

Incidence and Predictors of ART Treatment Failure among Children in East Gojjam, Ethiopia: A 15-Year Retrospective Cohort Study

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Abstract

Background: Human immunodeficiency virus (HIV) infection remains a major public health challenge for children in Ethiopia. Despite the rapid scale-up of antiretroviral therapy (ART), data regarding pediatric treatment failure remain limited. Therefore, this study assessed the incidence and predictors of ART treatment failure among children receiving first-line ART in East Gojjam, Ethiopia.

Methods: A fifteen-year retrospective follow-up study was conducted among 538 randomly selected under-15-year-old children who started antiretroviral medication between September 11, 2006, and September 10, 2021, in multicentre health facilities in East Gojjam.

Medical records were reviewed, and the required data were extracted using pretested structured checklists. The data were entered, cleaned, and analysed using SPSS version 25. The Kaplan–Meier survival curve, the log-rank test, and the scaled Schoenfeld residual test were applied for analysis.

Results: Of the 538 medical records reviewed, 114 children (21.2%; 95% CI: 17.8–24.9) experienced treatment failure. Among these, 85 (74.6%) were virological failures, 19 (16.7%) were immunological (CD4) failures, and 10 (8.8%) were clinical failures. The overall incidence density of treatment failure was 4.53 per 1,000 person-months, with a mean survival time of 43.8 months (95% CI: 37.65–50.89) until the failure event. Significant predictors of treatment failure included WHO clinical stage III/IV (AHR = 3.0; 95% CI: 1.3–7.1), lack of regimen change (AHR = 4.4; 95% CI: 1.7–11.7), poor ART adherence (AHR = 6.6; 95% CI: 4.11–10.66), stunting (AHR = 2.2; 95% CI: 1.43–3.44), and use of a nevirapine-containing regimen (AHR = 2.72; 95% CI: 1.13–6.54).

Conclusion: The incidence of ART treatment failure among the study participants was significantly high. WHO clinical stage III/IV, poor adherence to ART, regimen not changed, and nevirapine-containing regimen were all significant predictors of ART failure. Hence, by providing intensive care and close monitoring to higher-risk patients, a timely change in regimen was recommended. [*Ethiop. J. Health Dev.* 2026; 40(1)]

Keywords: Incidence, Predictors, ART treatment failure, Ethiopia

Introduction

By the end of 2024, an estimated 39.9 million people worldwide were living with HIV, including 1.4 million children under the age of 15. During that year, 1.3 million new infections were reported, along with 630,000 AIDS-related deaths (1). In Ethiopia, while specific data on the number of children living with HIV in 2023 is limited, the country reported 7,400 new HIV infections during that period (2).

Although antiretroviral therapy (ART) significantly improves the quality of life of PLWH, treatment failure is associated with a high risk of mortality following the initiation of ART. ART failure in children is classified as virologic, immunologic, clinical failure, or a combination of the three (3).

Children living with HIV are particularly vulnerable to adverse outcomes if they do not receive timely ART and regular medical supervision (4–6). Pediatric ART failure is influenced by various factors, including dependence on caregivers for healthcare access, challenges with adherence, regimen-related issues, nutritional status, and comorbidities, among others (7).

Globally, pediatric ART failure rates range from 19.3% to over 32% in resource-limited settings (8). In African countries, including Ethiopia, reported prevalence ranges from 15% to 57% (9–14). A recent meta-analysis

estimated the pooled prevalence of treatment failure among children in Ethiopia at 12.34% (10).

Studies have consistently identified poor ART adherence, advanced WHO clinical stage, opportunistic infections, baseline regimen type, and regimen changes as significant predictors of treatment failure (10–12, 15). Notably, children receiving nevirapine (NVP)-based regimens were approximately twice as likely to experience treatment failure compared to those on efavirenz or protease inhibitor-based regimens (12, 16).

Although this study includes children who received first-line ART regimens that are no longer standard of care, the findings remain highly relevant to current practice. Understanding predictors and timing of treatment failure in previous regimens provides critical lessons for optimizing the implementation of current and newer ART regimens. Many risk factors, including poor adherence, advanced WHO stage, and stunting, remain significant determinants of ART failure regardless of the regimen type. Addressing these persistent factors is essential to improving outcomes within updated treatment protocols (10–12, 39).

In Ethiopia, the 2019 pediatric ART guidelines introduced updated recommendations for regimen selection, monitoring, and the management of treatment failure. Notably, the guidelines emphasize

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early transition to integrase strand transfer inhibitor (INSTI)-based regimens—specifically dolutegravir (DTG)—for children experiencing failure on older NVP-based regimens. Furthermore, the guidelines advocate for more frequent viral load monitoring to facilitate earlier detection of failure. These protocols represent a significant shift from previous standards, which relied primarily on clinical and immunologic criteria and offered limited options for regimen switching.

