumptions were used for all calculations: Power = 80%, CI= 95%,

$\pi_1=\pi_2=$ ½, withdrawal 10%, N events = 92, and Pr (events) = 0.06. The sample size needed for achieving an 80% power ($\beta = 0.20$) at the 5% ($\alpha = 0.05$) level of significance after assuming that incompleteness was highest for the Hgb at ART initiation predictor with an estimate of 961 participants. Sample size calculations for all variables can be found in Table 1.

Table 1: Sample size determination for assessing treatment outcomes among ALHIV on ART in Amhara Regional State, Ethiopia, 2020

Variables	Hazard ratio	Calculated sample size	10% incompleteness	Total sample
Age group of the respondents	aHR = 2.3	755	8	765
Residence of the respondents	aHR = 2.8	494	5	499
CD4 count at ART initiation	aHR = 2.8	494	5	499
Hgb at ART initiation	aHR = 2.1	951	10	961

Note: Assumptions**;** power = 80%, CI= 95%, $\pi_1=\pi_2=$ ½, withdrawal 10%, N events =92, and Pr (events) =0.06. HRs described in the above table were obtained from one source [25].

Sampling procedures and source of data

This study included all five specialised comprehensive hospitals in the Amhara region, with proportional cases based on each hospital's patient load. The source of data for all variables of interest was the ART registration database. Medical records of adolescents who received chronic HIV care from all Hospitals were retrieved. The complete sampling procedure is outlined in Figure 1.

Data collection tool and data collection procedures

The data extraction tool was adopted from a standard ART treatment follow-up form currently used by Ethiopian health facilities, including hospitals. An online Open Data collection Kit (ODK) application tool that populated Microsoft Excel spreadsheets was used to facilitate the data collection [26]. Sociodemographic data were collected from patient charts and intake forms. The most recent laboratory test results preceding ART initiation were used as a baseline value. If no registered pre-ART laboratory test result was obtained within one month of ART initiation, the most recent laboratory test after initiation was used as the baseline value. The mean value was computed when the two results were obtained within one month. Researchers with relevant qualifications and experience in health were employed for the data collection activities.

Study Variables

The dependent variable of this study was the incidence of mortality (yes/no). Independent variables included sociodemographic and baseline clinical characteristics as well comorbidities. All variables were extracted from patient medical records.

Sociodemographic characteristics included age at ART initiation (10-19), sex (male/female), residence (urban/rural), religion, being an orphan (yes/no), social support (yes/no), ethnicity, marital status of the caregiver, parental status (alive/dead), educational and occupational status of the caregiver, and family size.

Baseline clinical and laboratory variables included WHO clinical staging, functional status, haemoglobin (Hgb) at ART initiation, baseline CD4 count**,** regimen substitute, regimen changes, and baseline body mass index (BMI). Comorbidities included a history of opportunistic infection, tuberculosis, malnutrition, depression, and anxiety symptoms.

The operational definitions of HIV/AIDS mortality [27], good adherence [28], fair-adherence [28], poor adherence [28], LTFU [29], viral load suppression [29], clinical failure, [30], immunologic failure [30], virological failure [30], CD4 count [31], and social support [32] are included as a supplementary file (see Supplementary material).

Patient and public involvement statement

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

Missing data handling

Missing data are unavoidable in epidemiological and clinical research, but their potential to undermine the validity of research results has often been overlooked in the medical literature [33]. Our data has incomplete records for Height (n=4, 0.4%), Weight (n=17, 1.8%), CD4 cell counts (n=42, 4.5%), Hgb (n=67, 7.1%), and viral suppression (n=87, %). After checking the pattern and mechanisms of missing values, we managed missing through multiple imputations (MI). We applied the little's test of missing completely at random test to check whether the values were missing at random or not [34]. The final imputation was performed using a multivariate normal imputation model. Variables included were sex, residence, Functional status, Clinical staging, ART adherence, nutritional status, OIs, CPT, Tuberculosis, and IPT.

Categorizing continuous variables

We categorized continuous variables with referring standards and references. BMI was categorized as undernutrition (BMI<18.5), healthy weight range (18.5 to 24.9), overweight (25.0 to 29.9), and obese (BMI>29.9) [35]. Clinical conditions, such as CD4, and viral suppression, were categorized based on the ART treatment guideline that has been used in Ethiopia [36].

Data processing and analysis

The collected data were cleaned, coded, entered into EpiData™ software version 4.2, then exported into Stata version 16 statistical software for further analysis. Descriptive measures such as means, median, interquartile ranges (IQR), percentage, frequency, standard deviations (SD), and graphs were used for descriptive statistics. The time to death from HIV/AIDS during the ART follow-up

period was estimated using the Kaplan-Meier survival curve method. A log-rank test was used to compare the estimated survival curve of patients based on categorical variables.

Assumptions for Cox-proportional analysis were checked using the Schoenfeld residual test with variables with a p-value of >0.1. Variables with p-values less than 0.25 in the bi-variable analysis were considered for the multivariable Cox regression model. Adjusted hazard ratios (aHR) with a 95% confidence interval and p-values less than 0.05 were used to measure the strength of the association and identify statistically significant predictors. The mean-variance inflation factors (VIF=1.16) indicated no meaningful multicollinearity between variables in the multivariable models.

Ethics consideration of the study

The study was approved by the University of Technology Sydney (UTS) Medical Research Ethics Committee (Approval number: ETH20-5255). Ethical approval was received from the Amhara Region Public Health Institution (No H/R/T/T/D/3/887), and permission letters were received from the five study comprehensive specialised hospitals. Identifiable data was not included in the data collection tool.

Results

Demographic characteristics

After reviewing 945 medical records, 17 were excluded due to incompleteness, and 928 were included in the final analysis. More than half (53.0%) of the sample were female (see Table 1). The median age of ALHIV was 13 [IQR: 11.0, 16.0] years; 63.3% of them were between 10 and 14 years old at the initiation of ART. The majority (74.6%) lived in urban environments, and 68.8% had a primary-school level of education. More than three-quarters (77.7%) had both parents alive. A total of 75.9% of the adolescents received social support while on ART. Most ALHIV (84.7%) were aware of their HIV status (Table 2).

Table 2: Baseline sociodemographic characteristics of ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	Frequency (N)	Percentage (%)
Age		
10-14 years old	590	63.6
15-19 years old	338	36.4
Sex		
Male	432	46.6
Female	496	53.5
Residence		
Urban	692	74.6
Rural	236	25.4
Education		
No formal education	14	1.5

Primary (grades 1-8)	639	68.9
Secondary (grades 9-12)	223	24.0
Higher (degree & above)	52	5.6
Ethnicity		
Amhara	886	95.6
Other*	52	4.5
Parental status		
Both alive	721	77.7
Father alive	74	8.0
Both died	133	14.3
Religion		
Orthodox Tewahido Christian	643	69.3
Muslim	224	24.1
Other	61	6.6
Caregiver marital status		
Single	114	12.3
Married	552	59.5
Divorced	80	8.6
Widowed	182	19.6
Family size		
Family size ≤4	683	73.6
Family size >4	245	26.4
Social support		
Yes	703	75.7
No	225	24.3

Disclosure status (knowledge of their own HIV status)		
Yes	786	84.7
No	142	15.3
History of PMTCT		
Yes	169	18.2
No	523	56.4
Unknown	236	25.4
Relation to caregiver		
Parent	611	65.9
Sister/Brother	159	17.1
Grandparents	65	7.0
Aunt/Uncle	76	8.1
Other*	17	1.9

Other *: other relatives (11) and guardian (8)

Baseline clinical, laboratory, and ART information

Of the 928 ALHIV, 237 (25.5%) presented with opportunistic infection (OIs) at ART initiation. We found that 579 (62.4 %) were asymptomatic or at early stages of infection (WHO stages I and II) at baseline, and about one-third (30%) had CD4 counts < 200 cells/mm^3. Nearly half, 440 (47.4%), were categorised as having working functional status. The nutritional status of ALHIV was assessed using body mass index (BMI): 81.9% of the sample were underweight (BMI < 18.5), 16.4%, were normal weight, (BMI 18.5 to 24.9), and 1.7% were overweight (BMI ≥ 25) at the time of ART initiation (Table 3).

Table 3: Clinical, laboratory, and treatment characteristics of ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	Frequency (N)	Percentage (%)
CD4 count		
Less that 200 cells/mm3	278	30.0
200 to 350 cells/mm3	249	26.8
More than 350 cells/mm3	401	43.2
WHO clinical staging		
Stage I and II	579	62.4
Stage II and IV	349	37.6
Functional status		
Working	440	47.4
Ambulatory	420	45.3
Bedridden	68	7.3
Haemoglobin level		
< 10 g/dl	56	6.0
≥10 g/dl)	872	94.0
Cotrimoxazole preventive therapy (CPT)		
Yes	820	88.4
No	108	11.6
Ionised Preventive Therapy		
Yes	682	73.5
No	246	26.5

ART adherence		
Good	827	89.1
Fair	47	5.1
Poor	54	5.8
Opportunistic Infections at baseline (OPs)		
Yes	237	25.5
No	691	74.5
ART eligibility criteria		
Immunologic/CD4	110	11.9
WHO clinical stage	93	10.0
Both clinical and immunologic	642	69.2
Test and treat approach	83	8.9
ART drug side effects		
Yes	66	7.1
No	862	92.9
Baseline viral load		
Below 1000	768	82.8
1000 and above	160	17.2
Tuberculosis developed		
After ART initiation	76	78.4
Pre-ART	21	21.6
History of treatment failure		
Yes	113	12.2
No	815	87.8
Regimen change		

Yes	433	46.7
No	495	53.3
Body Mass Index (BMI)		
Underweight	760	81.9%
Normal	152	16.4%
Overweight	16	1.7%

Baseline opportunistic infections

The top three OIs at ART initiation were diarrheal disease (n=127, 20.7%), pneumonia (n=122, 19.9%), and tuberculosis (n=90, 14.7%) (see Table 4).

Table 4: Baseline opportunistic infections of ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	Frequency (n)	Percentage (%)
Diarrheal disease		
Yes	127	20.7
Pneumonia		
Yes	122	19.9
Tuberculosis		
Yes	90	14.7
Herpes Zoster		
Yes	89	14.5
Skin infection/rash		
Yes	77	12.5
Candidiasis		
Yes	71	11.6
CNS toxoplasmosis		
Yes	18	2.9

Adolescents' follow-up characteristics

One quarter (n=238, 25.6%) of adolescents developed opportunistic infections (OIs) during follow-up. Nearly one-third (n=76, 31.9%) of them developed pneumonia (Table 4). During the follow-up time, 113 (12.3%) experienced treatment failure. Nearly half, 434 (46.8%), of the included adolescents had a history of ART regimen change during follow-up. Of these, 76 (17.6%) of them changed their regimen due to treatment failure, 56 (12.9%) due to side effects, and 5.5% developed OIs. The majority were virologic failures (n=70, 61.4%), followed by immunologic failures (n=22, 20.2%) and clinical failures (n=21, 18.4%). About half (46.7%) changed their regimens during ART follow-up (Table 5).

Table 5: Most common opportunistic infections developed during follow-up among ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020

Opportunistic Infections	Frequency	Percentage
Bacterial pneumonia	76	24%
Tuberculosis	67	21%
Diarrhea	55	17%
Candidiasis	27	9%
Skin rash	27	9%
Herpes zoster	23	7%
Central nurves system (CNS) toxoplasmosis	17	5%
Others	24	8%

Others: Malnutrition (n=9, 3.8%), Pneumocystis pneumonia (PCP) (n=9, 3.8%) and Cryptococcus meningitis (n=6, 2.5%),

Few (66, 6.8%) adolescents experienced drug side effects, with more than one-third (n=27, 37.9%) of drug side effects being toxicity (Table 6).

Table 6: Drug side effects among ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020.

Drug side effects	Frequency (n)	Percentage (%)
Toxicity	27	35.1%
Diarrhea	16	20.8%
Anemia	10	13.0%
Nausea	5	6.5%
Fatigue	4	5.2%
Skin rash	4	5.2%

Others: Facial dystrophy (n=3, 3.9%), vomiting(n=3, 3.9%), Lipodystrophy (n=3, 3.9%), and Headache (n=2, 2.6%),

Death rate during follow-up

A total of 928 adolescents on ART were observed for varying lengths of time, ranging from 7 to 233 months, with a median follow-up period of 82 (IQR: 44 –130) months. This retrospective cohort contributed a total follow-up time of 81,583 person-month observations. At the end of the project/follow-up period, 103 (11.1%) died, while 772 (83.2%) were still on follow-up, and 53 (5.7%) were transferred to other health institutions. The cumulative probability of surviving or being free from the event of interest at the end of 6, 12, 18, and 24 months was 98.6, 96.7, 95.8, and 95.0%, respectively (Fig. 2).

The cohort's overall mortality rate was 1.26 (95% CI: 1.04, 1.53) per 1000 person-months. The overall estimated median mortality time was 4.76 months (95% CI: 4.17, 5.02 months; Fig. 3).

Predictors of mortality incidence

In the final multivariable Cox regression model, several factors associated with higher mortality were identified (Table 3). The mortality hazard of those who did not attend a formal education was 3.58 (AHR: 3.58, 95% 1.49, 8.60), times higher than those with primary schooling. The hazard of death in participants who changed their previous regimen was 41% (AHR: 0.59, 95% 0.35, 0.98) times lower than those non-regimen change. We saw a higher hazard of death in adolescents with widowed parents (AHR: 1.73, 95% 1.03, 2.98) and those without social support (AHR: 2.64, 95% CI: 1.60, 4.36).

Adolescents with lower Hgb levels at ART initiation had more than double the hazard of death (AHR: 2.13 95%CI: 1.06, 4.22) than those with normal Hgb levels. Adolescents with bedridden functional status at ART initiation had three times the higher hazard of death than those with working status (AHR: 3.13, 95%CI: 1.69, 5.81). The hazard of death among adolescents who started treatment at WHO clinical stage IV was 2.4 times higher than those in stage I (AHR: 2.4, 95% CI: 1.16, 5.07). The hazard of death among adolescents with a CD4 count between 200 to 350 cells/mm^3 was 2.1-fold higher than adolescents with a CD4 count higher than 350 cells/mm^3 (AHR: 2.1, 95% CI: 1.01, 4.00). The mortality hazard among adolescents who did not receive CPT was nearly two times higher (AHR: 1.85, 95% CI: 1.07, 3.22) than their counterparts. The hazard of death among fairly adherent adolescents was two (AHR: 2.16, 95% CI: 1.13, 4.10) times higher than those with good adherence (Table 7).

Table 7: Bivariable and multivariable Cox regression analysis of mortality predictors among ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	cHR [95% CI]	aHR [95% CI]	p-value
Sex			
Male	1.10 (0.75, 1.62)	1.003 (0.65, 1.55)	0.990
Female	1	1	

Age			
10-14 years old	1	1	
15-19 years old	1.49 (1.00, 2.19)	1.08 (0.61, 1.93)	0.786
Education			
No formal education	5.70 (2.61, 12.48)	3.88 (1.63, 9.23)	0.002
Primary education	1	1	
Secondary education	1.35 (0.86, 2.15)	0.95 (0.52, 1.74)	0.891
Higher education	1.44 (0.66, 3.17)	0.67 (0.28, 1.61)	0.368
Caregiver marital status			
Single	1.98 (1.12, 3.50)	1.57 (0.84, 2.93)	0.157
Married	1	1	
Divorced	3.28 (1.90, 5.68)	1.85 (.98, 3.48)	0.057
Widowed	1.65 (1.01, 2.71)	1.77 (1.03, 3.03)	0.037
Social support			
Yes	1	1	
No	5.30 (3.58, 7.84)	2.84 (1.72, 4.69)	0.001
Disclosure status			
Yes	1		
No	4.55 (3.04, 6.82)		
Regimen change			
Yes	0.28 (0.18, 0.44)	0.59 (0.35, 0.98)	0.040
No	1	1	
Baseline haemoglobin level			
< 10 g/dl	2.67 (1.42, 5.02)	2.10 (1.05, 4.20)	0.036
≥10 g/dl)	1	1	

Baseline functional status			
Working	1	1	
Ambulatory	0.89 (0.57, 1.39)	0.91 (0.56, 1.46)	0.431
Bedridden	5.70 (3.47, 9.38)	3.13 (1.69, 5.81)	0.001
Baseline WHO clinical staging			
Stage I	1	1	
Stage II	1.24 (0.71, 2.15)		
Stage III	1.02 (0.57, 1.81)	1.03 (0.53, 1.97)	0.211
Stage IV	4.79 (2.75, 8.34)	2.42 (1.16, 5.07)	0.019
Baseline CD4 count			
≤ 200 cells/mm3	0.95 (0.61, 1.46)		
200 to 350 cells/mm3	0.55 (0.32, 0.95)	2.01 (1.01, 4.00)	0.048
> 350 cells/mm3	1	1	
Cotrimoxazole preventive therapy			
Yes	1	1	
No	4.72 (3.01, 7.41)	1.85 (1.07, 3.22)	0.029
Ionised preventive therapy			
Yes	1		
No	2.69 (1.82, 3 .97)		
ART adherence			
Good	1	1	
Fair	8.11 (4.69, 14.01)	2.16 (1.13, 4.10)	0.020
Poor	6.04 (3.52, 10.37)	1.79 (0.95, 3.37)	0.071
Opportunistic infection at baseline			
Yes	2.77 (1.84, 4.16)	2.30 (1.44, 3.65)	0.001

No	1	1	
Baseline BMI			
Underweight	1	1	
Normal	1.40 (0.87, 2.27)	1.16 (0.70, 1.93)	0.568
Overweight	1.45 (0.46, 4.61)	1.73 (0.53, 5.59)	0.363

Discussion

The objective of this retrospective cohort study was to assess the incidence and predictors of mortality among ALHIV receiving ART across the Amhara region of Ethiopia using a multi-facility retrospective follow-up approach. With a total follow-up time of 81,583 adolescent months, the overall incidence of mortality among ALHIV receiving ART was 0.015 (95% CI: 0.012, 0.018) per 100 person-years. This mortality incidence is lower than the incidence reported for adolescents by a global cohort collaboration in seven regions (0.97 deaths per 100 person-years) [37], a Nigerian study (0.8 deaths per 100 person-years) [17], a study of South African community-based ART clinics (1.2 deaths per 100 person-years) [38], and a study of ART in Zimbabwe (5.46 deaths per 100 person-years) [39]. The lower mortality rate found in our study might be due to differences in the clinical characteristics of study participants, differences in study periods, and, notably, differences in the study settings, as our study included only comprehensive specialised hospitals. It must also be noted that our sample was disproportionately urban (75%), relatively well educated, and had relatively low levels of orphaning and high levels of social support, which means that they may not be similar to adolescents populations studied in other sub-Saharan African settings.

Our estimated mortality incidence is also lower than those found in previous studies of adult PLHIV in Ethiopia, for example, in Gondar (5.3 deaths per 100 person-years) [40], Harar (4.8 deaths per 100 person-years) [41], Debre Berhan (4.8 deaths per 100 person-years) [42], Debre

Markos (13.6 deaths per 100 person-years) [43], and in Metema (6.7 deaths per 100 person-years) [44]. Our lower rates might be due to improvements in ART service quality over time in Ethiopia, the difference in the length of the study periods, the setting of our study in larger comprehensive facilities in a relatively well-resourced region of the country, and the differences in sample sizes as our study were significantly larger than several of the recent Ethiopian studies. It might also be due to a different population that is commonly less likely to have severe comorbidities present.

