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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 HR (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 HIV (ALHIV) were girls. The adolescent mortality rate was 1.52 (95% CI: 1.04 to 1.53) per 100 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% CI: 1.36 to 7.87), had widowed parents (aHR: 1.85, CI: 95% 1.01 to 3.56) or received no social support (aHR: 2.81, 95% CI: 1.69 to 4.67). Adolescents who had opportunistic infections (OIs) at ART initiation (aHR: 1.94, 95% CI: 1.19 to 3.14), low haemoglobin (Hgb/g/l) levels (aHR: 2.17, 95% CI: 1.08 to 4.18), a bedridden functional status (aHR: 3.11, 95% CI: 1.64 to 5.72), stage IV clinical staging (aHR: 3.03, 95% CI: 1.46 to 6.30), non-disclosing status (aHR: 2.24, 95% CI:1.36 to 3.69) and CD4 count 200–350 cells/mm^3 (aHR: 2.17, 95% CI: 1.08 to 4.18) also had a higher risk of death. Not receiving cotrimoxazole preventive therapy (aHR: 1.85, 95% CI: 1.07 to 3.22) and poor adherence to ART (aHR: 2.24, 95% CI: 1.27 to 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 to 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 Hgb levels into patient follow-up care, supporting recommendations that clinicians emphasise managing OIs and providing counselling services to improve adherence.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ 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 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.
⇒ 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

HIV/AIDS-associated mortality is a significant contributor to global adolescent mortality[1] and the leading cause of death among adolescents aged 10–19 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 3200 died of AIDS-related causes.[9]

Ethiopia's HIV prevalence has been falling steadily, 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 adolescents living with HIV (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 policy-makers 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 socioeconomic 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 antiretroviral therapy (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-income, middle-income 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 such as 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 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 36 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 policy-makers, programme 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 and 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 V.16 based on a survival

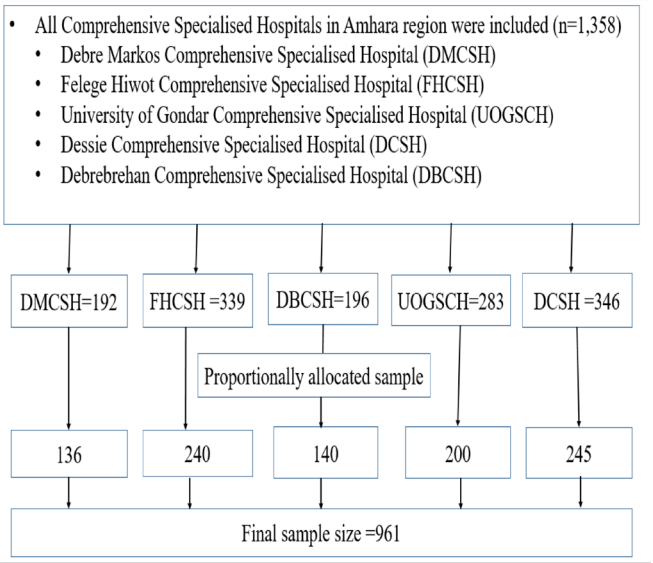

Figure 1 Sampling procedure to assess the predictors of mortality among adolescents living with HIV on antiretroviral therapy in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020.

analysis sample size determination formula. Sample size calculations were based on four predictors of mortality previously identified in the literature[36]: age (15–19 years old), residence (rural setting), CD4 count at ART initiation (<200 cells/mm^3) and haemoglobin (Hgb g/l) at ART initiation (<10 g/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 online supplemental 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.[36]

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 1 month following ART initiation were used as baseline values. The mean value was computed when the two results were obtained within 1 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 (OIs), including tuberculosis (TB), Cryptococci infection and other comorbidities, always need to be looked for and managed in clinical assessment for Immune Reconstitution Inflammatory Syndrome (IRIS), toxicity, etc. Clinical assessment: socioeconomic 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 Zidovudin (AZT), and at every visit, conduct screening for TB.
- Hgb is more commonly monitored in patients with symptoms of anaemia, and those on cotrimoxazole therapy. In addition, the use of zidovudine, which commonly caused anaemia, has been discontinued and as a result, Hgb is not routinely monitored.
- Lab assessment: baseline CD41, Complete Blood Count (CBC), Alanine Aminotransferase (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 Dolutegravir (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 Efavirenz (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, Hgb at ART initiation, baseline CD4 count, regimen substitute, regimen changes and baseline body mass index (BMI).