Despite these advancements, limited data exist regarding the rate and determinants of ART failure among children in East Gojjam, particularly in the context of the 2019 guideline implementation. Therefore, this study was designed to determine the incidence and predictors of ART failure among children receiving treatment at public health facilities in this region. The findings provide updated evidence to inform clinical practice and programmatic interventions aimed at improving pediatric HIV outcomes.

Methods

Study design, period, and setting

A multicentre facility-based retrospective follow-up study was conducted from September 11, 2006, to September 10, 2021, to assess the incidence and predictors of treatment failure at public health facilities in the East Gojjam Zone. The Zone is located 300 kilometres from Addis Ababa, the capital of Ethiopia, and has a total population of 2,719,118 and 632,353 households.

The health infrastructure of the Zone comprises 423 health posts, 102 health centres, 9 primary hospitals, one general hospital, and one referral hospital. Of these, only 34 health facilities provided ART services for a total of 903 HIV-positive children in 2021; 11 health facilities (5 hospitals and 6 health centres) were randomly selected as study sites. Specifically, Debre-Markos Referral Hospital, Shegaw Motta General Hospital, Lumame Primary Hospital, Bichena Primary Hospital, Mertule Mariam Primary Hospital, Debre Markos Health Centre, Dejen Health Centre, Mertule Mariam Health Centre, Lumame Health Centre, Bichena Health Centre, and Amber Health Centre were included as study sites.

Study population

The study population comprised all HIV-positive children under the age of 15 who started ART at East Gojjam Zone. Children who started ART between September 11, 2006, and September 10, 2021, and had been on treatment for a minimum of six months were eligible for inclusion. Conversely, children were excluded if their medical records contained incomplete baseline information, such as missing data on age, sex, address, type of caregiver, CD4 count, hemoglobin level, or the date of ART initiation.

Sample size determination and sampling procedure

The sample size was calculated using the Epi Info version 7 software's double population proportion difference formula. This took into account severe underweight, severe wasting, haemoglobin <10 g/dl, CD4 count or % below the threshold, and WHO

clinical stage III/IV from previously conducted studies (17, 18). The final and maximum sample size of 558 individual charts was provided by the sample size that we calculated based on the CD4 count or percentage below the threshold, considering the following assumptions: a percentage of exposed (26%) and non-exposed (16%), a ratio of one to one exposed to non-exposed (1:1), a 95% confidence level, a 1.63 hazard ratio, and 80% power. Medical records were arranged for all 903 children under 15 years of age who began ART between September 11, 2006, and September 10, 2021, at the 11 selected health facilities. Following a proportionate allocation of the 558 study participants to each study site, data were extracted using a basic random sample approach from the records of each enrolled child over a 15 year period.

Variables

The incidence rate of ART failure and time to ART failure were the primary dependent variables. The independent variables encompassed socio-demographic, laboratory, and clinical characteristics. In addition, socio-demographic variables of parents/caregivers, including residence, marital status, occupation, age, sex, and HIV serostatus, were included. Furthermore, WHO clinical stage, CD4 count, haemoglobin level, functional status (for ≥ 5 years), developmental status (for <5 years), opportunistic infection, prophylaxis therapy (CPT and INH), duration of ART treatment, type of ART regimen, pharmacological adverse effects, adherence to ART, and nutritional status (wasting, stunting, underweight and BMI for age) were considered predictor variables.

Data collection tool

The data extraction tools were developed using the standardized ART entry and follow-up formats provided by the Federal Ministry of Health

The data were collected from children's charts and electronic databases by data collectors using an Excel spread sheet and subsequently transferred to SPSS version 25 and STATA Version 14 for final analysis.

Data quality control

To insure data quality, the information was gathered by eleven nurses who had been trained in comprehensive HIV care and were involved in patient follow-up. A pretest was conducted on 10% of the sample at Debre Work Primary Hospital to validate the data extraction tool. Both the data collectors and supervisors received a one-day training session on the data collection tool and procedures. The of the data was also ensured by using the right data gathering instrument and maintaining constant oversight throughout the process. Checklists were assigned codes. ON a daily basis, the data collectors and supervisors examined all the obtained data to ensure completeness and accuracy.

Data processing and analysis

The collected data were checked for completeness and consistency, and then coded and recorded in SPSS version 25. The data were subsequently cleaned and analysed using STATA version 14. Descriptive

statistics, including frequencies and summary statistics (mean, standard deviation, and percentage), were computed. Nutritional status was determined using WHO AnthroPlus version 1.0.4 software to generate Z-scores, including weight-for-age (WAZ), height-for-age (HAZ), and weight-for-height/BMI-for-age (WHZ/BAZ).