Our low mortality rate might also be attributed to the clinical characteristics of the included study participants; about 82.8% of our study participants had baseline viral suppression. It is well-established that higher baseline viral load is associated with increased mortality risk [45], so our study participants' relatively good health may contribute to the low rates that we see. In addition, a high proportion of adolescents in this study received critical preventative interventions, such as IPT (73.5%) and CPT (88.4%), which might have also contributed to lower mortality.

Sociodemographic predictors of mortality

We identified several demographic predictors associated with mortality in adolescents receiving ART. Adolescents with no formal schooling had higher mortality rates than those with at least primary schooling. However, mortality was not associated with higher levels of education. This is consistent with the European cohort collaboration study and a study from Denmark, which found that lower levels of education were associated with increased mortality among PLHIV [46, 47] and that rates of mortality and AIDS decreased with increasing educational levels [48].

Our study found that the age and sex of adolescents were not associated with mortality. An analysis of adolescents in India had similar findings [49]. However, the lack of significance of

age and sex is in contrast to previous research in SSA, which has found that age (older adolescents) and sex (being female) increased the risk of mortality among ALHIV [50]. Being male was also reported as a risk for HIV-associated death among ALHIV in a large global study of perinatal infection, although the sex-related risk of death varied depending on whether the patients were perinatally infected and their region [51]. It could be that a generally high standard of care at the comprehensive hospitals that we studied reduced to sex and age disparities. However, further research may be needed to determine the importance of age and sex as factors driving mortality among ALHIV, and this research should consider taking perinatal infection into account.

Urban or rural residence was not a significant predictor for mortality in this study, in contrast to other studies that found higher mortality among ALHIV living in rural areas [52]. This might be because our study had a relatively small proportion of ALHIV from rural settings (25.4%), so the study may have been underpowered to find urban-rural differences in mortality.

We found that the risk of death was nearly twice as high among ALHIV from widowed parents, which is consistent with a study in the US reporting that mortality is higher in ALHIV from divorced and separated families [53]. Having married parents may allow greater economic support and social approval than single, divorced, and widowed parents. Studies from Uganda and South Africa indicate that adolescents who live with single parents receiving ART treatment experience economic insecurity, psychological challenges and weakened social protections [54, 55]. Besides, ALHIV living with widowed fathers and those living on their own were significantly more likely to show signs and symptoms of depression than their peers [56].

The risk of death was higher among ALHIV with no social support when compared to their counterparts. This finding is supported by studies from a range of low-and middle-income countries, including the United States and Uganda [20, 57, 58], as well as studies from Ethiopia,

the SSA region, and China that highlight the vital role of social support in coping with and recovering from illness in general [58-60]. Social support networks are essential in helping PLHIV/AIDS to maintain good physical and mental health, including adhering to their treatment. Social support could moderate the adverse effects of stressful events [61], and it is one of the most effective ways to cope with stress.

Clinical predictors of mortality

We found that poor health or advanced HIV disease at baseline was associated with a higher risk of death. We identified multiple baselines and follow up clinical predictors of mortality, specifically low Hgb levels, bedridden status, WHO stage IV clinical staging, CD4 counts < 350, the presence of OIs, ARV regimen change, and fair or poor treatment adherence, all of which were associated with increased mortality risk among ALHIV.

Several studies from low-, middle- and high-income countries have found that mortality risk is higher among ALHIV and PLHIV with lower Hgb levels [49, 52, 62, 63]. In addition, studies have found an association between haemoglobin levels, viral load, and CD4 cell counts [64]. This suggests that strengthening the routine monitoring of Hgb levels (e.g., concurrently with each CD4 cell count determination) may be a helpful addition to clinical guidelines.

We found a higher mortality risk among ALHIV who was bedridden at baseline, consistent with previous Ethiopian studies [65] and assuming that functional status correlates with patients' clinical and immunological status. Similarly, we found higher mortality among ALHIV who were categorised as WHO stage IV at baseline, consistent with study findings from Ethiopia [52, 65], India [49], and South Africa [62], as well as international guidelines [66]. The negative association between CD4 counts and mortality that was identified has been well-established in previous studies conducted globally [37], in Europe [48], and Ethiopia [52].

However, the association we found was relatively weak: 95% confidence interval that approached 1.00, and there was no significant association between being in the lowest CD4 category and mortality. The weakness of this may be due to the large number of variables in our model that also measured baseline HIV disease progression. Our final indicator of disease progression was the presence of an OI at baseline. ALHIV who presented with OIs at baseline had a higher mortality rate, consistent with other Ethiopian studies [44, 67]. Overall, these findings highlight the importance of starting ART as early as possible after HIV testing, even in young populations.

Good preventative treatment and ART adherence indicators were also associated with lower mortality risk. These findings support arguments that state the timely and consistent administration of CPT prevents OIs among PLHIV, improves the quality of life, and reduces associated mortality [68]. They also underscore the WHO recommendations to prescribe CPT for all ALHIV with CD4 cell counts below 350 regardless of their symptoms [69].

The risk of death in ALHIV with poor/fair ART adherence was higher than in those with good adherence. The importance of ART adherence in reducing death and illness in ALHIV is a consistent finding [70], as adherence is critical to controlling viral replication. Helping adolescents maintain good adherence is challenging because of the specific challenges they face around disclosure, risk-taking, and transitioning to adult services [71]. Medication-related barriers such as the complexity of regimens and treatment side effects can also impact adherence and may be particularly acute for perinatally-infected ALHIV who have been receiving ART for long periods [72]. The significance of adherence in our findings underscores the need to develop and test targeted interventions to improve adherence in this population.

Finally, we found a higher death rate among ALHIV who experienced an ART regimen change, consistent with a study finding reported in Ethiopia [73]. Medication shortages and stockouts

(35%), OIs (25%), side effects (20%), treatment failure (19%), and other factors (2%) were reported as the reasons for regimen changes in that study. In contrast, in other Ethiopian studies, the most common reason for medication changes or switches were toxicity, comorbidity, patient compliance, and treatment failure, similar to our findings [74, 75].

Study strengths and limitations

This study has several strengths. First, our analysis covers a wide geographic area of Ethiopia, unlike previous studies that usually focused on individual health facilities. Second, we had a large sample from which we could collect a range of sociodemographic and clinical data. In addition, we used the Online Open Data collection Kit (ODK) application for data collection. This tool facilitates the online monitoring of data collection activities and provides immediate feedback to the data collectors, improving the reliability of data entry.

Our study also has important limitations that should be considered when interpreting its findings. We used patient record data, and our analysis was constrained by the incompleteness or unavailability of important variables in these records, such as income and behavioural predictors, which might also influence mortality. We also did not assess health service quality, which affects HIV-related mortality. Finally, our study only collected data at comprehensive specialised hospitals, which, we can assume, offer a higher standard of care than smaller facilities. Therefore, the mortality rates reported in our study may represent a low, best-case scenario for HIV/AIDS treatment programs in Ethiopia.

Conclusion and recommendations

Our study found a lower mortality rate among ALHIV than previous studies of adolescents and adults in Ethiopia. Low levels of social support and a lack of education were associated with higher mortality, as were several indicators of advanced disease progression and poor health at baseline. The estimated impact of clinical predictors was relatively weak but nevelighted the

importance of treating HIV early for this population. Receiving CPT prophylaxis against OIs and maintaining good adherence was also associated with lower mortality, underscoring the importance of these preventative treatments and adherence counselling and support services. Our findings reveal a potential point for health service improvement in Ethiopia: incorporating the monitoring of haemoglobin levels into patient follow-up care. Furthermore, our findings support recommendations that clinicians emphasise managing OIs and provide counselling services to improve adherence. We recommend that future researchers consider conducting prospective follow-up studies to assess other potential predictors of survival.

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Contributors

CTL: conception of the project idea, design, analysis, interpretation, and manuscript drafting, and is responsible for the corresponding overall role during the publication process. DD, SB, and JF: rephrase the project idea, design, interpretation of results, reviewing and editing the manuscript. Finally, all authors have critically read and approved the manuscript.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethics approval

This study does not involve human participants.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Data availability statement

Data are available upon reasonable request. Data used for this study will be available upon request of the corresponding author.

Supplemental material

ORCI iD

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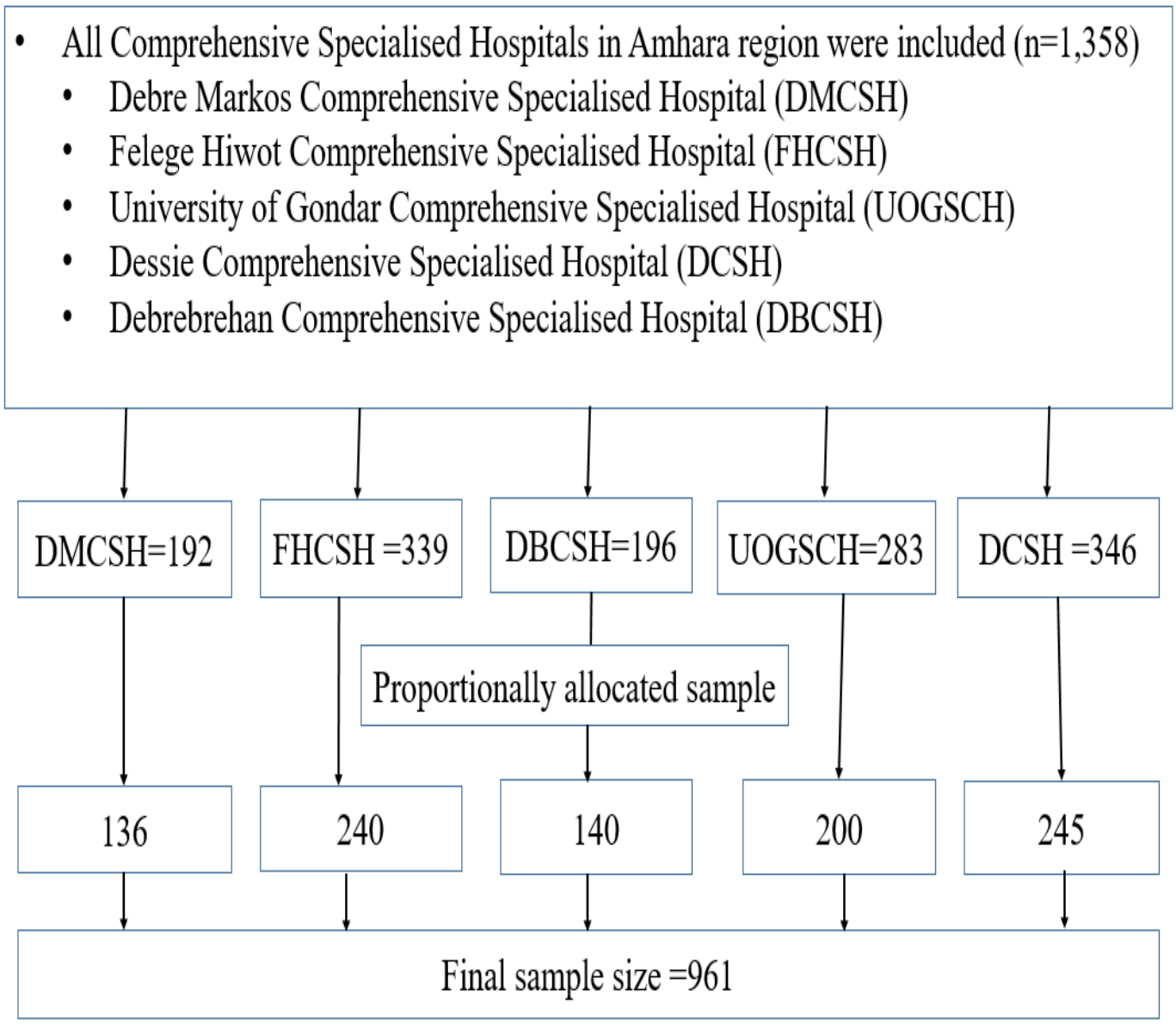
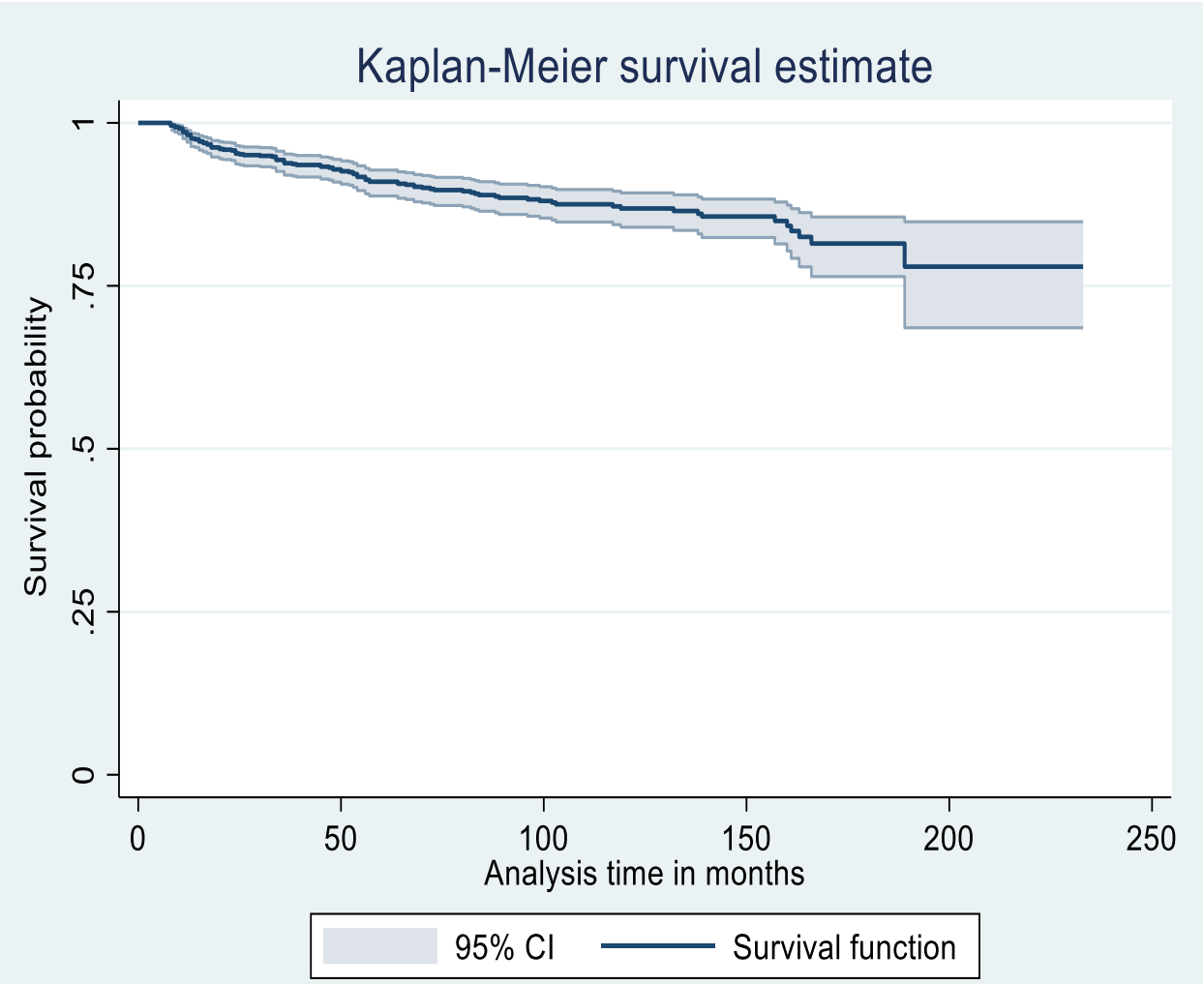
List of figures


All Comprehensive Specialised Hospitals in Amhara region were included (n=1,358)
Debre Markos Comprehensive Specialised Hospital (DMCSH)
Felege Hiwot Comprehensive Specialised Hospital (FHCSH)
University of Gondar Comprehensive Specialised Hospital (UOGSCH)
Dessie Comprehensive Specialised Hospital (DCSH)
Debrebrehan Comprehensive Specialised Hospital (DBCSH)
DMCSH=192
FHCSH =339
DBCSH=196
UOGSCH=283
DCSH =346
Proportionally allocated sample
136
240
140
200
245
Final sample size =961


Kaplan-Meier survival estimate
Survival probability
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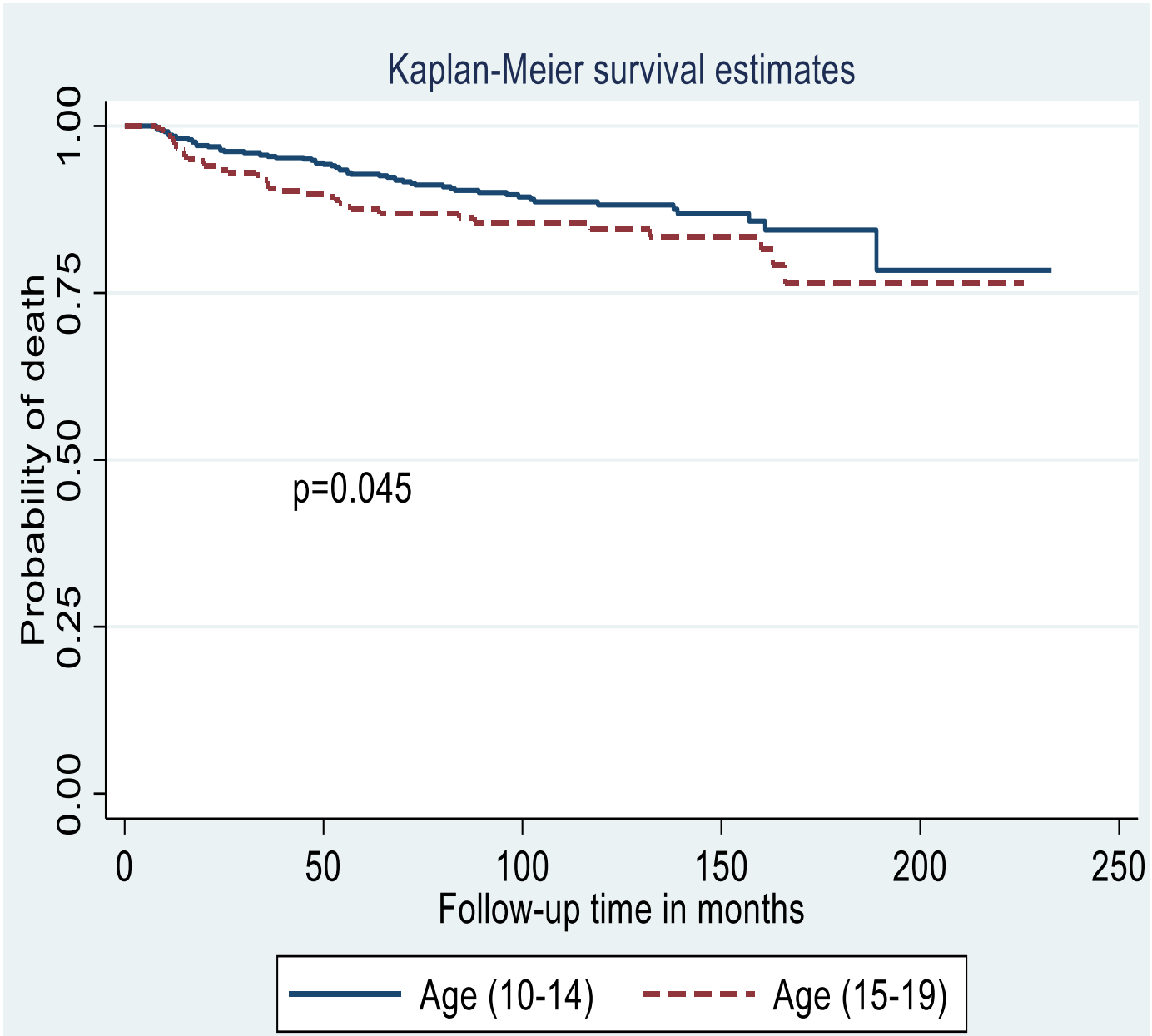
.25
.5
.75
1
0
50
100
150
200
250
Analysis time in months
95% CI
Survival function


Kaplan-Meier survival estimates
Probability of death
0.00
0.25
0.50
0.75
1.00
p=0.045
0
50
100
150
200
250
Follow-up time in months
Age (10-14)
Age (15-19)

Supplementary material: operational definitions

HIV/AIDS mortality: The total number of people who have died from AIDS-related causes per 100,000 population.