Comorbidities included a history of OI, 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 an online supplemental material 2.

Patient and public involvement

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. 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, 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 (18.5–24.9), overweight (25.0–29.9) 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 V.4.2, then exported into Stata V.16 statistical software for further analysis. Descriptive measures such as means, median, IQR, percentage, frequency, 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 bivariable analysis were considered for the multivariable model. Adjusted HRs (aHRs) with a 95% CI 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 (1.16) indicated no meaningful multicollinearity between variables in the multivariable models.

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 girls. 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).

Baseline clinical, laboratory and ART information

At the initiation of ART, 237 (25.5%) of the 928 ALHIV had 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. 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 18.5–24.9) and 1.7% were overweight (BMI 25) (table 2).

Baseline OIs

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%) (online supplemental 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 (online supplemental 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 (online supplemental material 5).

Table 1 Baseline sociodemographic characteristics of adolescents living with HIV receiving antiretroviral therapy 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	590	63.6
15–19 years	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 and 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 Tewahedo 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 relatives (11) and guardian (8).
PMTCT, Prevention of Mother-to-Child Transmission.

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 (figure 2).

The cohort's overall mortality rate was 1.26 (95% CI: 1.04 to 1.53) per 1000 person-months. The overall estimated median mortality time was 4.76 months (95% CI: 4.17 to 5.02, months; figure 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% CI 1.36 to 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 to 0.99). We saw a higher hazard of death in adolescents with widowed parents (aHR: 1.85, 95% CI: 1.01 to 3.56), those without social support (aHR: 2.81, 95% CI: 1.69 to 4.67) and those whose parents had not told them that they are HIV positive (aHR: 2.08, 95% CI: 1.07 to 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 to 4.08) compared with those with normal Hgb (g/l) 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 to 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,

Table 2 Clinical, laboratory and treatment characteristics of adolescents living with HIV receiving antiretroviral therapy (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/mm^3	278	30.0
200–350 cells/mm^3	249	26.8
More than 350 cells/mm^3	401	43.2
WHO clinical staging		
Stages I and II	579	62.4
Stages 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		
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 (OIs)		
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		
Underweight	760	81.9%
Normal	152	16.4%
Overweight	16	1.7%

ART, Antiretroviral Therapy ; CD4, Cluster Of Differentiation 4; WHO, World Health Organization .

95% CI: 1.46 to 6.30). The hazard of death among adolescents with a CD4 count between 200 and 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 to 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 to 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 to 3.95). Furthermore, the risk of death was two times higher among ALHIV who did not know their HIV status (aHR: 2.08, 95% CI: 1.07 to 2.81).

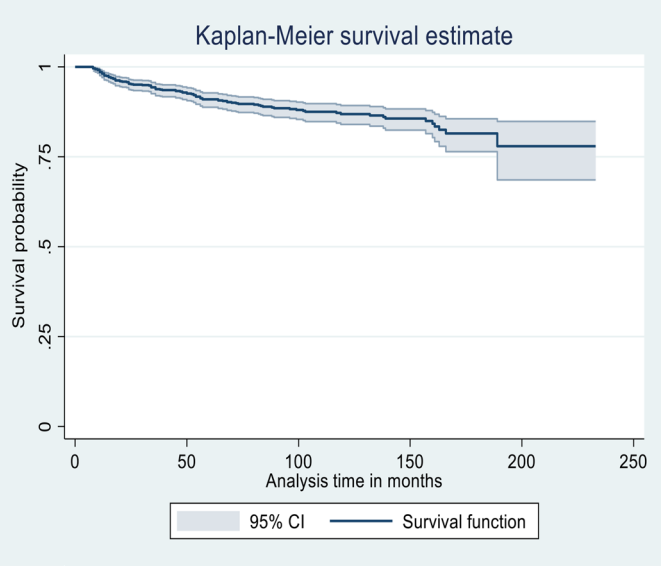

Figure 2 Kaplan-Meier survival curve with 95% CIs of adolescents living with HIV receiving antiretroviral therapy in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020.