The Kaplan–Meier survival curve was used to estimate the time to develop treatment failure after the initiation of antiretroviral therapy. Log-rank tests were applied to compare survival curves of categorical predictor variables. To determine the effect of the predictors on the duration of ART failure, a bivariable Cox regression proportional hazard model was fitted for each explanatory variable. Variables with p-values ≤ 0.25 in the bivariate analysis were included in the multivariable Cox proportional hazard regression model.

The Hazard Ratio (HR) with a 95% Confidence Interval (CI) was used to measure the strength of the association, and a p-value < 0.05 was considered statistically significant. The Cox proportional hazard model assumptions were verified using the scaled Schoenfeld residual test (where a p-value > 0.05 indicated the assumption was met) and graphically via log-log survival plots. Finally, the overall model fitness was assessed using the Cox–Snell residual test.

Operational definitions

In this study, “Event” was considered the time to treatment failure, treatment failure, and its predictors.

Censoring was other than the event (transfer outs, defaulters, deaths, patients who did not develop treatment failure during the study period, or switchers due to factors other than first-line ART failure). The time to the occurrence of an event or censored cases was measured in months. **Disclosure** is defined as when the child knows his/her HIV and treatment status, irrespective of the source. **Duration of ART**: the time between the start date of ART and the last contact date with the health facility during data collection.

Undernutrition: If the child has one height/age < -2 , weight/age < -2 , weight/height < -2 , or BMI for age < -2 standard deviations according to the WHO curve. **The functional status** was defined as working (playing, doing normal activities, and going to school),

ambulatory (able to perform daily living activities), or bedridden (not able to perform daily living activities) (23). **Adherence**: taking the right ARV medication at the right dose at the right time every day and exactly as long as they were prescribed for life. were classified as follows: good if adherence was $\geq 95\%$ (1 dose of 30 doses or 2 doses of 60 dose missed), fair if adherence was between 85 and 94% (2 and 4 doses of 30 dose or 4 and 9 doses of 60 dose were missed), and poor if adherence was $< 85\%$ (≥ 5 dose of 30 dose or ≥ 10 dose of 60 dose was missed) (19). **Developmental status** was defined as appropriate (if a child has reached a milestone for age), delay (if the child fails to reach a milestone for age) or regression (loss of appropriate developmental milestones due to illness) (19).

Treatment failure: Occurrence of virologic, immunologic, or clinical failure while on first-line ART, as defined by the WHO guidelines (39).

Virologic failure: A confirmed viral load $\geq 1,000$ copies/mL based on two consecutive measurements within 3 months, after at least 6 months of ART, with adherence support between measurements (39).

Immunologic failure: Persistent CD4 count below age-specific thresholds (e.g., < 200 cells/mm³ for children ≥ 5 years, or a fall to baseline levels) after at least 6 months of ART (39).

Clinical failure: Occurrence or recurrence of WHO stage 3 or 4 conditions after at least 6 months of ART (39).

Defaulter / Loss to follow-up (LTFU): A child who has not attended the ART clinic for ≥ 3 months after the last scheduled visit without documented transfer out or death (39).

Results

Socio-demographic characteristics of children on ART

A total of 538 (96.4%) records of children with HIV were included in the final analysis. Of these, 285 (53.0%) were males, the mean age was 7.25 (95% CI=6.95-7.58) years, and 398 (74%) of the children were older than five years. The majority, 389 (72.3%), were urban residents, 378 (70.3%) were living with their parents, and almost half of them had both mothers and fathers alive (274, 50.9%) (Table 1).

Table 1: Socio-demographic characteristics of children on ART and their parents/caregivers at public health facilities in East Gojjam Zone, Northwest Ethiopia, 2006–2021 (n = 538).

Variable	Category	Frequency	Percent
Sex of children	Male	285	53.0
	Female	253	47.0
Age of children	≥ 5 years	398	74.0
	1 to <5 years	128	23.8
	< 1 year	12	2.2
Relation of child to care giver	Parent	378	70.3
	Uncle/aunt	22	4.1
	Sister/brother	29	5.4
	Grand parent	35	6.5
	Guardian	73	13.6
Religion of parent /caregiver	Muslim	26	4.9
	Orthodox	452	85.4
Residence	Urban	389	72.3
	Rural	149	27.7
Marital status of caregiver	Married	318	59.1
	Single	38	7.1
	Widowed	118	21.9
	Divorced	64	11.9
HIV status of parent/caregiver	Both positive	163	30.3
	Mother positive	266	49.4
	Father positive	32	5.9
	Father negative	9	1.7
	Unknown	42	7.8
Parent status	Both alive	274	50.9
	Only mother alive	83	15.4
	Only father alive	49	9.1
	Both died	130	24.2
	Un known	2	0.4