Good adherence is defined as if the percentage of the taken dose is between >95 % (< 2 doses of 30 doses or <3 dose of 60 doses) as documented by the ART physician.

Fair adherence is defined as the percentage of missed doses between 85-94 % (3-5 doses of 30 doses or 3-9 doses of 60 doses) as documented by an ART physician.

Poor adherence is defined as if the percentage of missed doses is between <85 % (> 6 doses of 30 doses or >9 doses of 60 doses) as documented by an ART physician.

Lost to follow-up is defined as if a patient discontinued ART for three months as recorded by the physician

Viral load suppression: HIV RNA in the blood equates to less than 200 copies per millilitre of blood sample because of antiretroviral therapy.

Clinical failure: New/recurrent/ clinical event showing severe immunodeficiency (WHO clinical stage 4 and particular WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure) after six months of effective treatment.

I**mmunologic failure:** CD4 count at or below 250 cells/mm3 following clinical failure or Persistent CD4 levels below 100 cells/mm^3.

Virological failure: Viral load above 1000 copies per mL based on two consecutive viral load tests or measurements in 3 months, with adherence support following the first viral load test

CD4 count was classified below the threshold, CD4 count < 200 cells/mm3, and above the threshold, CD4 count ≥ 200 cells/mm3 for severe immunodeficiency.

Social support is the perception and actuality that one is cared for, has assistance available from other people, and, most popularly, is part of a supportive social network: supportive resources can be emotional (e.g., nurturance), informational (e.g., advice), or companionship (e.g., sense of belonging); tangible (e.g., financial assistance) or intangible (e.g., personal recommendation).

STROBE 2007 (v4) Statement

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2 to 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 to 5
Objectives	3	State-specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6 to 8
Participants	6	(*a*) Give the eligibility criteria and the sources and methods of selecting participants. Describe methods of follow-up	6 to 7
		(*b*) For matched studies, give matching criteria and the number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6 and 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9 and 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider the use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10 to 17
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	17
Outcome data	15*	Report numbers of outcome events or summary measures over time	17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17 to 21
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions and sensitivity analyses	17 to 21
Discussion			
Key results	18	Summarise key results with reference to study objectives	21 to 26
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, the multiplicity of analyses, results from similar studies, and other relevant evidence	26
Generalisability	21	Discuss the generalisability (external validity) of the study results	26 to 27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Incidence and predictors of mortality among adolescents on antiretroviral therapy in Amhara Region, Ethiopia: A retrospective cohort analysis

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Incidence and predictors of mortality among adolescents on antiretroviral therapy in Amhara Region, Ethiopia: A retrospective cohort analysis

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Abstract

Objective: This study aimed to assess the incidence and predictors of mortality in adolescents receiving **antiretroviral therapy (**ART) in Ethiopia's Amhara Region.

Design: We conducted an institution-based retrospective follow-up study.

Settings: The study was conducted at Amhara Region's comprehensive specialised hospitals in Ethiopia.

Participants: We included 961 randomly selected medical records of adolescents receiving ART between January 2005 and June 2020.

Primary and secondary outcomes: The incidence of mortality since ART treatment initiation served as the primary outcome, and predictors of mortality served as secondary outcomes. We used Cox proportional hazard regression to examine the relationship between mortality and its predictors. Variables with p-values <0.05 in the multivariable analysis were considered statistically significant mortality predictors. Adjusted Hazard Ratio (AHR) with 95%CI was used to measure the strength of association.

Results: More than half (n=496, 53.5%) of the adolescents living with human immunodeficiency virus (ALHIV) were female. The adolescent mortality rate was 1.26 (95% CI: 1.04, 1.53) per 1000 person-years throughout the follow-up period of 81,583 adolescent months. Mortality was higher for ALHIV who had not received formal education (AHR: 3.27, 95% 1.36, 7.87), had widowed parents (AHR: 1.85, 95% 1.01, 3.56), or received no social support (AHR: 2.81, 95% CI: 1.69, 4.67). Adolescents who had opportunistic infections at ART initiation (AHR=1.94, 95% CI: 1.19, 3.14), low Hgb levels (AHR=2.17, 95% CI: 1.08, 4.18), a bedridden functional status (AHR=3.11, 95% CI: 1.64, 5.72), stage IV clinical staging (AHR=3.03, 95% CI: 1.46, 6.30), non-disclosing status (AHR=2.24, 95% CI:1.36, 3.69), and CD4 count 200-350 cells/mm^3 (AHR=2.17, 95% CI: 1.08, 4.18) also had a higher risk of death.

Not receiving Cotrimoxazole preventive therapy (AHR=1.85, 95% CI: 1.07, 3.22) and being fairly adherent to ART (AHR=2.16, 95% CI: 1.13, 4.10), compared with adherent, was associated with higher mortality risk. Changed treatment regimens were associated with lower mortality (AHR=0.59, 95% CI: 0.35, 0.98).

Conclusions: Our study found a lower mortality rate for adolescents with HIV than previous Ethiopian studies, but our significant mortality predictors were similar to those found in earlier studies of adults and adolescents. Our findings reveal a potential point for health service improvement in Ethiopia: incorporating monitoring of haemoglobin levels into patient follow-up care, supporting recommendations that clinicians emphasise managing opportunistic infections, and providing counselling services to improve adherence.

Study strengths and limitations

This study has several strengths and limitations

- Our analysis covers a wide geographic area of Ethiopia, unlike previous studies that usually focused on individual health facilities, reaching a large sample from which we could collect a range of sociodemographic and clinical data.
- We used the Online Open Data Collection Kit (ODK) application for data collection, which facilitates the online monitoring of data collection activities and provides immediate feedback to the data collectors, improving the reliability of data entry.

Our study also experienced the following limitations that the reader should consider when interpreting its findings.

- We used patient record data, and our analysis was constrained by the incompleteness or unavailability of important variables in these records, such as income and behavioural predictors, which might also influence mortality.

- We also did not assess health service quality, which affects HIV-related mortality.
- Our study only collected data at comprehensive specialised hospitals, which, we can assume, offer a higher standard of care than smaller facilities.

Background

Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) associated mortality is a significant contributor to global adolescent mortality [1] and the leading cause of death among adolescents aged 10 to 19 years in sub-Saharan Africa (SSA) [2]. The SSA region has the highest prevalence of HIV in the world [3, 4], with more than 39 million deaths resulting from HIV/AIDS and more than 36 million people currently living with HIV [3, 5]. Substantial progress has been made in responses to HIV/AIDS under the Millennium Development Goals framework [6]. However, adolescents and young people [7] are still heavily affected by the disease, accounting for 37% of all new global HIV infections in 2017 and 15% of all people living with HIV [1, 2]. Globally, in 2016 an estimated 2.1 million adolescents (age 10–19 years) were living with HIV [8]. In 2020, 150,000 adolescents were diagnosed as HIV-positive, and 3,200 died from AIDS-related causes [9].

Ethiopia's HIV prevalence has been falling steadily, from 2.4 percent in 2001 to 0.9 percent in 2020 among adults [10]. According to the 2018 Ethiopia HIV statistics, 690,000 people in Ethiopia live with HIV [11], and in 2016, nearly 20,000 HIV-related deaths occurred [12]. There are no recent data on the number of ALHIV in Ethiopia, but as of 2021, approximately 140,000 (88%) of the global ALHIV population were from SSA [13], growing in proportion to the global ALHIV population [14]. The United Nations Children's Fund suggests that turning the tide against AIDS requires a stronger focus on adolescents [15], and policymakers agree that a critical factor contributing to gaps in HIV/AIDS service uptake among adolescents is the limited provision of adolescent-friendly services [16].

HIV-related mortality places significant emotional and financial burdens on households. The death of young parents often requires orphaned children to take on the responsibility of heading the household [17, 18]. Young adults, who are the most heavily impacted by HIV/AIDS mortality, are also the most economically productive members of society, so their illness and death have far-reaching socio-economic implications. Therefore, while HIV/AIDS-related mortality remains a crucial health concern, it is also a social, demographic, and economic issue [17] with effects on security, governance, gender relations, economic growth, and the stability of the public sector, agricultural and private sectors [17, 19].

Ethiopia's HIV/AIDS policies currently do not provide sufficient consideration to the special requirements of adolescents, despite the country's expanding teenage population and the high rate of adolescent HIV infections. [20-23]. Current HIV care and treatment guidelines in Ethiopia focus only on adults and children, with ART guidance for treating ALHIV split between tools for paediatric patients (0-14 years old) and adult patients (age 15 and above). There is a lack of adolescent-specific treatment literacy and adherence counselling tools [24].

The lack of attention to ALHIV in Ethiopia is in keeping with findings from high-, middle- and low-income countries that show services for adolescents are often highly fragmented and poorly coordinated [16, 25]. Pockets of excellence in adolescent services exist, however, overall, studies suggest that services need significant improvement and should be brought into conformity with global best-practice guidelines [16, 25]. Failure to consider the unique needs of ALHIV may not only lead to inappropriate or unresponsive care, but it may also lead to a lack of essential services for adolescents. These might include screening for mental health disorders, substance use disorder counselling, reproductive health counselling, screening for potential interactions between specific antiretroviral medications and hormonal contraceptives,

and counselling on transitioning to adult care settings [26]. Failure to consider such services could result in poor treatment adherence, viral suppression, and increased mortality [26, 27].

The first step in designing such interventions is understanding the current experiences and health outcomes of ALHIV in countries like Ethiopia. Research on this topic is, however, relatively sparse. The current study focuses on assessing the mortality rates and identifying potential predictors of mortality among ALHIV in Ethiopia's Amhara Region who are receiving antiretroviral therapy (ART). Several studies have named predictors of global HIV-related death, including sociodemographic factors [28-35], facility-level characteristics [34], economic status [36], and clinical predictors [28, 37, 38]. Survival chances for ALHIV vary significantly across the world [16], and few rigorous studies of mortality among ALHIV have been conducted in Ethiopia. By providing baseline mortality estimates from one of Ethiopia's most populous regions, our project will assist policymakers, program implementers, and non-governmental organisations in Ethiopia and similar settings to plan, monitor, evaluate, and take evidence-based actions to improve ALHIV health outcomes.

Methods

Study setting and period

We conducted an institution-based retrospective cohort analysis among all adolescents living with HIV who initiated ART between January 2005 and June 2020 at comprehensive specialised hospitals in Ethiopia's Amhara Region. At the time of data collection, the Amhara Region had five comprehensive specialised hospitals: Felege Hiwot, Gondar, Dessie, Debre Berhan, and Debre Markos. Each hospital had a catchment area of more than five million people and provided various HIV/AIDS services, including ART in outpatient and inpatient care. All adolescents living with HIV who initiated ART between 2005 to 2020 were considered for inclusion. The year 2005 was selected as the starting point for this study because

it was the year the government of Ethiopia began providing free ART treatment to all people living with HIV.

Inclusion and exclusion criteria

The study population comprised all ALHIV aged 10-19 who initiated ART between January 2005 and June 2020. This included adolescents who transferred into study facilities from elsewhere. Adolescents with at least one viral load test record were included. Charts with incomplete medical records for essential variables such as treatment outcome, age, CD4, and viral load were excluded. In addition, patients who transferred out of care to a non-study facility during the study period were excluded. The outcome of this study was death due to HIV while taking ART.

Sample size determination

The minimum required sample size was determined using Stata statistical software Version 16 based on a survival analysis sample size determination formula. Sample size calculations were based on four predictors of mortality previously identified in the literature [37]: age (15-19 years old), residence (rural setting), CD4 count at ART initiation (<200cells/mm3), and Hgb at ART initiation (<10g/dl). Identical assumptions were used for all calculations: Power = 80%, CI= 95%, $\square_1=\square_2=$ ½, withdrawal 10%, N events = 92, and Pr (events) = 0.06. The sample size needed for achieving an 80% power (2 = 0.20) at the 5% (3 = 0.05) significance level after assuming that incompleteness was highest for the Hgb at ART initiation predictor with an estimate of 961 participants, sample size calculations detailed in supplementary material 1.

Note: Assumptions**;** power = 80%, CI= 95%, $\square_1=\square_2=$ ½, withdrawal 10%, N events =92, and Pr (events) =0.06. HRs described in the above table were obtained from one source [37].

Sampling procedures and source of data

This study included all five comprehensive specialised hospitals in the Amhara region, with proportional cases based on each hospital's patient load. The data source for all variables of interest was the ART registration database. Medical records of adolescents who received chronic HIV care from all Hospitals were retrieved. The complete sampling procedure is outlined in Figure 1.

Data collection tool and data collection procedures

The data extraction tool was adopted from a standard ART intake and treatment follow-up form currently used by Ethiopian health facilities, including hospitals. An online Open Data collection Kit (ODK) application tool that populated Microsoft Excel spreadsheets was used to facilitate the data collection [39]. Sociodemographic data were collected from patient charts and intake forms. The laboratory test results obtained within one month following ART initiation were used as baseline values. The mean value was computed when the two results were obtained within one month. Researchers with relevant qualifications and experience in health were employed for the data collection activities.

The Ethiopian HIV treatment guideline recommends

The Ethiopia HIV treatment guideline [40] recommends standardised clinical assessment of patients and, when available, baseline CD4 count to determine immunosuppression and initiate prophylactic therapies. Opportunistic infections, including TB, Cryptococci infection, and other comorbidities, always need to be looked for and managed in clinical assessment for IRIS, toxicity, etc. Clinical assessment: socio-economic status, any HIV-related illnesses in the past, symptom screen for TB, other OI, comorbidities, pregnancy, past, and current medication.

- WHO staging, clinical assessment for IRIS, toxicity, assess and support adherence, Hgb if the patient is on AZT, and at every visit, conduct screening for TB.

- Hemoglobin is more commonly monitored in patients with symptoms of anemia, and those on Cotrimoxazole therapy. In addition, the use of Zidovudine, which commonly caused anemia, has been discontinued and as a result, hemoglobin is not routinely monitored.
- Lab assessment: Baseline CD41, CBC, ALT, creatinine (if available), If presumptive TB diagnosis, does Gene Xpert, Pregnancy* and other tests as necessary, review clinical and lab data,
- D4 testing may be used to determine the need and discontinuation of OI prophylaxis.
- When a woman of reproductive age is taking DTG containing regimen, the occurrence of pregnancy shall be prevented and monitored. If pregnancy happens while on DTG containing regimen, DTG shall be replaced with EFV.

Study variables

The dependent variable of this study was the incidence of mortality (yes/no). Independent variables included sociodemographic and baseline clinical characteristics as well as comorbidities. All variables were extracted from patient medical records.

Sociodemographic characteristics included age at ART initiation (10-19), sex (male/female), residence (urban/rural), religion, being an orphan (yes/no), social support (yes/no), ethnicity, marital status of the caregiver, parental status (alive/dead), educational and occupational status of the caregiver, and family size.

Baseline clinical and laboratory variables included WHO clinical staging, functional status, haemoglobin (Hgb) at ART initiation, baseline CD4 count**,** regimen substitute, regimen changes, and baseline body mass index (BMI). Comorbidities included a history of opportunistic infection, tuberculosis, and malnutrition CD4 will not be used for monitoring purposes once viral load determination becomes routine. The operational definitions of HIV/AIDS mortality [41], good adherence [42], fair-adherence [42], poor adherence [42],

LTFU [43], viral load suppression [43], clinical failure, [44], immunologic failure [44], virological failure [44], CD4 count [45], and social support [46] are included as a supplementary material 2.

Patient and public involvement statement

Neither patients nor the public was involved in our research design, conduct, reporting, or dissemination plans.

Handling missing data

Missing data are unavoidable in epidemiological and clinical research, but their potential to undermine the validity of research results has often been overlooked in the medical literature [47]. Our data has incomplete records for Height (n=4, 0.4%), Weight (n=17, 1.8%), CD4 cell counts (n=42, 4.5%), Hgb (n=67, 7.1%), and viral suppression (n=87, 9.4%). After checking the pattern and mechanisms of missing values, we managed missing through multiple imputations (MI). We applied the little's test of missing completely at random test to check whether the values were missing at random or not [48]. The final imputation was performed using a multivariate normal imputation model. Variables included sex, age, place of residence, functional status, clinical staging, ART adherence, dietary status, opportunistic infections (OIs), Cotrimoxazole preventive therapy (CPT), tuberculosis, and Isoniazid preventive therapy (IPT).

Categorising continuous variables

We categorised continuous variables with referring standards and references. BMI was categorised as undernutrition (BMI<18.5), healthy weight range (18.5 to 24.9), overweight (25.0 to 29.9), and obese (BMI>29.9) [49]. Clinical conditions, such as CD4, and viral suppression, were categorised based on the ART treatment guideline used in Ethiopia [50].

Data processing and analysis

The collected data were cleaned, coded, and entered into EpiData™ software version 4.2, then exported into Stata version 16 statistical software for further analysis. Descriptive measures such as means, median, interquartile ranges (IQR), percentage, frequency, standard deviations (SD), and graphs were used for descriptive statistics. The time to death from HIV/AIDS during the ART follow-up period was estimated using the Kaplan-Meier survival curve method. A log-rank test was used to compare the estimated survival curve of patients based on categorical variables.

Assumptions for Cox-proportional analysis were checked using the Schoenfeld residual test with variables with a p-value of >0.1. We used stepwise Cox regression to build the multivariable Cox regression model. Variables with p-values less than 0.25 in the bi-variable analysis were considered for the multivariable model. Adjusted hazard ratios (aHR) with a 95% confidence interval and p-values less than 0.05 were used to measure the strength of the association and identify statistically significant predictors. The mean-variance inflation factors (VIF=1.16) indicated no meaningful multicollinearity between variables in the multivariable models.

Ethics consideration of the study

Ethical approval for this study was granted by the University of Technology Sydney Medical Research Ethics Committee (ETH20-5255) and the Amhara Region Public Health Institution (No H/R/T/T/D/3/887). Permission letters were received from all included comprehensive specialised hospitals to conduct the study. Participants' verbal or written consent was not feasible as the study utilised existing medical records of PLHIV. A waiver of consent was granted by the primary ethics committee. The data abstraction tool did not include individual identifiers such as unique medical record numbers and names; thus, we could not identify participants.

Results

Demographic characteristics

After reviewing 945 medical records, 17 were excluded due to incompleteness, and 928 were included in the final analysis. More than half (n=496, 53.0%) of the sample were female. The median age of ALHIV was 13 [IQR: 11.0, 16.0] years; more than half (n=590, 63.3%) of them were between 10 and 14 years old at the initiation of ART. The majority (n=692, 74.6%) lived in urban environments, and more than one-third (n=639, 68.8%) had a primary-school level of education. More than three-quarters (n=721, 77.7%) had both parents alive. Most adolescents (n=703, 75.9%) received social support while on ART. Most ALHIV (n=786, 84.7%) were aware of their HIV status (Table 1).