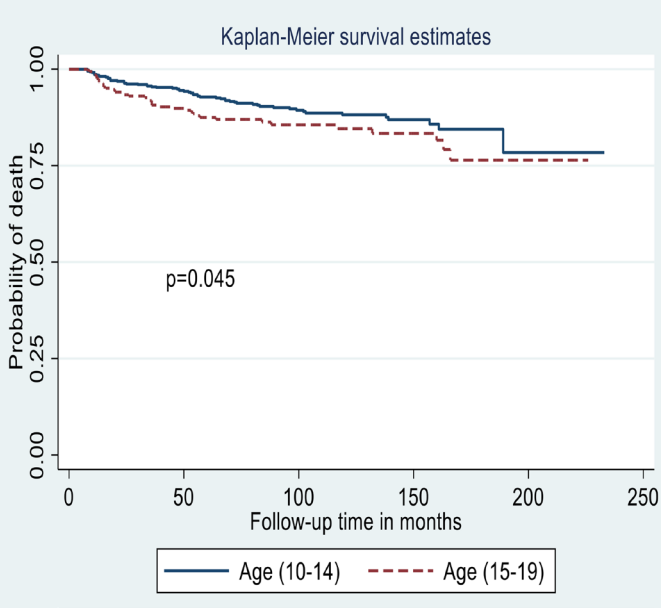

Figure 3 Kaplan-Meier survival curve of adolescents living with HIV receiving antiretroviral therapy in Amhara Region's comprehensive specialised hospitals from January 2005 to June 2020 (n=928) by age.

DISCUSSION

This study aimed to assess the incidence and predictors of mortality among ALHIV receiving ART across the Amhara region of Ethiopia using a multifacility retrospective follow-up approach. With a total follow-up time of 81583 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.[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),[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).[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

Table 3 Bivariable and multivariable Cox regression analysis of mortality predictors among adolescents living with HIV receiving antiretroviral therapy (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 to 1.62)	1.05 (0.68 to 1.61)
Age		
10–14 years old	1	1
15–19 years old	1.49 (1.00 to 2.19)	1.07 (0.60 to 1.90)
Education		
No formal education	5.70 (2.61 to 12.48)	3.27 (1.36 to 7.87)*
Primary education	1	1
Secondary education	1.35 (0.86 to 2.15)	0.99 (0.54 to 1.82)
Higher education	1.44 (0.66 to 3.17)	0.67 (0.27 to 1.64)
Caregiver marital status		
Single	1.98 (1.12 to 3.50)	1.50 (0.78 to 2.84)
Married	1	1
Divorced	3.28 (1.90 to 5.68)	1.89 (1.01 to 3.56)*
Widowed	1.65 (1.01 to 2.71)	1.85 (1.08 to 3.19)*
Hospitals (study setting)		
Dessie CSH	1	**1**
Debre Birhan CSH	6.09 (3.24 to 11.44)	6.54 (2.83 to 15.12)**
Debre Markos CSH	1.93 (0.83 to 4.46)	1.12 (0.40 to 3.09)
Felege Hiwot CSH	6.95 (3.80 to 12.70)	6.31 (2.79 to 14.27)**
UOGCSH	0.62 (0.25 to 1.53)	0.70 (0.40 to 2.83)
Social support		
Yes	1	1
No	5.30 (3.58 to 7.84)	2.81 (1.69 to 4.67)**
Disclosure status		
Yes	1	1
No	4.55 (3.04 to 6.82)	2.08 (1.07 to 2.81)*
Regimen change		
No	1	1
Yes	0.28 (0.18 to 0.44)	0.60 (0.36 to 0.99)*
Baseline haemoglobin level in g/l		
≥10 g/dL	1	1
<10 g/dL	2.67 (1.42 to 5.02)	2.04 (1.02 to 4.08)*
Baseline functional status		
Working	1	1
Ambulatory	0.89 (0.57 to 1.39)	0.64 (0.38 to 1.08)
Bedridden	5.70 (3.47 to 9.38)	3.11 (1.64 to 5.72)**
Baseline WHO clinical staging		
Stage I	1	1