Clinical, laboratory, and ART baseline characteristics

At the time of ART initiation, 318 children (59.1%) had opportunistic infections. The mean and median haemoglobin levels were 12.059 mg/dl and 12.2 mg/dl (95% CI=11.901, 12.217), respectively. In terms of WHO clinical stage, 281 (52.2%) patients were in stage

I or stage II, and 73.7% of the children who were enrolled in ART had a viral load lower than 1000 copies/ml at baseline. With respect to developmental status, 383 (71.1%) were appropriate for their age. At the time of ART initiation, 391 (72.7%) children's CD4 count was below the threshold. A total of 197

(36.6%) of the children-initiated ART based on low CD4 count eligibility criteria (Table 2).

Table 2: Baseline clinical and immunological characteristics of children on first-line ART in East Gojjam Zone Public Health Facilities, Ethiopia, 2006-2021 (n=538)

Variable	Category	Frequency	Percent
Opportunistic infections	Yes	318	59.1
	No	220	40.9
Types of opportunistic infections	Diarrhoea	65	20.4
	Candidiasis	53	16.7
	Pneumonia	54	17.0
	Tuberculosis	65	20.4
	Skin Rash	53	16.7
	Herpes Zoster	28	8.8
	Functional status \geq 5 years (N=398)	Working	207
Ambulatory		168	42.2
Bed ridden		23	5.8
Developmental status < 5 years (N=140)	Appropriate	100	71.4
	Delayed	36	25.7
	Regressed	4	2.9
WHO staging	Stage I/II	281	52.2
	Stage III/IV	257	47.8
Haemoglobin level	\geq 10 mg/dl	269	50
	< 10 mg/dl	269	50
CD4 count	Above threshold	150	27.9%
	Below threshold	388	72.1%
Viral load	< 1000 copies/mL	315	58.6
	\geq 1000 copies/mL	223	41.4
ART eligibility criteria	WHO staging	70	13
	CD4 count	197	36.6
	Both clinical and CD4	190	35.3
	Test and treat all	81	15.1

Follow-up Data on ART-Related Factors and Other Medications

The most common baseline regimen was **4c (AZT-3TC-NVP)**, utilized by 45.5% of the patients, followed by **4a (d4t-3TC-NVP)** at 22.5%. Overall, the majority of patients (393 [73.0%]) were on a nevirapine-based regimen. A significant majority of the children (92.6%) received prophylaxis, with 93% of those receiving Co-

trimoxazole Preventive Therapy (CPT). During the study period, only 108 (20.1%) patients changed their regimen; the primary reason for switching was drug stock-outs (28.7%). Regarding treatment adherence, 364 (64.3%) patients were found to have poor adherence. The nutritional status of the participants revealed that 86 (16.0%) children had stunted growth. Among children under five years of age, the prevalence of malnutrition was as follows: 94 (17.5%) experienced

wasting, 125 (23.2%) were underweight, and 86 (16.0%) were stunted (Table 3).

Table 3: Follow-up data on factors related to ART and other medications among children on first-line ART in East Gojjam Zone Public Health Facilities, Ethiopia, 2006-2021 (n=538)

Variable	Category	Frequency	Percent
Baseline regimen	4a(d4t-3TC-NVP)	121	22.5
	4b (d4t-3TC-EFV)	37	6.9
	4c (AZT-3TC-NVP)	245	45.5
	4d (AZT-3TC-EFV)	66	12.3
	1e (TDF-3TC-EFV)	13	2.4
	1 (ABC-3TC-NVP)	27	5.0
	1g(ABC-3TC-EFV)	11	2.0
	Other (1c,4i,4j,4g)	18	3.3
Regimen type	Nevirapine-based regimen	393	73.0
	None of the nevirapine-based regimen	145	27.0
Taking prophylaxis	Yes	498	92.6
	No	40	7.4
Type of prophylaxis	CPT	478	96.0
	INH	15	3.0
	Both CPT and INH	5	1.0
Side effect	Yes	24	4.5
	No	514	95.5
Type of side effect	Anaemia	10	41.7
	Toxicity	9	37.5
	Skin Rash	5	20.8
Regimen change	No	430	79.9
	Yes	108	20.1
Reason for drug change	Drug side effect	15	13.9
	Opportunistic infection	20	18.5
	Treatment failure	17	15.7
	Drug stock out	31	28.7
	Drug optimization	25	23.2
Adherence	Good	149	27.7
	Fair	43	8.0