Table 1: Baseline sociodemographic characteristics of ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	Frequency (N)	Percentage (%)
Age classification [35]		
10-14 years old	590	63.6
15-19 years old	338	36.4
Sex		
Male	432	46.6
Female	496	53.4
Residence		
Urban	692	74.6
Rural	236	25.4
Education		

No formal education	14	1.5
Primary (grades 1-8)	639	68.9
Secondary (grades 9-12)	223	24.0
Higher (degree & above)	52	5.6
Ethnicity		
Amhara	886	95
Other*	42	5
Parental status		
Both alive	721	77.7
Father alive	74	8.0
Both died	133	14.3
Religion		
Orthodox Tewahido Christian	643	69.3
Muslim	224	24.1
Other	61	6.6
Caregiver marital status		
Single	114	12.3
Married	552	59.5
Divorced	80	8.6
Widowed	182	19.6
Family size		
Family size ≤4	683	73.6
Family size >4	245	26.4
Social support		
Yes	703	75.7

No	225	24.3
Disclosure status (knowledge of their own HIV status)		
Yes	786	84.7
No	142	15.3
History of PMTCT		
Yes	169	18.2
No	523	56.4
Unknown	236	25.4
Relation to caregiver		
Parent	611	65.9
Sister/Brother	159	17.1
Grandparents	65	7.0
Aunt/Uncle	76	8.1
Other*	17	1.9

Other *: other relatives (11) and guardian (8)

Baseline clinical, laboratory, and ART information

At the initiation of ART, 237 (25.5%) of the 928 ALHIV had opportunistic infections (OIs). We found that 579 (62.4 %) were asymptomatic or at early stages of infection (WHO stages I and II) at baseline, and about one-third (30%) had CD4 counts < 200 cells/mm^3. Nearly half (n=440, 47.4%) were categorised as having working functional status. Body mass index (BMI) was used to assess the nutritional status of ALHIV. At the time when ART was initiated, 81.9% of the sample was underweight (BMI 18.5), 16.4% were normal weight (BMI 18.5 to 24.9), and 1.7% were overweight (BMI 25) (Table 2).

Table 2: Clinical, laboratory, and treatment characteristics of ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	Frequency (N)	Percentage (%)
CD4 count		
Less than 200 cells/mm3	278	30.0
200 to 350 cells/mm3	249	26.8
More than 350 cells/mm3	401	43.2
WHO clinical staging		
Stage I and II	579	62.4
Stage II and IV	349	37.6
Functional status		
Working	440	47.4
Ambulatory	420	45.3
Bedridden	68	7.3
Haemoglobin level		
< 10 g/dl	56	6.0
≥10 g/dl)	872	94.0
Cotrimoxazole preventive therapy (CPT)		
Yes	820	88.4
No	108	11.6
Isoniazid preventive therapy		
Yes	682	73.5
No	246	26.5

ART adherence		
Good	827	89.1
Fair	47	5.1
Poor	54	5.8
Opportunistic infections at baseline (OPs)		
Yes	237	25.5
No	691	74.5
ART eligibility criteria		
Immunologic/CD4	110	11.9
WHO clinical stage	93	10.0
Both clinical and immunologic	642	69.2
Test and treat approach	83	8.9
ART drug side effects		
Yes	66	7.1
No	862	92.9
Baseline viral load		
Below 1000	768	82.8
1000 and above	160	17.2
Tuberculosis		
After ART initiation	76	78.4
Pre-ART	21	21.6
History of treatment failure		
Yes	113	12.2
No	815	87.8
Regimen change		

Yes	433	46.7
No	495	53.3
Body Mass Index (BMI)		
Underweight	760	81.9%
Normal	152	16.4%
Overweight	16	1.7%

Baseline opportunistic infections

The top three OIs at ART initiation were diarrheal disease (n=127, 20.7%), pneumonia (n=122, 19.9%), and tuberculosis (n=90, 14.7%) (Supplementary material 3).

Adolescents' follow-up characteristics

One quarter (n=238, 25.6%) of adolescents developed OIs during follow-up, and nearly one-third (n=76, 31.9%) developed pneumonia. During the follow-up time, 113 (12.3%) adolescents experienced treatment failure. Nearly half, 434 (46.8%), of the included adolescents had a history of ART regimen change during follow-up. Of these, 76 (17.6%) changed their regimen due to treatment failure, 56 (12.9%) due to side effects, and 5.5% developed OIs. The majority of treatment failures were virologic failures (n=70, 61.4%), followed by immunologic failures (n=22, 20.2%) and clinical failures (n=21, 18.4%). Nearly half of all included ALHIV (n=433, 46.7%) changed their regimens during ART follow-up (Supplementary material 4). Few (n=66, 6.8%) adolescents experienced ART side effects, with more than one-third (n=27, 37.9%) of side effects reported as drug toxicity (Supplementary material 5).

Death rate during follow-up

With a median follow-up period of 82 (IQR: 44 -130) months, a total of 928 adolescents on ART were observed for varying lengths of time, ranging from 7 to 233 months. This retrospective cohort contributed a total follow-up time of 81,583 person-month observations. At the end of the project/follow-up period, 103 (11.1%) died, while 772 (83.2%) were still on follow-up, and 53 (5.7%) were transferred to other health institutions. The cumulative probability of surviving or being free from the event of interest at the end of 6, 12, 18, and 24 months was 98.6, 96.7, 95.8, and 95.0%, respectively (Fig. 2).

The cohort's overall mortality rate was 1.26 (95% CI: 1.04, 1.53) per 1000 person-months. The overall estimated median mortality time was 4.76 months (95% CI: 4.17, 5.02 months; Fig. 3).

Predictors of mortality incidence

In the final multivariable Cox regression model, several factors associated with higher mortality were identified (See table 3). The mortality risk was 3.27 times greater (AHR: 3.27, 95% 1.36, 7.87) for those without formal education than those who had completed primary school. ALHIV who changed their previous regimen had a 40% decreased risk of death than participants who did not (AHR: 0.60, 95% CI: 0.36, 0.99). We saw a higher hazard of death in adolescents with widowed parents (AHR: 1.85, 95% 1.01, 3.56), those without social support (AHR: 2.81, 95% CI: 1.69, 4.67), and those whose parents had not told them that they are HIV positive (AHR: 2.08, 95% CI: 1.07, 2.81).

Adolescents with lower Hgb levels at ART initiation had more than double the hazard of death (AHR: 2.04, 95% CI: 1.02, 4.08) compared with those with normal Hgb levels. Adolescents with bedridden functional status at ART initiation had three times the higher hazard of death than those with working status (AHR: 3.11, 95% CI: 1.64, 5.72). The hazard of death among adolescents who started treatment at WHO clinical stage IV was 3.03 times higher than those in stage I (AHR: 3.03, 95% CI: 1.46, 6.30). The hazard of death among adolescents with a CD4

count between 200 to 350 cells/mm^3 was 2.17-fold higher than adolescents with a CD4 count higher than 350 cells/mm^3 (AHR: 2.17, 95% CI: 1.08, 4.18). The mortality hazard among adolescents who did not receive CPT was nearly two times higher than their counterparts (AHR: 1.85, 95% CI: 1.07, 3.22). The hazard of death among poor adherent adolescents was two times higher than those with good and fair adherence (AHR: 2.24, 95% CI: 1.27, 3.95). Furthermore, the risk of death were twice higher among ALHIV who did not know their HIV status (AHR: 2.08, 95% CI: 1.07, 2.81).

Table 3: Bivariable and multivariable Cox regression analysis of mortality predictors among ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	CHR [95% CI]	AHR [95% CI]
Sex		
Female	1	1
Male	1.10 (0.75, 1.62)	1.05 (0.68, 1.61)
Age		
10-14 years old	1	1
15-19 years old	1.49 (1.00, 2.19)	1.07 (0.60, 1.90)
Education		
No formal education	5.70 (2.61, 12.48)	3.27 (1.36, 7.87)*
Primary education	1	1
Secondary education	1.35 (0.86, 2.15)	0.99 (0.54, 1.82)
Higher education	1.44 (0.66, 3.17)	0.67 (0.27, 1.64)
Caregiver marital status		
Single	1.98 (1.12, 3.50)	1.50 (0.78, 2.84)
Married	1	1
Divorced	3.28 (1.90, 5.68)	1.89 (1.01, 3.56)*
Widowed	1.65 (1.01, 2.71)	1.85 (1.08, 3.19)*
Hospitals (study setting)		
Dessie CSH	1	**1**

Debre Birehan CSH	6.09 (3.24, 11.44)	6.54 (2.83, 15.12)**
Debre Markos CSH	1.93 (0.83, 4.46)	1.12 (0.40, 3.09)
Felege Hiwot CSH	6.95 (3.80, 12.70)	6.31 (2.79, 14.27)**
UOGCSH	0.62 (0.25, 1.53)	0.70 (0.40, 2.83)
Social support		
Yes	1	1
No	5.30 (3.58, 7.84)	2.81 (1.69, 4.67)**
Disclosure status		
Yes	1	1
No	4.55 (3.04, 6.82)	2.08 (1.07, 2.81)*
Regimen change		
No	1	1
Yes	0.28 (0.18, 0.44)	0.60 (0.36, 0.99)*
Baseline haemoglobin level		
≥10 g/dl)	1	1
< 10 g/dl	2.67 (1.42, 5.02)	2.04 (1.02, 4.08)*
Baseline functional status		
Working	1	1
Ambulatory	0.89 (0.57, 1.39)	0.64 (0.38, 1.08)
Bedridden	5.70 (3.47, 9.38)	3.11 (1.64, 5.72)**
Baseline WHO clinical staging		
Stage I	1	1
Stage II	1.24 (0.71, 2.15)	1.57 (0.88, 2.83)
Stage III	1.02 (0.57, 1.81)	1.23 (0.65, 2.33)
Stage IV	4.79 (2.75, 8.34)	3.03 (1.46, 6.30)*
Baseline CD4 count		
> 350 cells/mm3	1	1
200 to 350 cells/mm3	0.55 (0.32, 0.95)	2.17 (1.08, 4.18)*
≤ 200 cells/mm3	0.95 (0.61, 1.46)	1.49 (0.91, 2.46)
Cotrimoxazole preventive therapy		
Yes	1	1
No	4.72 (3.01, 7.41)	1.85 (1.07, 3.22)*

Ionised preventive therapy		
Yes	1	1
No	2.69 (1.82, 3 .97)	0.90 (0.55, 1.46)
ART adherence		
Good/ Fair	1	1
Poor	4.60 (2.72, 7.80)	2.24 (1.27, 3.95)**
Opportunistic infection at baseline		
No	1	1
Yes	2.77 (1.84, 4.16)	1.94 (1.19, 3.14)**
Baseline BMI		
Underweight	1	1
Normal	1.40 (0.87, 2.27)	1.17 (0.74, 1.96)
Overweight	1.45 (0.46, 4.61)	1.88 (0.57, 5.63)

*Significant at P< 0.05, *Significant at P< 0.01 and **Significant < 0.001*

Discussion

This study aimed to assess the incidence and predictors of mortality among ALHIV receiving ART across the Amhara region of Ethiopia using a multi-facility retrospective follow-up approach. With a total follow-up time of 81,583 adolescent months, the overall incidence of mortality among ALHIV receiving ART was 1.52 per 100 person-years.

The mortality rate for ALHIV in our study is lower than the rate found in other single-country African studies, for example, in Ethiopia (2.29 deaths per 100 person-years) [35] and Zimbabwe, 5.46 deaths per 100 person-years [51]. However, our study's overall mortality rate is higher than the rate reported by a global cohort collaboration across seven regions (0.97 deaths per 100 person-years) [34], an African cross-national study (0.8 deaths per 100 person-years) [20], and a recent South African community-based ART study (1.2 deaths per 100 person-years) [52]. Our estimated mortality incidence is also lower than those found in previous

studies of adult PLHIV in Ethiopia, for example, in Gondar (5.3 deaths per 100 person-years) [53], Harar (4.8 deaths per 100 person-years) [54], Debre Berhan (4.8 deaths per 100 person-years) [55], Debre Markos (13.6 deaths per 100 person-years) [56], and in Metema (6.7 deaths per 100 person-years) [57].

The difference between our mortality rate and those reported in previous studies, as well as the variation in mortality rates between these studies themselves, may be due to differences in the clinical characteristics of study participants and differences in study periods, sample sizes, and study settings, as our study included only comprehensive specialised hospitals. The adolescents' ages may have also differed between studies; for example, several studies included children under the age of nine in their samples [35].

Most prior studies on adolescent mortality do not report detailed sociodemographic information, so comparing our sample's characteristics to those of previous mortality studies is difficult. However, when we compare outcomes for ALHIV in our sample with other studies, we found that our cohort has a lower proportion of male adolescents (46.6%) compared to other cohorts (50.9%) of samples). The high proportion of males in our sample may have shifted our mortality estimates upward as it is well established that male adolescents have a higher mortality rate than female adolescents [58-60]. Although it is difficult to make direct comparisons, our sample may not be similar to adolescent populations studied in other sub-Saharan African settings, particularly as our cohort was disproportionately urban and relatively well-educated compared to a study in Ethiopian adolescents [35]. Our study's relatively low mortality rate might also be attributed to the clinical characteristics of the included study participants; for example, 82.8% of our study participants had baseline viral suppression. It is well-established that a higher baseline viral load is associated with increased mortality risk [61], so our study participants' relatively good health may contribute to a lower mortality rate.

In addition, a high proportion of adolescents in our study received critical preventative interventions, such as IPT (73.5%) and CPT (88.4%), which may have also contributed to lower mortality.

Sociodemographic predictors of mortality

We identified several demographic predictors associated with mortality in adolescents receiving ART. Adolescents with no formal schooling had higher mortality rates than those with at least primary schooling. However, having schooling beyond primary school did not lower mortality risks. As previously noted, most ALHIV mortality studies in sub-Saharan Africa do not report sociodemographic data, but our findings are consistent with a European cohort collaboration study and a study from Denmark, which found that lower levels of education were associated with increased mortality among PLHIV [62, 63]. The lack of a protective effect for secondary and post-secondary levels of education contrasts with findings from the United States (US) that HIV/AIDS-related mortality rates decreased with increasing educational levels [64]; however, the US study was not adolescent-specific, and the education effect may not be applicable to younger populations.

Our study found that the age and sex of adolescents were not associated with mortality. An analysis of adolescents in India had similar findings [65]. However, the lack of significance of age and sex is in contrast to previous research in SSA, which has found that age (older adolescents) and sex (being female) increased the risk of mortality among ALHIV [66]. Being male was also reported as a risk for HIV-associated death among ALHIV in a large global study of perinatal infection. However, the sex-related risk of death varied depending on whether the patients were perinatally infected and their region [67]. It could be that a generally high standard of care at the comprehensive hospitals that we studied reduced sex and age disparities. However, further research may be needed to determine the importance of age and

sex as factors driving mortality among ALHIV, and this research should consider perinatal infection.

Urban or rural residence was not a significant predictor for mortality in this study, in contrast to other studies that found higher mortality among ALHIV living in rural areas [68]. This might be because our study had a relatively small proportion of ALHIV from rural settings (25.4%). Therefore our study may have been underpowered to find urban-rural differences in mortality.

We found that the risk of death was nearly twice as high among ALHIV from widowed parents, which is consistent with a study in the US reporting that mortality is higher in ALHIV from divorced and separated families [69]. Having married parents may allow greater economic support and social approval than single, divorced, and widowed parents. Studies from Uganda and South Africa indicate that adolescents who live with single parents receiving ART treatment experience economic insecurity, psychological challenges, and weakened social protections [70, 71]. Besides, ALHIV living with widowed fathers and those living on their own were significantly more likely to show signs and symptoms of depression than their peers [72].

The risk of death was higher among ALHIV with no social support compared to their counterparts. This finding is supported by studies from a range of low-and middle-income countries, including the United States and Uganda [23, 73, 74], as well as studies from Ethiopia, the SSA region, and China that highlight the vital role of social support in coping with and recovering from illness in general [74-76]. Social support networks are essential in helping PLHIV/AIDS to maintain good physical and mental health, including adhering to their treatment. Social support could moderate the adverse effects of stressful events [77], which is one of the most effective ways to cope with stress.

Clinical predictors of mortality

We found that poor health or advanced HIV disease at baseline was associated with a higher risk of death. We identified multiple baselines and follow-up, clinical predictors of mortality, specifically low Hgb levels, bedridden status, WHO stage IV clinical staging, CD4 counts < 350, the presence of OIs, ARV regimen change, and poor treatment adherence, all of which were associated with increased mortality risk among ALHIV.

Several studies from low- and middle-income countries indicated that ALHIV and PLHIV with low Hgb risk of increased mortality [29, 65, 68, 78]. Additionally, studies have found an association between CD4 cell count, viral load, and haemoglobin level [79]. The problem of food insecurity worth in low-income countries than in high-income countries. A study also showed that food insecurity increases poor treatment outcomes [80]. This suggests that strengthening the routine monitoring of Hgb levels (e.g., concurrently with each CD4 cell count determination) and improving food access may be a helpful addition to clinical guidelines.

We found a higher mortality risk among ALHIV who was bedridden at baseline, consistent with previous Ethiopian studies [81] and assuming that functional status correlates with patients' clinical and immunological status. Similarly, we found higher mortality among ALHIV who were categorised as WHO stage IV at baseline, consistent with study findings from Ethiopia [68, 81], India [65], and South Africa [29], as well as international guidelines [82]. The negative association between CD4 counts and mortality that was identified has been well-established in previous studies conducted globally [34], in Europe [64], and in Ethiopia [68]. However, the association we found was relatively weak: 95% confidence interval approached 1.00, and there was no significant association between being in the lowest CD4 category and mortality. The weakness of this may be due to the large number of variables in our model that also measured baseline HIV disease progression. Our final indicator of disease progression was the presence of OIs at baseline. ALHIV, who presented with OIs at baseline,

had a higher mortality rate, consistent with other Ethiopian studies [57, 83]. The presence of OIs may indicate low CD4 cell counts, decreased humoral and cellular immunity and possibly AIDS [84, 85]. Overall, these findings highlight the importance of starting ART as early as possible after an HIV diagnosis to suppress the virus and stabilise CD4 counts.

Good preventative treatment and ART adherence indicators were also associated with lower mortality risk. These findings support arguments that state the timely and consistent administration of CPT prevents OIs among PLHIV, improves the quality of life, and reduces associated mortality [86]. The WHO recommends the prescription of CPT for all ALHIV with CD4 cell counts below 350 regardless of their symptoms [87] to improve CD4 counts, quality of life, and patient outcomes.

The risk of death in ALHIV with poor ART adherence was higher than in those with good/fair adherence. The importance of ART adherence in reducing death and illness in ALHIV is a consistent finding [88], as adherence is critical to controlling viral replication. Helping adolescents maintain good adherence is challenging because of the specific challenges they face around disclosure, risk-taking, and transitioning to adult services [89]. Medication-related barriers such as the complexity of regimens and treatment side effects can also impact adherence and may be particularly acute for perinatally-infected ALHIV who have been receiving ART for long periods [90]. The significance of adherence in our findings underscores the need to develop and test targeted interventions to improve adherence in this population. This may be related to ART adherence, lower comorbidities, OIs, improved viral suppression, higher CD4 count, and higher Hgb. Such conditions improve patient treatment outcomes and a lower mortality rate.