Continued

Table 3 Continued

Variables	CHR (95% CI)	AHR (95% CI)
Stage II	1.24 (0.71 to 2.15)	1.57 (0.88 to 2.83)
Stage III	1.02 (0.57 to 1.81)	1.23 (0.65 to 2.33)
Stage IV	4.79 (2.75 to 8.34)	3.03 (1.46 to 6.30)*
Baseline CD4 count		
> 350 cells/mm^3	1	1
200–350 cells/mm^3	0.55 (0.32 to 0.95)	2.17 (1.08 to 4.18)*
≤ 200 cells/mm^3	0.95 (0.61 to 1.46)	1.49 (0.91 to 2.46)
Cotrimoxazole preventive therapy		
Yes	1	1
No	4.72 (3.01 to 7.41)	1.85 (1.07 to 3.22)*
Ionised preventive therapy		
Yes	1	1
No	2.69 (1.82 to 3 .97)	0.90 (0.55 to 1.46)
ART adherence		
Good/fair	1	1
Poor	4.60 (2.72 to 7.80)	2.24 (1.27 to 3.95)**
Opportunistic infection at baseline		
No	1	1
Yes	2.77 (1.84 to 4.16)	1.94 (1.19 to 3.14)**
Baseline body mass index		
Underweight	1	1
Normal	1.40 (0.87 to 2.27)	1.17 (0.74 to 1.96)
Overweight	1.45 (0.46 to 4.61)	1.88 (0.57 to 5.63)

Significant at p<0.05, *significant at p<0.01 and **significant<0.001.

CSH, Comprehensive Specialised Hospital; UOGCSH, University of Gondar Comprehensive Specialised Hospital.

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 with other cohorts (50.9% of samples). The high proportion of boys 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 SSA settings, particularly as our cohort was disproportionately urban and relatively well educated compared with 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,[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 SSA 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 postsecondary levels of education contrasts with findings from the USA 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 boy 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.[36] 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 two times as high among ALHIV from widowed parents, which is consistent with a study in the USA reporting that mortality is higher in ALHIV from divorced and separated families.[68] 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.[69 70] 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.[71]

The risk of death was higher among ALHIV with no social support compared with their counterparts. This finding is supported by studies from a range of low-income and middle-income countries, including the USA and Uganda,[24 72 73] 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.[73–75] 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,[76] 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-income and middle-income countries indicated that ALHIV and PLHIV with low Hgb (g/l) risk of increased mortality.[30 36 65 77] Additionally, studies have found an association between CD4 cell count, viral load and Hgb level.[78] 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.[79] This suggests that strengthening the routine monitoring of Hgb (g/l) levels (eg, 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 were bedridden at baseline, consistent with previous Ethiopian studies[80] 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,[36 80] India[65] and South Africa,[30] as well as international guidelines.[81] The negative association between CD4 counts and mortality that was identified has been well-established in previous studies conducted globally,[35] in Europe[64] and in Ethiopia.[36] However, the association we found was relatively weak: 95% CI 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 82] The presence of OIs may indicate low CD4 cell counts, decreased humoral and cellular immunity and possibly AIDS.[83 84] 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.[85] 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.[86]

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,[87] 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.[88] 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.[87] 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 (g/l). Such conditions improve patient treatment outcomes and a lower mortality rates.

Unusually, this study found that CD4 counts of less than 200 cells/mm^3 are not associated with HIV-related mortality, while CD4 counts between 200 and 350 cells/mm^3 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.[89]

The current study found a lower mortality rate among ALHIV who underwent an ART regimen change compared with their counterparts. Conversely, a prior Ethiopian study found that ALHIV who underwent an ART regimen change had a higher death rate.[90] 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.[91 92]

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 two times higher among ALHIV who did not know their HIV status, which is consistent with a study finding in Kenya.[93] Besides, adolescents who are aware of their HIV infection status have better HIV treatment outcomes.[94 95] WHO promotes disclosing HIV infection status to adolescents and suggests informing younger children sequentially to accommodate cognitive and emotional development.[96] 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.[97]

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 used the online 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 programmes 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 Hgb (g/l) 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 (g/l) and OIs.

Significant differences in treatment outcomes (mortality rates) between the studied health institutions would suggest that policy-makers 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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