	Poor	346	64.3
Survey end point	Alive	348	64.7
	Dead	31	5.8
	Lost to follow -up	5	0.9
	Transferred out	134	24.9
	Drop out	20	3.7
First line Treatment Failure	Yes	114	21.2
	No	424	78.8
Types of Treatment Failure	Virological	85	74.5
	Immunological	19	16.7
	Clinical	10	8.8
Weight for height/length (< 5 years)	Normal	444	82.5
	Wasted	94	17.5
Weigh for age (<5 years)	Normal	413	76.8
	Under weight	125	23.2
Height for age (< 5years)	Normal	452	84.0
	Stunted	86	16.0
Weight for age (age < 10 years)	Normal	409	76.0
	Under weight	129	24.0
Body mass index for age (\geq 5 year)	Normal weight	452	84.0
	Thinness	86	16.0
Height/length for age (<15 years)	Normal	445	82.8
	Stunted	93	17.2

Abbreviations of ARV:d4t – Stavudine, 3TC – Lamivudine, NVP – Nevirapine, EFV – Efavirenz, AZT – Zidovudine, TDF – Tenofovir disoproxil fumarate, ABC – Abacavir. 1e (TDF–3TC–EFV), 4i – ABC + 3TC + NVP, 4j – AZT + 3TC + NVP, 4g – AZT + 3TC + EFV.

Incidence and Survival Status of Treatment Failure

In this study, 538 participants were followed for a total of 15 years, with follow-up durations ranging from a minimum of 6 months to a maximum of 180 months. This resulted in a total of 81,295 child-months of observation, with mean and median follow-up times of 43.6 and 37 months, respectively. Out of the 538 participants, 114 (21.2%) experienced treatment failure (cases), while 424 (78.8%) were censored. Among the censored participants, 342 (63.6%) were alive and on follow-up, 137 (25.5%) had transferred out, 34 (6.3%) died, 20 (3.7%) dropped out, and 5 (0.9%) were lost to follow up. Regarding the type of treatment failure, 85 (74.6%) were virological, 19 (16.7%) were immunological, and 10 (8.8%) were clinical failures (Table 3). The cumulative incidence of treatment

failure was 21% (95% CI: 17.7-24.7), and the overall treatment failure incidence density rate (IDR) in the study was 4.53 per 1000 person-months. This study observed that the highest incidence of treatment failure occurred during the intervals of 10–11 months, 24–25 months, and 108–109 months after initiating ART. As the survival time increased, the hazard of treatment failure also showed an upward trend (Figure 1).

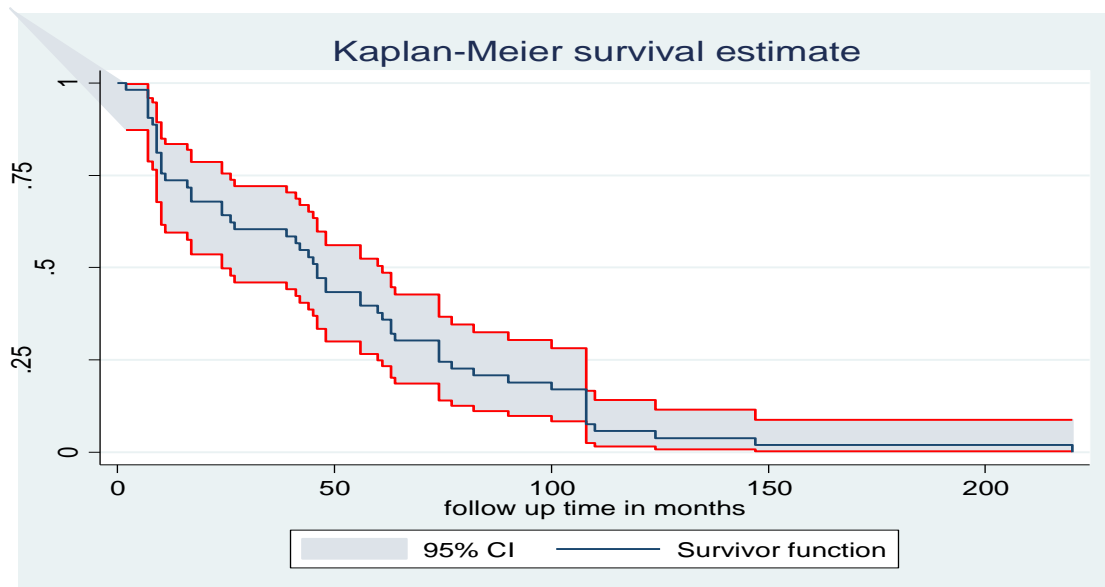


Figure 1: The overall Kaplan–Meier survival estimates for time to treatment failure based on duration of ART (with 95% CI) in East Gojjam Zone public health facilities, North West Ethiopia, 2022.