Unusually, this study found that CD4 counts of less than 200 cells/mm3 are not associated with HIV-related mortality, while CD4 counts between 200 and 350 cells/mm3 increased mortality

among adolescents receiving ART. This may be the result of an inadequate sample size. Small sample size affects the reliability of a survey's results because it leads to a higher variability, which may cause bias [91].

The current study found a lower mortality rate among ALHIV who underwent an ART regimen change compared to their counterparts. Conversely, a prior Ethiopian study found that ALHIV who underwent an ART regimen change had a higher death rate [92]. The contradictory findings may be due to different populations, reasons for regimen change, and stage of disease, for example, medication shortages and stockouts (35%), OIs (25%), side effects (20%), and treatment failure (19%) were the main reasons for regimen changes in the earlier study. In contrast, in previous Ethiopian studies, the most common reason for medication changes or switches were toxicity, comorbidity, patient compliance, and treatment failure, which are similar to our findings [93, 94].

Furthermore, in the current study, 84.7% of the adolescents living with HIV had been told they were infected with HIV. The study also found that the risk of death was twice higher among ALHIV who did not know their HIV status, which is consistent with a study finding in Kenya [95]. Besides, adolescents who are aware of their HIV infection status have better HIV treatment outcomes [96, 97]. WHO promotes disclosing HIV infection status to adolescents and suggests informing younger children sequentially to accommodate cognitive and emotional development [98]. This may be explained by patients who are aware they infected with HIV have better treatment adherence. Adherence improve treatment outcome, which is consistent with a study conducted elsewhere [99].

Study strengths and limitations

This study has several strengths. First, in contrast to earlier research that concentrated on specific healthcare facilities, our analysis covers a large geographic area of Ethiopia. Second,

we had a large sample that allowed us to gather various sociodemographic and clinical data. Additionally, we utilised the Online Open Data collection Kit (ODK) programme to collect the necessary data. This tool facilitates the online monitoring of data collection activities and provides immediate feedback to the data collectors, improving the reliability and accuracy of data entry.

Our study also has important limitations that should be considered when interpreting its findings. We used patient record data, and our analysis was constrained by the incompleteness or unavailability of important variables in these records, such as income and behavioural predictors, which might also influence mortality. We also did not assess health service quality, which affects HIV-related mortality. Finally, our study only collected data at comprehensive specialised hospitals, which, we can assume, offer a higher standard of care than smaller facilities. Therefore, the mortality rates reported in our study may represent a low, best-case scenario for HIV/AIDS treatment programs in Ethiopia.

Policy and clinical implications

There is a strong need to strengthen monitoring activities to improve clinical management and OIs to improve treatment outcomes for ALHIV. Our findings support recommendations that clinicians monitor haemoglobin levels during patient follow-up care; prioritise the management of OIs; and provide counselling services to improve adherence. We recommend that future researchers consider conducting prospective follow-up studies to assess other potential predictors of survival. These studies should include sociodemographic factors in addition to clinical factors.

Implications for modifiable factors include

- Increasing educational support and social support,
- Intensifying peer support for adherence and disclosure,

- Improved outreach and routine testing to ensure early treatment,
- Continued support for prophylaxis treatment and monitoring of Hgb & OIs.

Significant differences in treatment outcomes (mortality rates) between the studied health institutions would suggest that policymakers should strengthen the health system across facilities to bring them up all to the same level seems important.

Conclusion and recommendations

Our study found a lower mortality rate among ALHIV than in previous studies of adolescents in Ethiopia. Low levels of social support and a lack of education were associated with higher mortality, as were several indicators of advanced disease progression and poor health at baseline. The estimated impact of clinical predictors was relatively weak but highlighted the importance of treating HIV early in this population. Receiving CPT prophylaxis against OIs and maintaining good adherence was also associated with lower mortality, underscoring the importance of these preventative treatments and adherence counselling and support services.

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Contributors

CTL: conception of the project idea, design, analysis, interpretation, and manuscript drafting, and is responsible for the corresponding overall role during the publication process. DD, SB, and JF: rephrase the project idea, design, interpretation of results, reviewing and editing the manuscript. Finally, all authors have critically read and approved the manuscript.

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Data availability statement

Data are available upon reasonable request. Data used for this study will be available upon request of the corresponding Author.

Supplemental material

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Supplementary files

Supplementary material 1: Sample size calculation

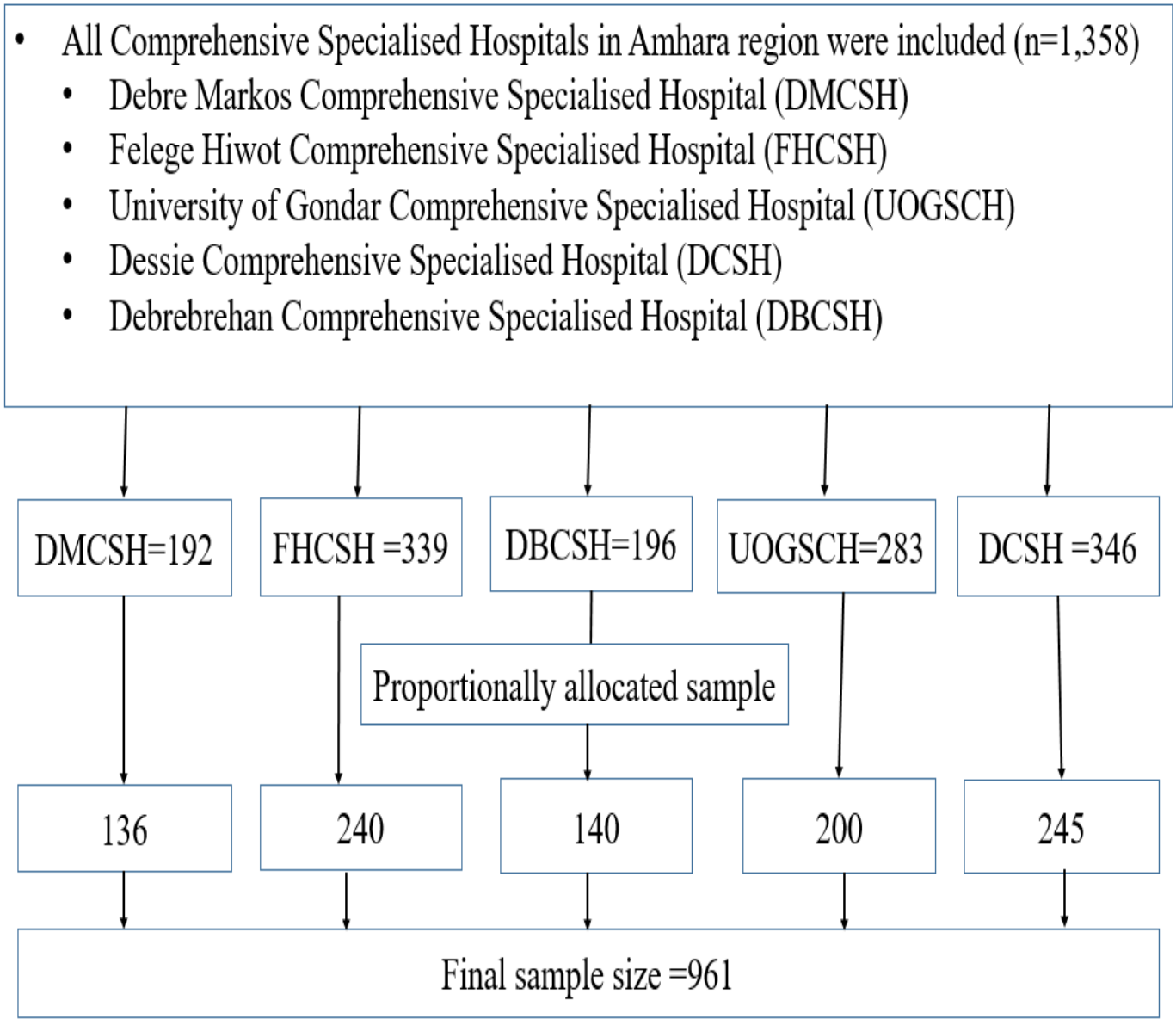
Supplementary material 2: operational definitions

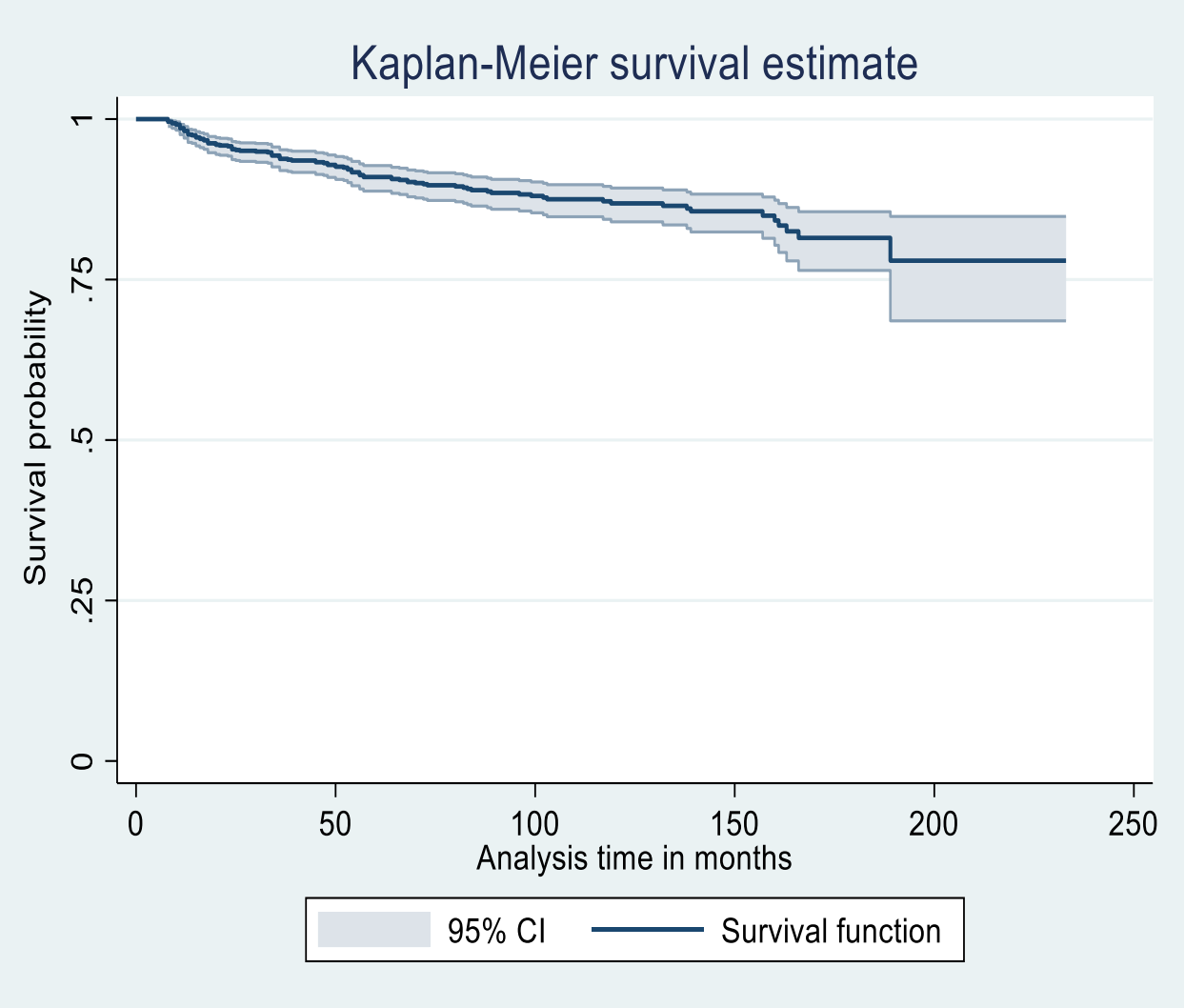
Supplementary material 3: Baseline opportunistic infections

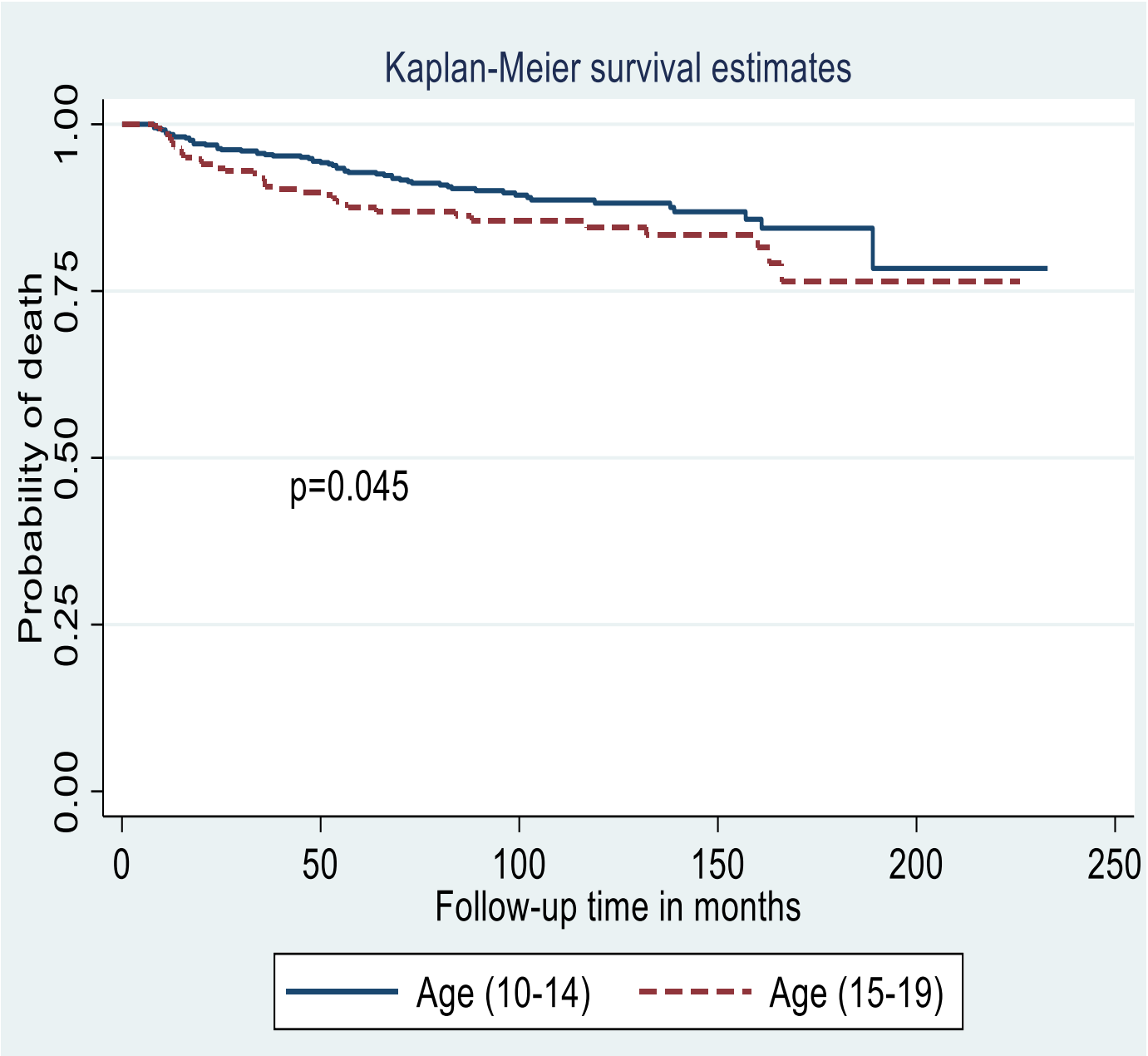
Supplementary material 4: Most common opportunistic infections developed during follow-up

Supplementary material 5: Drug side effects among ALHIV receiving ART

List of Figures


All Comprehensive Specialised Hospitals in Amhara region were included (n=1,358)
Debre Markos Comprehensive Specialised Hospital (DMCSH)
Felege Hiwot Comprehensive Specialised Hospital (FHCSH)
University of Gondar Comprehensive Specialised Hospital (UOGSCH)
Dessie Comprehensive Specialised Hospital (DCSH)
Debrebrehan Comprehensive Specialised Hospital (DBCSH)
DMCSH=192
FHCSH =339
DBCSH=196
UOGSCH=283
DCSH =346
Proportionally allocated sample
136
240
140
200
245
Final sample size =961


Kaplan-Meier survival estimate
Survival probability
0
.25
.5
.75
1
0
50
100
150
200
250
Analysis time in months
95% CI
Survival function


Kaplan-Meier survival estimates
Probability of death
0.00
0.25
0.50
0.75
1.00
p=0.045
0
50
100
150
200
250
Follow-up time in months
Age (10-14)
Age (15-19)

Supplementary material 1: Sample size determination for assessing treatment outcomes among ALHIV on ART in Amhara Regional State, Ethiopia, 2020

Variables	Hazard ratio	Calculated sample size	10% incompleteness	Total sample
Age group of the respondents	aHR = 2.3	755	8	765
Residence of the respondents	aHR = 2.8	494	5	499
CD4 count at ART initiation	aHR = 2.8	494	5	499
Hgb at ART initiation	aHR = 2.1	951	10	961

Supplementary material: operational definitions

HIV/AIDS mortality: The total number of people who have died from AIDS-related causes per 100,000 population.

Good adherence is defined as if the percentage of the taken dose is between >95 % (< 2 doses of 30 doses or <3 dose of 60 doses) as documented by the ART physician.

Fair adherence is defined as the percentage of missed doses between 85-94 % (3-5 doses of 30 doses or 3-9 doses of 60 doses) as documented by an ART physician.

Poor adherence is defined as if the percentage of missed doses is between <85 % (> 6 doses of 30 doses or >9 doses of 60 doses) as documented by an ART physician.

Lost to follow-up is defined as if a patient discontinued ART for three months as recorded by the physician

Viral load suppression: HIV RNA in the blood equates to less than 200 copies per millilitre of blood sample because of antiretroviral therapy.

Virological failure: Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test.

Clinical failure: New/recurrent/ clinical event showing severe immunodeficiency (WHO clinical stage 4 and particular WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure) after six months of effective treatment.

I**mmunologic failure:** CD4 count at or below 250 cells/mm3 following clinical failure or Persistent CD4 levels below 100 cells/mm^3.

Virological failure: Viral load above 1000 copies per mL based on two consecutive viral load tests or measurements in 3 months, with adherence support following the first viral load test

CD4 count was classified below the threshold, CD4 count < 200 cells/mm3, and above the threshold, CD4 count ≥ 200 cells/mm3 for severe immunodeficiency.

Social support is the perception and actuality that one is cared for, has assistance available from other people, and, most popularly, is part of a supportive social network: supportive resources can be emotional (e.g., nurturance), informational (e.g., advice), or companionship (e.g., sense of belonging); tangible (e.g., financial assistance) or intangible (e.g., personal recommendation). It is supported (psychological, economic, and physical support) given to an incredible person. n addition, the social support for HIV patients form includes.

Supplementary material 3: Baseline opportunistic infections of ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	Frequency (n)	Percentage (%)
Diarrheal disease		
Yes	127	20.7
Pneumonia		
Yes	122	19.9
Tuberculosis		
Yes	90	14.7
Herpes Zoster		
Yes	89	14.5
Skin infection/rash		
Yes	77	12.5
Candidiasis		
Yes	71	11.6
CNS toxoplasmosis		
Yes	18	2.9

Supplementary material 4: Most common opportunistic infections developed during follow-up among ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020

Opportunistic Infections	Frequency	Percentage
Bacterial pneumonia	76	24%
Tuberculosis	67	21%
Diarrhea	55	17%
Candidiasis	27	9%
Skin rash	27	9%
Herpes zoster	23	7%
Central nurves system (CNS) toxoplasmosis	17	5%
Others	24	8%

Others: Malnutrition (n=9, 3.8%), Pneumocystis pneumonia (PCP) (n=9, 3.8%) and Cryptococcus meningitis (n=6, 2.5%).

Supplementary material 5: Drug side effects among ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020.

Drug side effects	Frequency (n)	Percentage (%)
Toxicity	27	35.1%
Diarrhea	16	20.8%
Anemia	10	13.0%
Nausea	5	6.5%
Fatigue	4	5.2%
Skin rash	4	5.2%

Others: Facial dystrophy (n=3, 3.9%), vomiting (n=3, 3.9%), Lipodystrophy (n=3, 3.9%), and Headache (n=2, 2.6%),

STROBE 2007 (v4) Statement

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2 to 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 to 6
Objectives	3	State-specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6 to 11
Participants	6	(*a*) Give the eligibility criteria and the sources and methods of selecting participants. Describe methods of follow-up	6 to 7
		(*b*) For matched studies, give matching criteria and the number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6 and 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9 and 12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider the use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12 to 20
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	18
Outcome data	15*	Report numbers of outcome events or summary measures over time	18
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17 to 21
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions and sensitivity analyses	17 to 21
Discussion			
Key results	18	Summarise key results with reference to study objectives	21 to 27
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, the multiplicity of analyses, results from similar studies, and other relevant evidence	27-28
Generalisability	21	Discuss the generalisability (external validity) of the study results	29
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	30

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in the cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Incidence and predictors of mortality among adolescents on antiretroviral therapy in Amhara Region, Ethiopia: A retrospective cohort analysis

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Abstract

Objective: This study aimed to assess the incidence and predictors of mortality in adolescents receiving **antiretroviral therapy (**ART) in Ethiopia's Amhara Region.

Design: We conducted an institution-based retrospective follow-up study.

Settings: The study was conducted at Amhara Region's comprehensive specialised hospitals in Ethiopia.

Participants: We included 961 randomly selected medical records of adolescents receiving ART between January 2005 and June 2020.

Primary and secondary outcomes: The incidence of mortality since ART treatment initiation served as the primary outcome, and predictors of mortality served as secondary outcomes. We used Cox proportional hazard regression to examine the relationship between mortality and its predictors. Variables with p-values <0.05 in the multivariable analysis were considered statistically significant mortality predictors. Adjusted Hazard Ratio (AHR) with 95%CI was used to measure the strength of association.

Results: More than half (n=496, 53.5%) of the adolescents living with human immunodeficiency virus (ALHIV) were female. The adolescent mortality rate was 1.26 (95% CI: 1.04, 1.53) per 1000 person-years throughout the follow-up period of 81,583 adolescent months. Mortality was higher for ALHIV who had not received formal education (AHR: 3.27, 95% 1.36, 7.87), had widowed parents (AHR: 1.85, 95% 1.01, 3.56), or received no social support (AHR: 2.81, 95% CI: 1.69, 4.67). Adolescents who had opportunistic infections at ART initiation (AHR=1.94, 95% CI: 1.19, 3.14), low Hgb levels (AHR=2.17, 95% CI: 1.08, 4.18), a bedridden functional status (AHR=3.11, 95% CI: 1.64, 5.72), stage IV clinical staging (AHR=3.03, 95% CI: 1.46, 6.30), non-disclosing status (AHR=2.24, 95% CI:1.36, 3.69), and CD4 count 200-350 cells/mm^3 (AHR=2.17, 95% CI: 1.08, 4.18) also had a higher risk of death.

Not receiving Cotrimoxazole preventive therapy (AHR=1.85, 95% CI: 1.07, 3.22) and poor adherence to ART (AHR=2.24, 95% CI: 1.27, 3.95), compared with adherent, was associated with higher mortality risk. Changed treatment regimens were associated with lower mortality (AHR=0.59, 95% CI: 0.35, 0.98).

Conclusions: Our study found a lower mortality rate for adolescents with HIV than previous Ethiopian studies, but our significant mortality predictors were similar to those found in earlier studies of adults and adolescents. Our findings reveal a potential point for health service improvement in Ethiopia: incorporating monitoring of haemoglobin levels into patient follow-up care, supporting recommendations that clinicians emphasise managing opportunistic infections, and providing counselling services to improve adherence.

Study strengths and limitations

This study has several strengths and limitations

- Our analysis covers a wide geographic area of Ethiopia, unlike previous studies that usually focused on individual health facilities, reaching a large sample from which we could collect a range of sociodemographic and clinical data.
- We used the Online Open Data Collection Kit (ODK) application for data collection, which facilitates the online monitoring of data collection activities and provides immediate feedback to the data collectors, improving the reliability of data entry.

Our study also experienced the following limitations that the reader should consider when interpreting its findings.

- We used patient record data, and our analysis was constrained by the incompleteness or unavailability of important variables in these records, such as income and behavioural predictors, which might also influence mortality.

- We also did not assess health service quality, which affects HIV-related mortality.
- Our study only collected data at comprehensive specialised hospitals, which, we can assume, offer a higher standard of care than smaller facilities.

Background

Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) associated mortality is a significant contributor to global adolescent mortality [1] and the leading cause of death among adolescents aged 10 to 19 years in sub-Saharan Africa (SSA) [2]. The SSA region has the highest prevalence of HIV in the world [3, 4], with more than 39 million deaths resulting from HIV/AIDS and more than 36 million people currently living with HIV [3, 5]. Substantial progress has been made in responses to HIV/AIDS under the Millennium Development Goals framework [6]. However, adolescents and young people [7] are still heavily affected by the disease, accounting for 37% of all new global HIV infections in 2017 and 15% of all people living with HIV [1, 2]. Globally, in 2016 an estimated 2.1 million adolescents (aged 10–19 years) were living with HIV [8]. In 2020, 150,000 adolescents were diagnosed as HIV-positive, and 3,200 died from AIDS-related causes [9].

Ethiopia's HIV prevalence has been falling steadily, from 2.4 percent in 2001 to 0.9 percent in 2020 among adults [10]. According to the 2018 Ethiopia HIV statistics, 690,000 people in Ethiopia live with HIV [11], and in 2016, nearly 20,000 HIV-related deaths occurred [12]. There are no recent data on the number of ALHIV in Ethiopia, but as of 2021, approximately 140,000 (88%) of the global ALHIV population were from SSA [13], growing in proportion to the global ALHIV population [14]. The United Nations Children's Fund suggests that turning the tide against AIDS requires a stronger focus on adolescents [15], and policymakers agree that a critical factor contributing to gaps in HIV/AIDS service uptake among adolescents is the limited provision of adolescent-friendly services [16, 17].

HIV-related mortality places significant emotional and financial burdens on households. The death of young parents often requires orphaned children to take on the responsibility of heading the household [18, 19]. Young adults, who are the most heavily impacted by HIV/AIDS mortality, are also the most economically productive members of society, so their illness and death have far-reaching socio-economic implications. Therefore, while HIV/AIDS-related mortality remains a crucial health concern, it is also a social, demographic, and economic issue [18] with effects on security, governance, gender relations, economic growth, and the stability of the public sector, agricultural and private sectors [18, 20].

Ethiopia's HIV/AIDS policies currently do not provide sufficient consideration to the special requirements of adolescents, despite the country's expanding teenage population and the high rate of adolescent HIV infections. [21-24]. Current HIV care and treatment guidelines in Ethiopia focus only on adults and children, with ART guidance for treating ALHIV split between tools for paediatric patients (0-14 years old) and adult patients (age 15 and above). There is a lack of adolescent-specific treatment literacy and adherence counselling tools [25].

The lack of attention to ALHIV in Ethiopia is in keeping with findings from high-, middle- and low-income countries that show services for adolescents are often highly fragmented and poorly coordinated [16, 26]. There are some areas of excellence in adolescent care; however, overall studies suggest that these programmes need to be significantly improved and brought into compliance with international best-practice guidelines. [16, 26]. Failure to consider the unique needs of ALHIV may not only lead to inappropriate or unresponsive care, but it may also lead to a lack of essential services for adolescents. These might include screening for mental health disorders, substance use disorder counselling, reproductive health counselling, screening for potential interactions between specific antiretroviral medications and hormonal contraceptives, and counselling on transitioning to adult care settings [27]. Failure to consider

such services could result in poor treatment adherence, viral suppression, and increased mortality [27, 28].

The first step in designing such interventions is understanding the current experiences and health outcomes of ALHIV in countries like Ethiopia. Research on this topic is, however, relatively sparse. The current study focuses on assessing the mortality rates and identifying potential predictors of mortality among ALHIV in Ethiopia's Amhara Region who are receiving antiretroviral therapy (ART). Several studies have named predictors of global HIV-related death, including sociodemographic factors [29-36], facility-level characteristics [35], economic status [37], and clinical predictors [29, 38, 39]. Survival chances for ALHIV vary significantly across the world [16], and few rigorous studies of mortality among ALHIV have been conducted in Ethiopia. By providing baseline mortality estimates from one of Ethiopia's most populous regions, our project will assist policymakers, program implementers, non-governmental organisations in Ethiopia and similar settings to plan, monitor, evaluate, and take evidence-based actions to improve ALHIV health outcomes.

Methods

Study setting and period

We conducted an institution-based retrospective cohort analysis among all adolescents living with HIV who initiated ART between January 2005 and June 2020 at comprehensive specialised hospitals in Ethiopia's Amhara Region. At the time of data collection, the Amhara Region had five comprehensive specialised hospitals: Felege Hiwot, Gondar, Dessie, Debre Berhan, and Debre Markos. Each hospital had a catchment area of more than five million people and provided various HIV/AIDS services, including ART in outpatient and inpatient care. All adolescents living with HIV who initiated ART between 2005 to 2020 were considered for inclusion. The year 2005 was selected as the starting point for this study because

it was the year the government of Ethiopia began providing free ART treatment to all people living with HIV.

Inclusion and exclusion criteria

The study population comprised all ALHIV aged 10-19 who initiated ART between January 2005 and June 2020. This included adolescents who transferred into study facilities from elsewhere. Adolescents with at least one viral load test record were included. Charts with incomplete medical records for essential variables such as treatment outcome, age, CD4, and viral load were excluded. In addition, patients who transferred out of care to a non-study facility during the study period were excluded. The outcome of this study was death due to HIV while taking ART.

Sample size determination

The minimum required sample size was determined using Stata statistical software Version 16 based on a survival analysis sample size determination formula. Sample size calculations were based on four predictors of mortality previously identified in the literature [38]: age (15-19 years old), residence (rural setting), CD4 count at ART initiation (<200cells/mm3), and Hgb at ART initiation (<10g/dl). Identical assumptions were used for all calculations: Power = 80%, CI= 95%, $\pi_1=\pi_2=$ ½, withdrawal 10%, N events = 92, and Pr (events) = 0.06. The sample size needed for achieving an 80% power (β = 0.20) at the 5% (α = 0.05) significance level after assuming that incompleteness was highest for the Hgb at ART initiation predictor with an estimate of 961 participants, sample size calculations detailed in supplementary material 1.

Note: Assumptions**;** power = 80%, CI= 95%, $\pi_1=\pi_2=$ ½, withdrawal 10%, N events =92, and Pr (events) =0.06. HRs described in the above table were obtained from one source [38].

Sampling procedures and source of data

This study included all five comprehensive specialised hospitals in the Amhara region, with proportional cases based on each hospital's patient load. The data source for all variables of interest was the ART registration database. Medical records of adolescents who received chronic HIV care from all Hospitals were retrieved. The complete sampling procedure is outlined in Figure 1.

Data collection tool and data collection procedures

The data extraction tool was adopted from a standard ART intake and treatment follow-up form currently used by Ethiopian health facilities, including hospitals. An online Open Data collection Kit (ODK) application tool that populated Microsoft Excel spreadsheets was used to facilitate the data collection [40]. Sociodemographic data were collected from patient charts and intake forms. The laboratory test results obtained within one month following ART initiation were used as baseline values. The mean value was computed when the two results were obtained within one month. Researchers with relevant qualifications and experience in health were employed for the data collection activities.

The Ethiopian HIV treatment guideline recommends

The Ethiopia HIV treatment guideline [41] recommends standardised clinical assessment of patients and, when available, baseline CD4 count to determine immunosuppression and initiate prophylactic therapies. Opportunistic infections, including TB, Cryptococci infection, and other comorbidities, always need to be looked for and managed in clinical assessment for IRIS, toxicity, etc. Clinical assessment: socio-economic status, any HIV-related illnesses in the past, symptom screen for TB, other OI, comorbidities, pregnancy, past, and current medication.

- WHO staging, clinical assessment for IRIS, toxicity, assess and support adherence, Hgb if the patient is on AZT, and at every visit, conduct screening for TB.

- Hemoglobin is more commonly monitored in patients with symptoms of anemia, and those on Cotrimoxazole therapy. In addition, the use of Zidovudine, which commonly caused anemia, has been discontinued and as a result, hemoglobin is not routinely monitored.
- Lab assessment: Baseline CD41, CBC, ALT, creatinine (if available), If presumptive TB diagnosis, does Gene Xpert, Pregnancy* and other tests as necessary, review clinical and lab data,
- D4 testing may be used to determine the need and discontinuation of OI prophylaxis.
- When a woman of reproductive age is taking DTG containing regimen, the occurrence of pregnancy shall be prevented and monitored. If pregnancy happens while on DTG containing regimen, DTG shall be replaced with EFV.

Study variables

The dependent variable of this study was the incidence of mortality (yes/no). Independent variables included sociodemographic and baseline clinical characteristics as well as comorbidities. All variables were extracted from patient medical records.

Sociodemographic characteristics included age at ART initiation (10-19), sex (male/female), residence (urban/rural), religion, being an orphan (yes/no), social support (yes/no), ethnicity, marital status of the caregiver, parental status (alive/dead), educational and occupational status of the caregiver, and family size.

Baseline clinical and laboratory variables included WHO clinical staging, functional status, haemoglobin (Hgb) at ART initiation, baseline CD4 count**,** regimen substitute, regimen changes, and baseline body mass index (BMI). Comorbidities included a history of opportunistic infection, tuberculosis, and malnutrition CD4 will not be used for monitoring purposes once viral load determination becomes routine. The operational definitions of HIV/AIDS mortality [42], good adherence [43], fair-adherence [43], poor adherence [43],

LTFU [44], viral load suppression [44], clinical failure, [45], immunologic failure [45], virological failure [45], CD4 count [46], and social support [47] are included as a supplementary material 2.

Patient and public involvement statement

Neither patients nor the public was involved in our research design, conduct, reporting, or dissemination plans.

Handling missing data

Missing data are unavoidable in epidemiological and clinical research, but their potential to undermine the validity of research results has often been overlooked in the medical literature [48]. Our data has incomplete records for Height (n=4, 0.4%), Weight (n=17, 1.8%), CD4 cell counts (n=42, 4.5%), Hgb (n=67, 7.1%), and viral suppression (n=87, 9.4%). After checking the pattern and mechanisms of missing values, we managed missing through multiple imputations (MI). We applied the little's test of missing completely at random test to check whether the values were missing at random or not [49]. The final imputation was performed using a multivariate normal imputation model. Variables included sex, age, place of residence, functional status, clinical staging, ART adherence, dietary status, opportunistic infections (OIs), Cotrimoxazole preventive therapy (CPT), tuberculosis, and Isoniazid preventive therapy (IPT).

Categorising continuous variables

We categorised continuous variables with referring standards and references. BMI was categorised as undernutrition (BMI<18.5), healthy weight range (18.5 to 24.9), overweight (25.0 to 29.9), and obese (BMI>29.9) [50]. Clinical conditions, such as CD4, and viral suppression, were categorised based on the ART treatment guideline used in Ethiopia [51].

Data processing and analysis

The collected data were cleaned, coded, and entered into EpiData™ software version 4.2, then exported into Stata version 16 statistical software for further analysis. Descriptive measures such as means, median, interquartile ranges (IQR), percentage, frequency, standard deviations (SD), and graphs were used for descriptive statistics. The time to death from HIV/AIDS during the ART follow-up period was estimated using the Kaplan-Meier survival curve method. A log-rank test was used to compare the estimated survival curve of patients based on categorical variables.

Assumptions for Cox-proportional analysis were checked using the Schoenfeld residual test with variables with a p-value of >0.1. We used stepwise Cox regression to build the multivariable Cox regression model. Variables with p-values less than 0.25 in the bi-variable analysis were considered for the multivariable model. Adjusted hazard ratios (aHR) with a 95% confidence interval and p-values less than 0.05 were used to measure the strength of the association and identify statistically significant predictors. The mean-variance inflation factors (VIF=1.16) indicated no meaningful multicollinearity between variables in the multivariable models.

Ethics consideration of the study

Ethical approval for this study was granted by the University of Technology Sydney Medical Research Ethics Committee (ETH20-5255) and the Amhara Region Public Health Institution (No H/R/T/T/D/3/887). Permission letters were received from all included comprehensive specialised hospitals to conduct the study. Participants' verbal or written consent was not feasible as the study utilised existing medical records of PLHIV. A waiver of consent was granted by the primary ethics committee. The data abstraction tool did not include individual identifiers such as unique medical record numbers and names; thus, we could not identify participants.

Results

Demographic characteristics

After reviewing 945 medical records, 17 were excluded due to incompleteness, and 928 were included in the final analysis. More than half (n=496, 53.0%) of the sample were female. The median age of ALHIV was 13 [IQR: 11.0, 16.0] years; more than half (n=590, 63.3%) of them were between 10 and 14 years old at the initiation of ART. The majority (n=692, 74.6%) lived in urban environments, and more than one-third (n=639, 68.8%) had a primary-school level of education. More than three-quarters (n=721, 77.7%) had both parents alive. Most adolescents (n=703, 75.9%) received social support while on ART. Most ALHIV (n=786, 84.7%) were aware of their HIV status (Table 1).

Table 1: Baseline sociodemographic characteristics of ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	Frequency (N)	Percentage (%)
Age classification [36]		
10-14 years old	590	63.6
15-19 years old	338	36.4
Sex		
Male	432	46.6
Female	496	53.4
Residence		
Urban	692	74.6
Rural	236	25.4
Education		

No formal education	14	1.5
Primary (grades 1-8)	639	68.9
Secondary (grades 9-12)	223	24.0
Higher (degree & above)	52	5.6
Ethnicity		
Amhara	886	95
Other*	42	5
Parental status		
Both alive	721	77.7
Father alive	74	8.0
Both died	133	14.3
Religion		
Orthodox Tewahido Christian	643	69.3
Muslim	224	24.1
Other	61	6.6
Caregiver marital status		
Single	114	12.3
Married	552	59.5
Divorced	80	8.6
Widowed	182	19.6
Family size		
Family size ≤4	683	73.6
Family size >4	245	26.4
Social support		
Yes	703	75.7

No	225	24.3
Disclosure status (knowledge of their own HIV status)		
Yes	786	84.7
No	142	15.3
History of PMTCT		
Yes	169	18.2
No	523	56.4
Unknown	236	25.4
Relation to caregiver		
Parent	611	65.9
Sister/Brother	159	17.1
Grandparents	65	7.0
Aunt/Uncle	76	8.1
Other*	17	1.9

Other *: other relatives (11) and guardian (8)

Baseline clinical, laboratory, and ART information

At the initiation of ART, 237 (25.5%) of the 928 ALHIV had opportunistic infections (OIs). We found that 579 (62.4 %) were asymptomatic or at early stages of infection (WHO stages I and II) at baseline, and about one-third (30%) had CD4 counts < 200 cells/mm^3. Nearly half (n=440, 47.4%) were categorised as having working functional status. Body mass index (BMI) was used to assess the nutritional status of ALHIV. At the time when ART was initiated, 81.9% of the sample was underweight (BMI 18.5), 16.4% were normal weight (BMI 18.5 to 24.9), and 1.7% were overweight (BMI 25) (Table 2).