Bivariate and multivariate Cox proportional hazard analyses

In the bivariate analysis, children in WHO clinical stage III/IV demonstrated shorter survival compared with those in stage I/II. The mean survival time was 52.4 months (95% CI=41.70, 63.08) for WHO stage I/II and 38.7 months (95% CI=30.66, 48.82) for WHO stage III/IV (P value =0.04).

Children with stunted nutritional status had also experienced shorter survival times than those with normal nutritional status. The mean and median survival times of 36.3 months (95% CI=29.292, 43.216) and 31.0 months (95% CI=19.603, 42.397), respectively, versus 51.7 months (95% CI= 41.004, 62.340) and 44.0 months (95% CI=35.609, 52.391) (p value =0.012).

Adherence levels significantly impacted survival. Participants with poor adherence had shorter survival times than those with fair or good adherence. Specifically, the mean survival times were 26.2 months (95 % CI: 18.97, 33.41) for poor adherence and 46.2 months (95% CI: 28.98, 63.46) for fair adherence, while the median survival time for the good adherence group was 48.6 months (95% CI: 40.06, 57.21) (p = 0.003).

Interestingly, children whose regimen was never changed had shorter survival times than those whose regimen was modified, with mean survival times of 36.5 months (95% CI: 29.90, 43.11) and 50.7 months (95% CI: 40.11, 61.27), respectively (p = 0.019\$). This indicates that prolonging the initial regimen was more hazardous for treatment failure than switching regimens. The mean duration of treatment on the initial regimen was 42.1 months. Finally, children on a nevirapine-based regimen had a shorter mean survival time (39.2 months) than those on alternative regimens (44.2 months) (p = 0.043).

Predictors of ART treatment failure

A Cox proportional hazard regression model was used to examine any associations between baseline factors and the probability of ART failure.. In the bivariable analysis, the child's sex, baseline viral load, OI (before and during the follow-up) , disclosure status, baseline regimen, duration of ART, use of prophylaxis, CD4 count, WHO clinical stage, adherence level, height for age, and the treatment guidelines utilized were all eligible for multivariate Cox regression analysis

Upon multivariable analysis, WHO stage, ART adherence, height-for-age, regimen change, baseline regimen, and the treatment guideline utilized remained significant predictors of ART failure (Table 4).

Upon multivariable analysis, WHO stage, ART adherence, height-for-age, regimen change, baseline regimen, and the treatment guideline utilized remained significant predictors of ART failure (Table 4).

The risk of ART failure was three times higher among children with WHO stage III/IV disease compared with those in stage I/II (AHR = 3.0; 95% CI: 1.3–7.1)

Regarding treatment adherence, children with poor adherence to ART treatment had a 6.6 times greater risk of treatment failure than did their counterparts (AHR= 6.6, 95%CI =4.11, 10.66). Furthermore, children with fair adherence were 2.2 times more likely to experience treatment failure than those with good adherence.

In addition, the risk of ART failure was 2.2 times greater in stunted children (HFA-2 Z score) than in their peers (AHR=2.2, 95% CI=1.43, 3.44). Regarding regimen changes, children whose regimen was not changed were 4.4 times more likely to experience ART failure than those whose regimen was changed (AHR 4.4, 95% CI 1.7-11.7). Children treated according to

the previous treatment guidelines were 1.5 times more likely to experience ART failure than were those treated according to the new treatment guidelines (AHR=1.5, 95% CI=1.20, 2.273). Similarly, children who received the nevirapine-based regimen were 2.72

times more likely to experience ART treatment failure than children who received the non-nevirapine treatment regimen (Table 4).

Table 4: Cox regression analysis of predictors of ART failure among children on ART in East Gojjam Zone public health facilities, North-western Ethiopia, 2022