Table 2: Clinical, laboratory, and treatment characteristics of ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	Frequency (N)	Percentage (%)
CD4 count		
Less than 200 cells/mm3	278	30.0
200 to 350 cells/mm3	249	26.8
More than 350 cells/mm3	401	43.2
WHO clinical staging		
Stage I and II	579	62.4
Stage II and IV	349	37.6
Functional status		
Working	440	47.4
Ambulatory	420	45.3
Bedridden	68	7.3
Haemoglobin level		
< 10 g/dl	56	6.0
≥10 g/dl)	872	94.0
Cotrimoxazole preventive therapy (CPT)		
Yes	820	88.4
No	108	11.6
Isoniazid preventive therapy		
Yes	682	73.5
No	246	26.5

ART adherence		
Good	827	89.1
Fair	47	5.1
Poor	54	5.8
Opportunistic infections at baseline (OPs)		
Yes	237	25.5
No	691	74.5
ART eligibility criteria		
Immunologic/CD4	110	11.9
WHO clinical stage	93	10.0
Both clinical and immunologic	642	69.2
Test and treat approach	83	8.9
ART drug side effects		
Yes	66	7.1
No	862	92.9
Baseline viral load		
Below 1000	768	82.8
1000 and above	160	17.2
Tuberculosis		
After ART initiation	76	78.4
Pre-ART	21	21.6
History of treatment failure		
Yes	113	12.2
No	815	87.8
Regimen change		

Yes	433	46.7
No	495	53.3
Body Mass Index (BMI)		
Underweight	760	81.9%
Normal	152	16.4%
Overweight	16	1.7%

Baseline opportunistic infections

The top three OIs at ART initiation were diarrheal disease (n=127, 20.7%), pneumonia (n=122, 19.9%), and tuberculosis (n=90, 14.7%) (Supplementary material 3).

Adolescents' follow-up characteristics

One quarter (n=238, 25.6%) of adolescents developed OIs during follow-up, and nearly one-third (n=76, 31.9%) developed pneumonia. During the follow-up time, 113 (12.3%) adolescents experienced treatment failure. Nearly half, 434 (46.8%), of the included adolescents had a history of ART regimen change during follow-up. Of these, 76 (17.6%) changed their regimen due to treatment failure, 56 (12.9%) due to side effects, and 5.5% developed OIs. The majority of treatment failures were virologic failures (n=70, 61.4%), followed by immunologic failures (n=22, 20.2%) and clinical failures (n=21, 18.4%). Nearly half of all included ALHIV (n=433, 46.7%) changed their regimens during ART follow-up (Supplementary material 4). Few (n=66, 6.8%) adolescents experienced ART side effects, with more than one-third (n=27, 37.9%) of side effects reported as drug toxicity (Supplementary material 5).

Death rate during follow-up

With a median follow-up period of 82 (IQR: 44 -130) months, a total of 928 adolescents on ART were observed for varying lengths of time, ranging from 7 to 233 months. This retrospective cohort contributed a total follow-up time of 81,583 person-month observations. At the end of the project/follow-up period, 103 (11.1%) died, while 772 (83.2%) were still on follow-up, and 53 (5.7%) were transferred to other health institutions. The cumulative probability of surviving or being free from the event of interest at the end of 6, 12, 18, and 24 months was 98.6, 96.7, 95.8, and 95.0%, respectively (Fig. 2).

The cohort's overall mortality rate was 1.26 (95% CI: 1.04, 1.53) per 1000 person-months. The overall estimated median mortality time was 4.76 months (95% CI: 4.17, 5.02 months; Fig. 3).

Predictors of mortality incidence

In the final multivariable Cox regression model, several factors associated with higher mortality were identified (See table 3). The mortality risk was 3.27 times greater (AHR: 3.27, 95% 1.36, 7.87) for those without formal education than those who had completed primary school. ALHIV who changed their previous regimen had a 40% decreased risk of death than participants who did not (AHR: 0.60, 95% CI: 0.36, 0.99). We saw a higher hazard of death in adolescents with widowed parents (AHR: 1.85, 95% 1.01, 3.56), those without social support (AHR: 2.81, 95% CI: 1.69, 4.67), and those whose parents had not told them that they are HIV positive (AHR: 2.08, 95% CI: 1.07, 2.81).

Adolescents with lower Hgb levels at ART initiation had more than double the hazard of death (AHR: 2.04, 95% CI: 1.02, 4.08) compared with those with normal Hgb levels. Adolescents with bedridden functional status at ART initiation had three times the higher hazard of death than those with working status (AHR: 3.11, 95% CI: 1.64, 5.72). The hazard of death among adolescents who started treatment at WHO clinical stage IV was 3.03 times higher than those in stage I (AHR: 3.03, 95% CI: 1.46, 6.30). The hazard of death among adolescents with a CD4

count between 200 to 350 cells/mm^3 was 2.17-fold higher than adolescents with a CD4 count higher than 350 cells/mm^3 (AHR: 2.17, 95% CI: 1.08, 4.18). The mortality hazard among adolescents who did not receive CPT was nearly twice higher than their counterparts (AHR: 1.85, 95% CI: 1.07, 3.22). The hazard of death among poor adherent adolescents was two times higher than those with good and fair adherence (AHR: 2.24, 95% CI: 1.27, 3.95). Furthermore, the risk of death was twice higher among ALHIV who did not know their HIV status (AHR: 2.08, 95% CI: 1.07, 2.81).

Table 3: Bivariable and multivariable Cox regression analysis of mortality predictors among ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	CHR [95% CI]	AHR [95% CI]
Sex		
Female	1	1
Male	1.10 (0.75, 1.62)	1.05 (0.68, 1.61)
Age		
10-14 years old	1	1
15-19 years old	1.49 (1.00, 2.19)	1.07 (0.60, 1.90)
Education		
No formal education	5.70 (2.61, 12.48)	3.27 (1.36, 7.87)*
Primary education	1	1
Secondary education	1.35 (0.86, 2.15)	0.99 (0.54, 1.82)
Higher education	1.44 (0.66, 3.17)	0.67 (0.27, 1.64)
Caregiver marital status		
Single	1.98 (1.12, 3.50)	1.50 (0.78, 2.84)
Married	1	1
Divorced	3.28 (1.90, 5.68)	1.89 (1.01, 3.56)*
Widowed	1.65 (1.01, 2.71)	1.85 (1.08, 3.19)*
Hospitals (study setting)		
Dessie CSH	1	**1**

Debre Birehan CSH	6.09 (3.24, 11.44)	6.54 (2.83, 15.12)**
Debre Markos CSH	1.93 (0.83, 4.46)	1.12 (0.40, 3.09)
Felege Hiwot CSH	6.95 (3.80, 12.70)	6.31 (2.79, 14.27)**
UOGCSH	0.62 (0.25, 1.53)	0.70 (0.40, 2.83)
Social support		
Yes	1	1
No	5.30 (3.58, 7.84)	2.81 (1.69, 4.67)**
Disclosure status		
Yes	1	1
No	4.55 (3.04, 6.82)	2.08 (1.07, 2.81)*
Regimen change		
No	1	1
Yes	0.28 (0.18, 0.44)	0.60 (0.36, 0.99)*
Baseline haemoglobin level		
≥10 g/dl)	1	1
< 10 g/dl	2.67 (1.42, 5.02)	2.04 (1.02, 4.08)*
Baseline functional status		
Working	1	1
Ambulatory	0.89 (0.57, 1.39)	0.64 (0.38, 1.08)
Bedridden	5.70 (3.47, 9.38)	3.11 (1.64, 5.72)**
Baseline WHO clinical staging		
Stage I	1	1
Stage II	1.24 (0.71, 2.15)	1.57 (0.88, 2.83)
Stage III	1.02 (0.57, 1.81)	1.23 (0.65, 2.33)
Stage IV	4.79 (2.75, 8.34)	3.03 (1.46, 6.30)*
Baseline CD4 count		
> 350 cells/mm3	1	1
200 to 350 cells/mm3	0.55 (0.32, 0.95)	2.17 (1.08, 4.18)*
≤ 200 cells/mm3	0.95 (0.61, 1.46)	1.49 (0.91, 2.46)
Cotrimoxazole preventive therapy		
Yes	1	1
No	4.72 (3.01, 7.41)	1.85 (1.07, 3.22)*

Ionised preventive therapy		
Yes	1	1
No	2.69 (1.82, 3 .97)	0.90 (0.55, 1.46)
ART adherence		
Good/ Fair	1	1
Poor	4.60 (2.72, 7.80)	2.24 (1.27, 3.95)**
Opportunistic infection at baseline		
No	1	1
Yes	2.77 (1.84, 4.16)	1.94 (1.19, 3.14)**
Baseline BMI		
Underweight	1	1
Normal	1.40 (0.87, 2.27)	1.17 (0.74, 1.96)
Overweight	1.45 (0.46, 4.61)	1.88 (0.57, 5.63)

*Significant at P< 0.05, *Significant at P< 0.01 and **Significant < 0.001*

Discussion

This study aimed to assess the incidence and predictors of mortality among ALHIV receiving ART across the Amhara region of Ethiopia using a multi-facility retrospective follow-up approach. With a total follow-up time of 81,583 adolescent months, the overall incidence of mortality among ALHIV receiving ART was 1.52 per 100 person-years.

The mortality rate for ALHIV in our study is lower than the rate found in other single-country African studies, for example, in Ethiopia (2.29 deaths per 100 person-years) [36] and Zimbabwe, 5.46 deaths per 100 person-years [52]. However, our study's overall mortality rate is higher than the rate reported by a global cohort collaboration across seven regions (0.97 deaths per 100 person-years) [35], an African cross-national study (0.8 deaths per 100 person-years) [21], and a recent South African community-based ART study (1.2 deaths per 100 person-years) [53]. Our estimated mortality incidence is also lower than those found in previous

studies of adult PLHIV in Ethiopia, for example, in Gondar (5.3 deaths per 100 person-years) [54], Harar (4.8 deaths per 100 person-years) [55], Debre Berhan (4.8 deaths per 100 person-years) [56], Debre Markos (13.6 deaths per 100 person-years) [57], and in Metema (6.7 deaths per 100 person-years) [58].

The difference between our mortality rate and those reported in previous studies, as well as the variation in mortality rates between these studies themselves, may be due to differences in the clinical characteristics of study participants and differences in study periods, sample sizes, and study settings, as our study included only comprehensive specialised hospitals. The adolescents' ages may have also differed between studies; for example, several studies included children under the age of nine in their samples [36].

Most prior studies on adolescent mortality do not report detailed sociodemographic information, so comparing our sample's characteristics to those of previous mortality studies is difficult. However, when we compare outcomes for ALHIV in our sample with other studies, we found that our cohort has a lower proportion of male adolescents (46.6%) compared to other cohorts (50.9%) of samples). The high proportion of males in our sample may have shifted our mortality estimates upward as it is well established that male adolescents have a higher mortality rate than female adolescents [59-61]. Although it is difficult to make direct comparisons, our sample may not be similar to adolescent populations studied in other sub-Saharan African settings, particularly as our cohort was disproportionately urban and relatively well-educated compared to a study in Ethiopian adolescents [36]. Our study's relatively low mortality rate might also be attributed to the clinical characteristics of the included study participants; for example, 82.8% of our study participants had baseline viral suppression. It is well-established that a higher baseline viral load is associated with increased mortality risk [62], so our study participants' relatively good health may contribute to a lower mortality rate.

In addition, a high proportion of adolescents in our study received critical preventative interventions, such as IPT (73.5%) and CPT (88.4%), which may have also contributed to lower mortality.

Sociodemographic predictors of mortality

We identified several demographic predictors associated with mortality in adolescents receiving ART. Adolescents with no formal schooling had higher mortality rates than those with at least primary schooling. However, having schooling beyond primary school did not lower mortality risks. As previously noted, most ALHIV mortality studies in sub-Saharan Africa do not report sociodemographic data, but our findings are consistent with a European cohort collaboration study and a study from Denmark, which found that lower levels of education were associated with increased mortality among PLHIV [63, 64]. The lack of a protective effect for secondary and post-secondary levels of education contrasts with findings from the United States (US) that HIV/AIDS-related mortality rates decreased with increasing educational levels [65]; however, the US study was not adolescent-specific, and the education effect may not be applicable to younger populations.

Our study found that the age and sex of adolescents were not associated with mortality. An analysis of adolescents in India had similar findings [66]. However, the lack of significance of age and sex is in contrast to previous research in SSA, which has found that age (older adolescents) and sex (being female) increased the risk of mortality among ALHIV [67]. Being male was also reported as a risk for HIV-associated death among ALHIV in a large global study of perinatal infection. However, the sex-related risk of death varied depending on whether the patients were perinatally infected and their region [68]. It could be that a generally high standard of care at the comprehensive hospitals that we studied reduced sex and age disparities. However, further research may be needed to determine the importance of age and

sex as factors driving mortality among ALHIV, and this research should consider perinatal infection.

Urban or rural residence was not a significant predictor for mortality in this study, in contrast to other studies that found higher mortality among ALHIV living in rural areas [69]. This might be because our study had a relatively small proportion of ALHIV from rural settings (25.4%). Therefore our study may have been underpowered to find urban-rural differences in mortality.

We found that the risk of death was nearly twice as high among ALHIV from widowed parents, which is consistent with a study in the US reporting that mortality is higher in ALHIV from divorced and separated families [70]. Having married parents may allow greater economic support and social approval than single, divorced, and widowed parents. Studies from Uganda and South Africa indicate that adolescents who live with single parents receiving ART treatment experience economic insecurity, psychological challenges, and weakened social protections [71, 72]. Besides, ALHIV living with widowed fathers and those living on their own were significantly more likely to show signs and symptoms of depression than their peers [73].

The risk of death was higher among ALHIV with no social support compared to their counterparts. This finding is supported by studies from a range of low-and middle-income countries, including the United States and Uganda [24, 74, 75], as well as studies from Ethiopia, the SSA region, and China that highlight the vital role of social support in coping with and recovering from illness in general [75-77]. Social support networks are essential in helping PLHIV/AIDS to maintain good physical and mental health, including adhering to their treatment. Social support could moderate the adverse effects of stressful events [78], which is one of the most effective ways to cope with stress.

Clinical predictors of mortality

We found that poor health or advanced HIV disease at baseline was associated with a higher risk of death. We found a wide range of baseline and follow-up clinical predictors of mortality, including low Hgb levels, bedridden status, WHO stage IV clinical staging, CD4 counts below 350, the presence of OIs, a change in ARV regimen, and poor treatment adherence, all of which were associated to an increased mortality risk among ALHIV.

Several studies from low- and middle-income countries indicated that ALHIV and PLHIV with low Hgb risk of increased mortality [30, 66, 69, 79]. Additionally, studies have found an association between CD4 cell count, viral load, and haemoglobin level [80]. The problem of food insecurity is worth in low-income countries than in high-income countries. A study also showed that food insecurity increases poor treatment outcomes [81]. This suggests that strengthening the routine monitoring of Hgb levels (e.g., concurrently with each CD4 cell count determination) and improving food access may be a helpful addition to clinical guidelines.

We found a higher mortality risk among ALHIV who was bedridden at baseline, consistent with previous Ethiopian studies [82] and assuming that functional status correlates with patients' clinical and immunological status. Similarly, we found higher mortality among ALHIV who were categorised as WHO stage IV at baseline, consistent with study findings from Ethiopia [69, 82], India [66], and South Africa [30], as well as international guidelines [83]. The negative association between CD4 counts and mortality that was identified has been well-established in previous studies conducted globally [35], in Europe [65], and in Ethiopia [69]. However, the association we found was relatively weak: 95% confidence interval approached 1.00, and there was no significant association between being in the lowest CD4 category and mortality. The weakness of this may be due to the large number of variables in our model that also measured baseline HIV disease progression. Our final indicator of disease progression was the presence of OIs at baseline. ALHIV, who presented with OIs at baseline,

had a higher mortality rate, consistent with other Ethiopian studies [58, 84]. The presence of OIs may indicate low CD4 cell counts, decreased humoral and cellular immunity and possibly AIDS [85, 86]. Overall, these findings highlight the importance of starting ART as early as possible after an HIV diagnosis to suppress the virus and stabilise CD4 counts.

Good preventative treatment and ART adherence indicators were also associated with lower mortality risk. These findings support arguments that state the timely and consistent administration of CPT prevents OIs among PLHIV, improves the quality of life, and reduces associated mortality [87]. In order to enhance CD4 counts, quality of life, and patient outcomes, the WHO suggests the prescription of CPT for all ALHIV with CD4 cell counts below 350, regardless of their symptoms[88].

The risk of death in ALHIV with poor ART adherence was higher than in those with good/fair adherence. The importance of ART adherence in reducing death and illness in ALHIV is a consistent finding [89], as adherence is critical to controlling viral replication. Helping adolescents maintain good adherence is challenging because of the specific challenges they face around disclosure, risk-taking, and transitioning to adult services [90]. Medication-related barriers such as the complexity of regimens and treatment side effects can also impact adherence and may be particularly acute for perinatally-infected ALHIV who have been receiving ART for long periods [91]. The significance of adherence in our findings underscores the need to develop and test targeted interventions to improve adherence in this population. This may be related to ART adherence, lower comorbidities, OIs, improved viral suppression, higher CD4 count, and higher Hgb. Such conditions improve patient treatment outcomes and a lower mortality rates.

Unusually, this study found that CD4 counts of less than 200 cells/mm3 are not associated with HIV-related mortality, while CD4 counts between 200 and 350 cells/mm3 increased mortality

among adolescents receiving ART. This may be the result of an inadequate sample size. Small sample size affects the reliability of a survey's results because it leads to a higher variability, which may cause bias [92].

The current study found a lower mortality rate among ALHIV who underwent an ART regimen change compared to their counterparts. Conversely, a prior Ethiopian study found that ALHIV who underwent an ART regimen change had a higher death rate [93]. The contradictory findings may be due to different populations, reasons for regimen change, and stage of disease, for example, medication shortages and stockouts (35%), OIs (25%), side effects (20%), and treatment failure (19%) were the main reasons for regimen changes in the earlier study. In contrast, in previous Ethiopian studies, the most common reason for medication changes or switches were toxicity, comorbidity, patient compliance, and treatment failure, which are similar to our findings [94, 95].

Furthermore, in the current study, 84.7% of the adolescents living with HIV had been told they were infected with HIV. The study also found that the risk of death was twice higher among ALHIV who did not know their HIV status, which is consistent with a study finding in Kenya [96]. Besides, adolescents who are aware of their HIV infection status have better HIV treatment outcomes [97, 98]. WHO promotes disclosing HIV infection status to adolescents and suggests informing younger children sequentially to accommodate cognitive and emotional development [99]. This may be explained by patients who are aware they infected with HIV have better treatment adherence. Adherence improve treatment outcome, which is consistent with a study conducted elsewhere [100].

Study strengths and limitations

This study has several strengths. First, in contrast to earlier research that concentrated on specific healthcare facilities, our analysis covers a large geographic area of Ethiopia. Second,

we had a large sample that allowed us to gather various sociodemographic and clinical data. Additionally, we utilised the Online Open Data collection Kit (ODK) programme to collect the necessary data. This tool facilitates the online monitoring of data collection activities and provides immediate feedback to the data collectors, improving the reliability and accuracy of data entry.

Our study also has important limitations that should be considered when interpreting its findings. We used patient record data, and our analysis was constrained by the incompleteness or unavailability of important variables in these records, such as income and behavioural predictors, which might also influence mortality. We also did not assess health service quality, which affects HIV-related mortality. Finally, our study only collected data at comprehensive specialised hospitals, which, we can assume, offer a higher standard of care than smaller facilities. Therefore, the mortality rates reported in our study may represent a low, best-case scenario for HIV/AIDS treatment programs in Ethiopia.

Policy and clinical implications

There is a strong need to strengthen monitoring activities to improve clinical management and OIs to improve treatment outcomes for ALHIV. Our findings support recommendations that clinicians monitor haemoglobin levels during patient follow-up care; prioritise the management of OIs; and provide counselling services to improve adherence. We recommend that future researchers consider conducting prospective follow-up studies to assess other potential predictors of survival. These studies should include sociodemographic factors in addition to clinical factors.

Implications for modifiable factors include

- Increasing educational support and social support,
- Intensifying peer support for adherence and disclosure,

- Improved outreach and routine testing to ensure early treatment,
- Continued support for prophylaxis treatment and monitoring of Hgb & OIs.

Significant differences in treatment outcomes (mortality rates) between the studied health institutions would suggest that policymakers should strengthen the health system across facilities to bring them up all to the same level seems important.

Conclusion and recommendations

Our study found a lower mortality rate among ALHIV than in previous studies of adolescents in Ethiopia. Low levels of social support and a lack of education were associated with higher mortality, as were several indicators of advanced disease progression and poor health at baseline. The estimated impact of clinical predictors was relatively weak but highlighted the importance of treating HIV early in this population. Receiving CPT prophylaxis against OIs and maintaining good adherence was also associated with lower mortality, underscoring the importance of these preventative treatments and adherence counselling and support services.

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Contributors

CTL: conception of the project idea, design, analysis, interpretation, and manuscript drafting, and is responsible for the corresponding overall role during the publication process. DD, SB, and JF: rephrase the project idea, design, interpretation of results, reviewing and editing the manuscript. Finally, all authors have critically read and approved the manuscript.

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Data availability statement

Data are available upon reasonable request. Data used for this study will be available upon request of the corresponding Author.

Supplemental material

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Supplementary files

Supplementary material 1: Sample size calculation

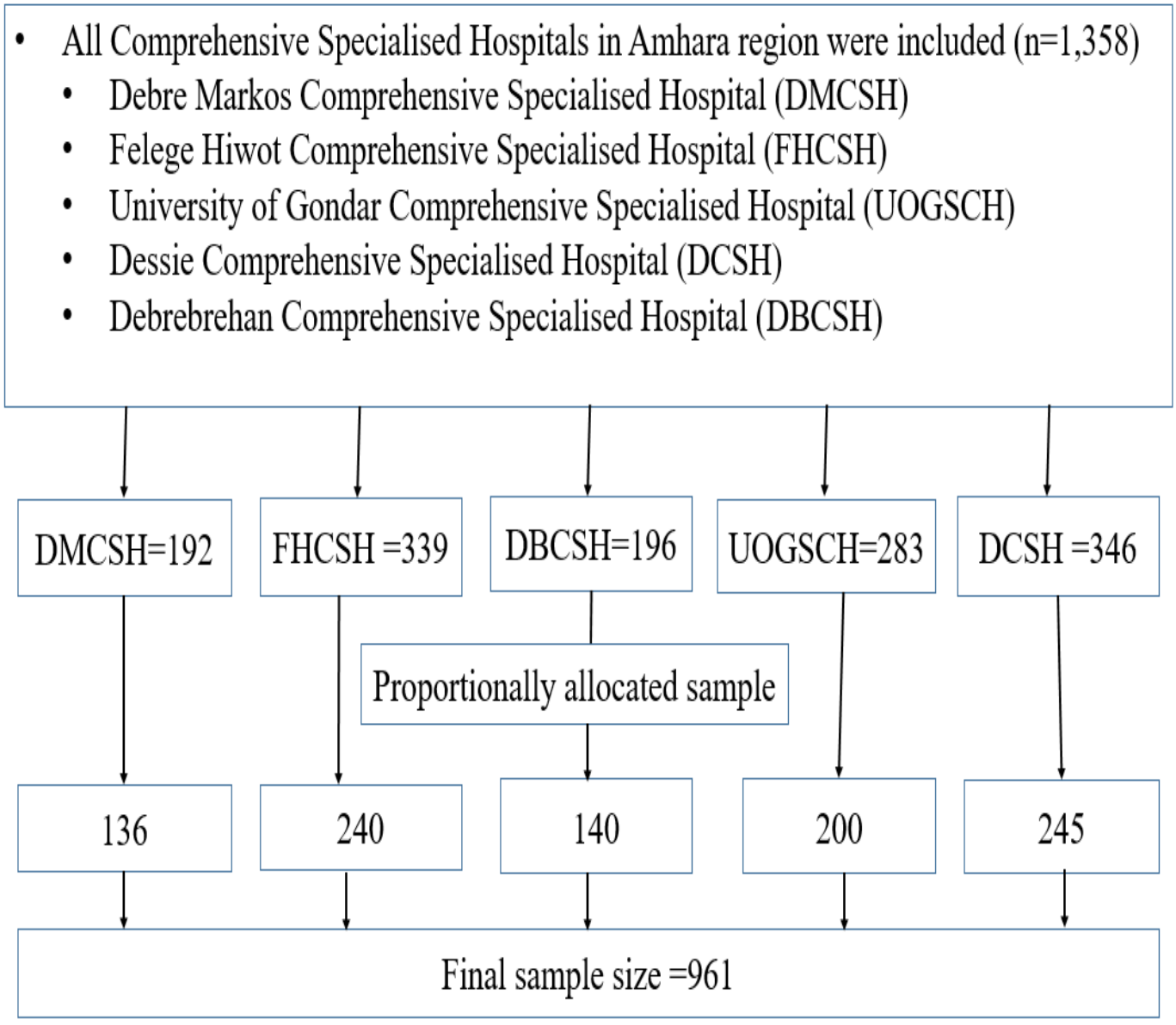
Supplementary material 2: operational definitions

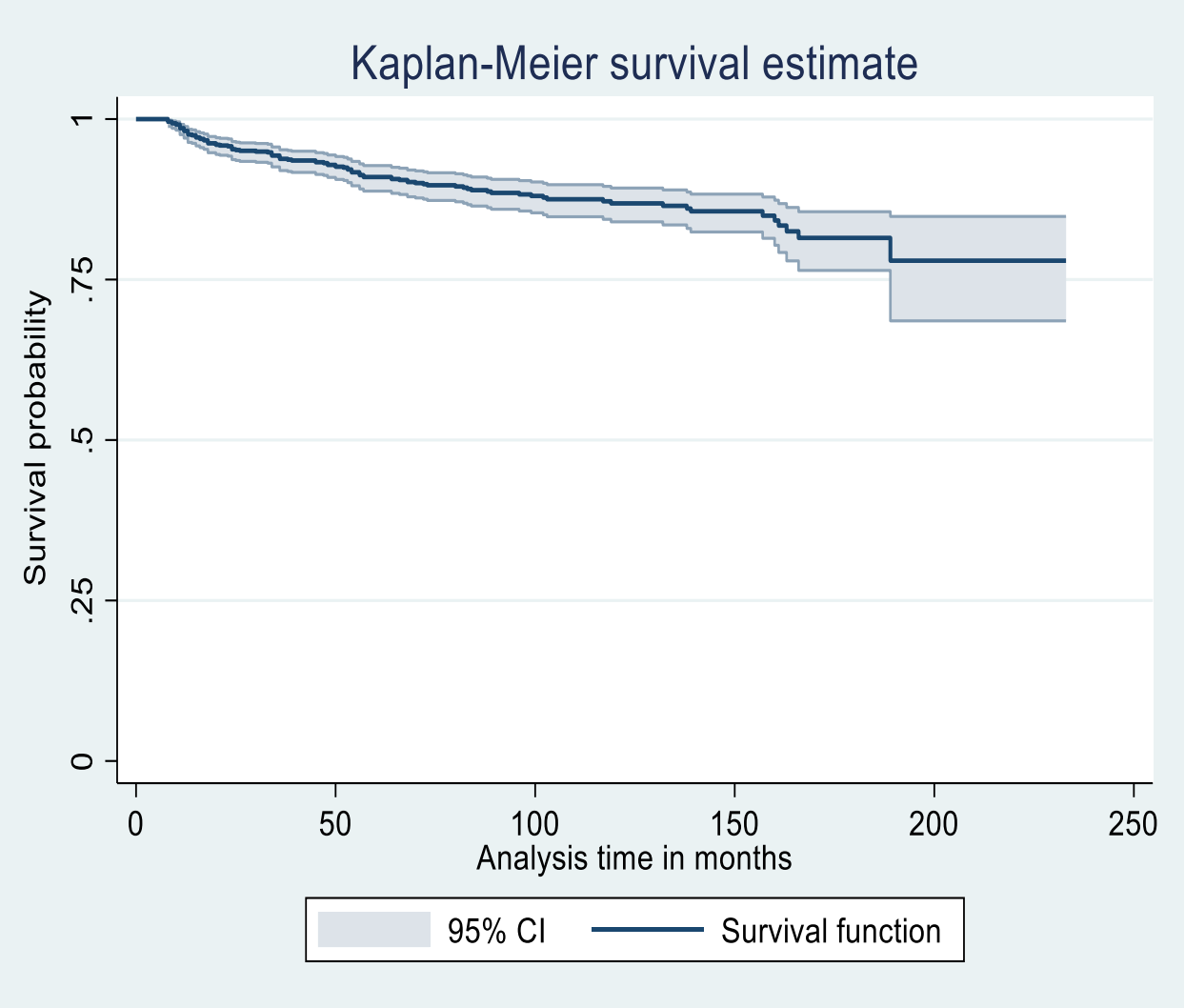
Supplementary material 3: Baseline opportunistic infections

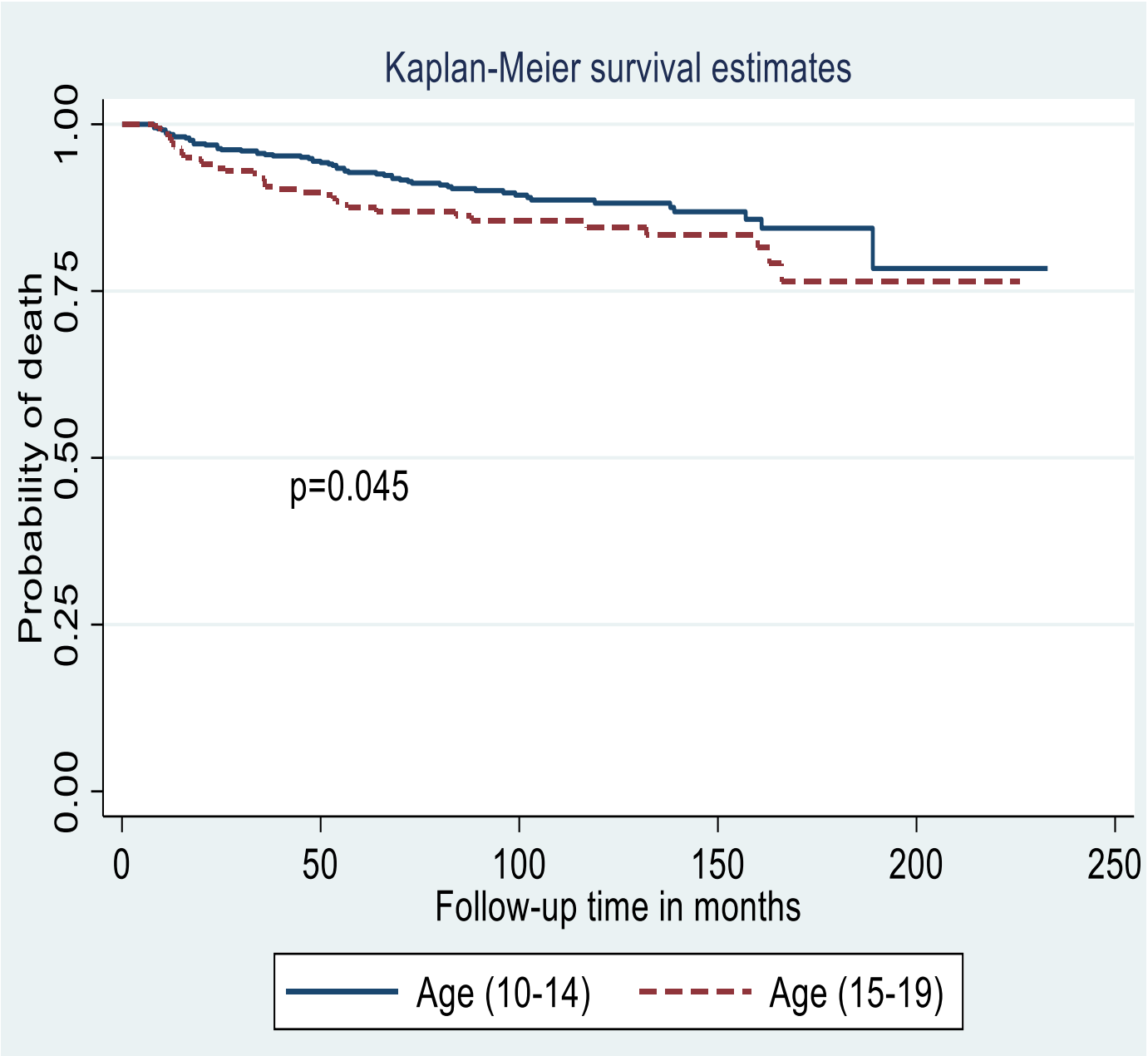
Supplementary material 4: Most common opportunistic infections developed during follow-up

Supplementary material 5: Drug side effects among ALHIV receiving ART

List of Figures


All Comprehensive Specialised Hospitals in Amhara region were included (n=1,358)
Debre Markos Comprehensive Specialised Hospital (DMCSH)
Felege Hiwot Comprehensive Specialised Hospital (FHCSH)
University of Gondar Comprehensive Specialised Hospital (UOGSCH)
Dessie Comprehensive Specialised Hospital (DCSH)
Debrebrehan Comprehensive Specialised Hospital (DBCSH)
DMCSH=192
FHCSH =339
DBCSH=196
UOGSCH=283
DCSH =346
Proportionally allocated sample
136
240
140
200
245
Final sample size =961


Kaplan-Meier survival estimate
Survival probability
0
.25
.5
.75
1
0
50
100
150
200
250
Analysis time in months
95% CI
Survival function


Kaplan-Meier survival estimates
Probability of death
0.00
0.25
0.50
0.75
1.00
p=0.045
0
50
100
150
200
250
Follow-up time in months
Age (10-14)
Age (15-19)

Supplementary material 1: Sample size determination for assessing treatment outcomes among ALHIV on ART in Amhara Regional State, Ethiopia, 2020

Variables	Hazard ratio	Calculated sample size	10% incompleteness	Total sample
Age group of the respondents	aHR = 2.3	755	8	765
Residence of the respondents	aHR = 2.8	494	5	499
CD4 count at ART initiation	aHR = 2.8	494	5	499
Hgb at ART initiation	aHR = 2.1	951	10	961

Supplementary material: operational definitions

HIV/AIDS mortality: The total number of people who have died from AIDS-related causes per 100,000 population.

Good adherence is defined as if the percentage of the taken dose is between >95 % (< 2 doses of 30 doses or <3 dose of 60 doses) as documented by the ART physician.

Fair adherence is defined as the percentage of missed doses between 85-94 % (3-5 doses of 30 doses or 3-9 doses of 60 doses) as documented by an ART physician.

Poor adherence is defined as if the percentage of missed doses is between <85 % (> 6 doses of 30 doses or >9 doses of 60 doses) as documented by an ART physician.

Lost to follow-up is defined as if a patient discontinued ART for three months as recorded by the physician

Viral load suppression: HIV RNA in the blood equates to less than 200 copies per millilitre of blood sample because of antiretroviral therapy.

Virological failure: Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test.

Clinical failure: New/recurrent/ clinical event showing severe immunodeficiency (WHO clinical stage 4 and particular WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure) after six months of effective treatment.

I**mmunologic failure:** CD4 count at or below 250 cells/mm3 following clinical failure or Persistent CD4 levels below 100 cells/mm^3.

Virological failure: Viral load above 1000 copies per mL based on two consecutive viral load tests or measurements in 3 months, with adherence support following the first viral load test

CD4 count was classified below the threshold, CD4 count < 200 cells/mm3, and above the threshold, CD4 count ≥ 200 cells/mm3 for severe immunodeficiency.

Social support is the perception and actuality that one is cared for, has assistance available from other people, and, most popularly, is part of a supportive social network: supportive resources can be emotional (e.g., nurturance), informational (e.g., advice), or companionship (e.g., sense of belonging); tangible (e.g., financial assistance) or intangible (e.g., personal recommendation). It is supported (psychological, economic, and physical support) given to an incredible person. n addition, the social support for HIV patients form includes.

Supplementary material 3: Baseline opportunistic infections of ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928)

Variables	Frequency (n)	Percentage (%)
Diarrheal disease		
Yes	127	20.7
Pneumonia		
Yes	122	19.9
Tuberculosis		
Yes	90	14.7
Herpes Zoster		
Yes	89	14.5
Skin infection/rash		
Yes	77	12.5
Candidiasis		
Yes	71	11.6
CNS toxoplasmosis		
Yes	18	2.9

Supplementary material 4: Most common opportunistic infections developed during follow-up among ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020

Opportunistic Infections	Frequency	Percentage
Bacterial pneumonia	76	24%
Tuberculosis	67	21%
Diarrhea	55	17%
Candidiasis	27	9%
Skin rash	27	9%
Herpes zoster	23	7%
Central nurves system (CNS) toxoplasmosis	17	5%
Others	24	8%

Others: Malnutrition (n=9, 3.8%), Pneumocystis pneumonia (PCP) (n=9, 3.8%) and Cryptococcus meningitis (n=6, 2.5%).

Supplementary material 5: Drug side effects among ALHIV receiving ART in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020.

Drug side effects	Frequency (n)	Percentage (%)
Toxicity	27	35.1%
Diarrhea	16	20.8%
Anemia	10	13.0%
Nausea	5	6.5%
Fatigue	4	5.2%
Skin rash	4	5.2%

Others: Facial dystrophy (n=3, 3.9%), vomiting (n=3, 3.9%), Lipodystrophy (n=3, 3.9%), and Headache (n=2, 2.6%),

STROBE 2007 (v4) Statement

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2 to 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 to 6
Objectives	3	State-specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6 to 11
Participants	6	(*a*) Give the eligibility criteria and the sources and methods of selecting participants. Describe methods of follow-up	6 to 7
		(*b*) For matched studies, give matching criteria and the number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6 and 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9 and 12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider the use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12 to 20
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) Summarise follow-up time (eg, average and total amount)	18
Outcome data	15*	Report numbers of outcome events or summary measures over time	18
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17 to 21
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions and sensitivity analyses	17 to 21
Discussion			
Key results	18	Summarise key results with reference to study objectives	21 to 27
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, the multiplicity of analyses, results from similar studies, and other relevant evidence	27-28
Generalisability	21	Discuss the generalisability (external validity) of the study results	29
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	30

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in the cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.