Variables	Survival status		AHR (95%CI)
	TF, N (%)	Censored, N (%)	
Age			
<1yer	3(2.63)	9(2.1)	1
1-5 years	30(26.3)	97(22.9)	1.2 (0.388, 3.924)
≥5 years	81(71.1)	318(75)	0.677(0.443,1.034)
Residence			
Urban	83(72.8)	306(72.2)	1
Rural	31(27.2)	118(27.8)	0.679 (0.443, 1.041)
OI during follow-up			
Yes	100(87.7)	218(51.4)	2.5 (1.0, 6.0)
No	14(12.3)	206(48.6)	1
WHO clinical staging			
Stage I and II	24(21.0)	168(39.6)	1
Stage III and IV	90(79.0)	256 (60.4)	3.0 (1.3, 7.1) *
CD4 count or percent			
Below the threshold	51(44.7)	337(79.5)	4.4 (1.7, 11.7)
Above the threshold	63(53.30)	87(20.5)	1
Haemoglobin level			
<10 g/dl	87(76.3)	182(42.9)	3.1 (1.4, 6.7)
≥10 g/dl	27(23.7)	242(50.1)	1
Change of regimen			
Yes	15(13.2)	289(68.2)	1
No	62(86.8)	135(31.8)	4.4 (1.7, 11.7) *
Adherence			
Good	75(65.8)	74(17.5)	1
Fair	18 (15.8)	25(5.9)	2.2(1.13,4.20)
Poor	21(18.4)	325(76.7)	6.6(4.11,10.66) *
Underweight			
Normal	68 (59.6)	278(65.6)	1
Moderate (WAZ <-2)	50(43.9)	65(15.3)	2.0 (0.8, 4.7)
Severely (WAZ < -3)	33(28.5)	96(22.6)	1.2 (0.4, 3.3)
Stunting			
Normal	58(50.9)	215(50.7)	1
Stunted (HAZ < -2)	56(49.1)	209(49.3)	2.2 (1.43, 3.44) *
Treatment guideline			
Old	71(62.8)	272(64.2)	1.5(CI=1.20,2.27) *
New	42(37.2)	152(35.8)	1
Baseline regimen			
Non nevirapine	34(29.9)	153(36.1)	1
Nevirapine	80(70.1)	271(63.9)	2.72 (1.13–6.54) *

*Significant predictors in the multivariate analysis, at $p \leq 0.05$

Discussion

This study provides important insights into the predictors and timing of treatment failure among HIV-positive children on antiretroviral therapy (ART), offering valuable evidence to guide planners and decision-makers in implementing interventions to prevent early first-line treatment failure.

There were 114 (21.2%) treatment failures among children who began ART from September 11, 2006, to September 10, 2021. Compared to the UNAIDS cut-off reference range of less than 10%, this rate of treatment

failure was unacceptably high (20). The most common type of failure was virological failure, followed by clinical and immunological failure.

These results are higher than those reported in various regions of Ethiopia, including Addis Ababa (14.1%) (21), the Amhara Regional State (12.19%) (20) and Jimma University Hospital (11.5%) (22). In addition, the pooled prevalence of treatment failure was 15.3% (22).

Moreover, ART treatment failure among children has been reported in other parts of Ethiopia, including the University of Gondar Hospital (18.2%) (23), Black Lion Hospital (22.6%) (24), and Fiche and Kuyu Hospitals (18.9%) (23), which is consistent with our findings. This may be due to similarities in the study period and design.

However, this percentage was lower than reported in Ghana (29%), Tanzania (57%), Uganda (29%), and Mozambique (29%) (25). This difference may be explained by the current study's inclusion of children under 15 years, whereas the other studies included participants up to 18 years. Additionally, the time to diagnosis of treatment failure differed: this study required at least 6 months of follow-up, while the other studies included shorter durations.

In the present study, the first-line ART failure rate was 4.53 per 1000 person-months (95% CI: 3.62–5.65). This rate is greater than the 2.2 per 1000 person-months observed in the Amhara Region, Ethiopia (26).

WHO stage III and IV, poor adherence to ART, stunting, no change in regimen, and poor ART adherence were found to be statistically significant predictors of ART failure.

Children in advanced WHO clinical stages (stages III and IV) were three times more likely than their peers in WHO stages I and II to experience treatment failure during the commencement of ART, similar to the findings of other studies conducted in Mozambique and Uganda (20). Children in advanced WHO clinical stages are more likely to have extensive immune suppression and a higher rate of comorbidities, which increases the chance of ART failure. Furthermore, children with advanced disease may experience drug side effects, particularly in the first six months, complicating disease progression even further (27).

Children with poor adherence to ART regimens had a 6.6 times greater risk of first-line ART failure than did their peers (AHR=6.6, 95% CI= 4.11–10.66). Previous studies conducted in Ethiopia (28), Rwanda (29), Uganda (30), and Tanzania (31) reported similar results. This is because a high degree of sustained adherence is required to suppress viral replication and improve immunological and clinical results, lowering the likelihood of ARV treatment resistance and reducing the danger of HIV transmission. In contrast, poor adherence to antiretroviral therapy (ART) is common in the treatment of HIV-positive children and adolescents due to a variety of factors, including regimens for children, which often require the use of multiple pills with frequent dosing requirements, each with the potential for adverse effects and drug interactions, a limited selection of paediatric formulations, and poor palatability of liquid formulations. Adherence may also be influenced by a child's age and developmental stage, as this age group needs assistance from others to take medication on time and may have difficulty swallowing tablets (19). Another possibility is that poor drug adherence leads to HIV-related viral resistance and, as a result, treatment failure. Furthermore, because children rely on their

caregivers for their care, if the child's progress is poor, caregivers may experience hopelessness, carelessness, and loss as a result of the treatment cascade.

With respect to nutritional status, children with stunted nutritional status were 2.2 times more likely to develop ART treatment failure than were those with normal nutritional status. The findings of studies undertaken in Ethiopia and other African countries were consistent with the current findings (32–34). This could be because stunted children may have had poorer baseline health and ART compliance than normal children. In reality, HIV affects nutritional status on its own, increasing susceptibility to the virus and hastening disease progression in malnourished children (21, 35). Furthermore, stunted children may have had a simultaneous opportunistic infection that caused them to miss out on receiving their medications (36).

In addition, children whose regimens were not changed were 4.4 times more likely to experience ART treatment failure than were those whose regimens were changed. The majority of previous regimens may include adverse effects that lead to advanced disease and complications, which can ultimately lead to death. For example, AZT regimens can lead to anaemia, which exacerbates the progression of the disease (23). This was further confirmed by the fact that the failure rate before 2019 was greater than the rate from 2019 onwards, and children who received NVP-based NNRT had a 2.72-fold greater chance of treatment failure than did those who did not receive nevirapine. This finding was supported by studies conducted in South Africa (37), Uganda and Tanzania (31, 38). This could be because nevirapine produces adverse symptoms such as rash, nausea, fatigue, fever, headache, vomiting, diarrhoea, and abdominal discomfort, which can make it difficult to adhere to a treatment regimen and lead to treatment failure (25).

Finally, children who were treated according to the old guidelines were 1.5 times more likely to experience ART failure compared with those treated under the new guidelines. This finding is supported by the comprehensive National ART Guidelines (2018), which recommend switching nevirapine-based regimens to dolutegravir (DTG)-based regimens for children aged 6 weeks to 10 years and weighing ≥ 20 kg, due to concerns about side effects and treatment failure (22).

However, among those children who developed treatment failure, only 37.2% changed their guidelines to new ones. These findings are consistent with the results of the change in regimen and nevirapine-based regimen use. Ethiopia's phased dolutegravir rollout, which prioritized children with treatment failure and faced operational constraints, likely explains the low regimen-switching rate (22).

Moreover, among children with treatment failure, 71.1% were aged ≥ 5 years, and 73.3% had a viral load < 1000 copies/mL. While these criteria could inform the new guidelines, they may not be practical in routine settings, possibly due to inadequate training for health professionals or drug shortages.

Conclusion

Compared to the UNAIDS cut-off value of 10%, the prevalence of ART treatment failure (21.2%) in this study area was unacceptably high (39). Despite efforts to improve access to ART, the issue of a higher treatment failure rate has recently become a hot topic. Advanced WHO stages, poor adherence to ART, stunting, use of a nevirapine-based regimen, treatment in the old guidelines, and no change in regimen were associated with a greater risk of treatment failure. Therefore, continuous and extensive follow-up, strict adherence to the new treatment guidelines, training of ART clinic staff, a prospective study design, and investigation of the reasons why the majority of children were put on the old guidelines were recommended.

The high rate of pediatric ART failure underscores the need for early identification and close follow-up of high-risk children, strengthened adherence and nutritional support, and timely regimen switching in line with updated guidelines, supported by continuous training of ART clinic staff.

Abbreviations

AHR-	Adjusted Hazard Ratio
AIDS-	Acquired Immune Deficiency Syndrome
ART-	Antiretroviral Therapy
CPT-	Cotrimoxazole prophylaxis
CD4-	Cluster of Differentiation 4 cells
CHR-	Crude hazard ratio
HIV-	Human immunodeficiency viruses
HAART-	Highly active antiretroviral therapy
HAZ-	Height for Age Z score
UNICEF-	United Nations International Children's Emergency Fund
UNAIDS-	Joint United Nations Program on HIV/AIDS
WAZ-	Weight for Age Z score
WHO-	World Health Organization

Declarations

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the **Research Ethics Committee of the School of Nursing, College of Health Sciences, Addis Ababa University**. A waiver of informed consent was granted by the committee because the study was a retrospective review of medical records. All patient data were anonymized during collection and analysis to ensure confidentiality.

Consent for publication: Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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