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Incidence and predictors of treatment failure among children with HIV on first-line antiretroviral therapy in Wolaita zone, Southern Ethiopia: A multicenter retrospective cohort study

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ABSTRACT

Background: Antiretroviral therapy has improved the life expectancy of HIV-positive children. Treatment failure and drug resistance among children with HIV remain major public health concerns despite the rise in ART use. A dearth of evidence exists regarding treatment failure among Ethiopian children from multicenter settings. Therefore, this study sought to assess the incidence and predictors of treatment failure among children with HIV on first-line antiretroviral therapy at health facilities in Wolaita zone, Southern Ethiopia.

Methods: A facility-based retrospective cohort study was conducted from January 1, 2017, to December 30, 2021, at health facilities providing ART in Wolaita zone, Southern Ethiopia. A total of 425 children with HIV on first-line ART were selected using a simple random sampling technique. Data were extracted by reviewing the patient's medical record. The data were entered using epi-data version 4.6 and exported to STATA version 15 for analysis. Both bi-variable and multivariable Cox regression analysis were employed. A p-value of less than 0.05 and a hazard ratio with 95 % CI was used to estimate the association between the predictor factors and treatment failure.

Results: The overall incidence density rate of treatment failure was 3.2 per 1000 person-months of observation (95 % CI: 2.4–4.6). The factors significantly associated with antiretroviral treatment failure were caregiver marital status, single (AHR = 4.86, 95 % CI: 1.52, 15.60), and widowed (AHR = 3.75, 95 % CI: 1.16, 12.11), duration of follow-up (AHR = 4.95, 95 % CI: 1.81, 13.54), and baseline CD4 count (AHR = 4.70, 95 % CI: 1.68, 13.14).

Conclusion: The incidence rate of ART failure among children with HIV was found to be significant. Low baseline CD4 count, short follow-up duration on ART, and having a single or widowed caregiver were significantly associated with antiretroviral treatment failure. Early identification of children with low CD4 count and subsequent initiation of ART should be emphasized by stakeholders working in HIV care programs. Healthcare professionals should pay special attention to and regularly monitor the treatment progress of children who have single or widowed caregivers, and those with shorter duration of follow-ups.

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1. Introduction

The human immunodeficiency virus (HIV) causes acquired immune deficiency syndrome (AIDS), which weakens the immune system and makes the body more vulnerable to secondary and opportunistic infections [1,2]. Globally, 38 million people are estimated to be living with HIV/AIDS by 2020, including 1.7 million children under 15 years old. In Sub-Saharan Africa, two-thirds of all children live with HIV/AIDS [1,3]. As of 2020, 1.5 million people have become newly infected with HIV; of those, 150,000 are children under 15 years of age [1]. AIDS continues to be the biggest cause of death worldwide, killing 680,000 people in 2020, with 99,000 of those being children [4]. Infants and young children infected with HIV have significantly high morbidity and mortality. In the absence of any intervention, up to 52 % and 75 % of children die before the age of two and five years respectively [5,6]. According to the United Nations HIV/AIDS report, Ethiopia has over 700,000 HIV/AIDS patients in 2020. 36,000 of them were children <15 years, with 2800 new cases a year [7].

The world is working on a fast-track strategy to end the AIDS pandemic by 2030 [8]. The Joint United Nations Program on HIV/AIDS (UNAIDS) introduced the 95-95-95 targets in 2014. The goal was to diagnose 95 % of all HIV-positive people, provide ART to 95 % of those diagnosed and attain viral suppression for 95 % of those treated [9]. In 2020, 84 % of people living with HIV worldwide were aware of their status, 73 % were receiving treatment, and 66 % had viral suppression [1]. Ethiopia has enrolled hundreds of thousands of patients in its free combination antiretroviral therapy (cART) program, with overall cART coverage of 73% [10]. Ethiopia adopted the new three-ninety-five-point targets and expanded the program to encompass a substantial number of viral load-testing sites to implement the third ninety-five-point target [3].

Due to the scaling-up of antiretroviral medication, the global new cases of HIV infection and AIDS-related fatalities in Sub-Saharan Africa have decreased [11,12]. In HIV-infected children, ART has a positive effect on their quality of life and their course of treatment [13]. However, as the use of ART increases, medication resistance, and treatment failure remain a problem [14]. Treatment failure can be a virological, immunological, or clinical failure [6,15]. The gold standard for ART monitoring is viral load testing [16,17]. Clinical and immunological criteria are being employed to track treatment failure in resource-limited settings due to cost considerations [12].

In low- and middle-income countries (LMICs), HIV-infected individuals have access to ART, but diagnosis of treatment failure is delayed, resulting in a high mortality rate [5,14]. Globally, treatment failure is the most common reason for ART modification or regimen change [18]. According to studies, treatment failure and frequent drug substitution are significant economic setbacks in Ethiopia because the cost of medications is covered by the government [19].

Several factors such as age, male gender, being orphan, ARV prophylaxis not being available, TB infection at baseline, cART regimen, follow-up duration, poor adherence, WHO clinical stage, and baseline CD4 count were reported to affect antiretroviral treatment failure (ARTF) among HIV infected children receiving ART [2,3,10,14,15,17,18,20–29]. Ethiopian Federal Ministry of Health (FMOH) and some studies reported that children experiencing drug side effects were more likely to change the regimen and develop treatment failure [6,20,30].

Despite the study populations being children, important predictors including immunization and nutritional status were not addressed in previous investigations. Additionally, previous studies focused children in hospital settings and excluded children in health centers and private facilities. Therefore, we sought to assess the incidence and predictors of first-line treatment failure by including children on ART in health centers and private health facilities in Wolaita zone, Southern Ethiopia. The finding will help healthcare practitioners in the early identification and management of first-line treatment failure, which could reduce the workload burden and the economic costs associated with treatment failure. Additionally, it helps to lower child mortality brought on by ART failure.

2. Materials and methods

2.1. Study setting and design

The study was conducted in Wolaita zone health facilities that give ART services. Wolaita Sodo town is the administrative town of the zone and 154 km from Hawassa, the capital of SNNPR, and 330 km southwest of Addis Ababa, the capital of Ethiopia. Based on the 2007 Census conducted by the Central Statistical Agencyof Ethiopia (CSA), the zone has a total population of 2,473,190 with an area of 4208.64 square kilometers. Wolaita zone has a latitude and longitude of 6° 54′N 37°45′E with an average elevation of 1850 m above sea level [31,32].

Data from Wolaita zone health department shows; regarding health facilities, the zone is served by 10 hospitals (1 comprehensive specialized hospital, 2 private general hospitals, and 7 primary hospitals) and 69 health centers. Currently, the zone has 20 health facilities that have been providing ART service (1 comprehensive specialized hospital, 2 private general hospitals, 7 primary hospitals, and 10 health centers). A total of 932 under-15 children were enrolled from January 1, 2017, to December 30, 2021. A facility-based retrospective cohort study was conducted from January 1, 2017, to December 30, 2021.

2.2. Population of the study

All children under 15 years of age, who initiated ART between January 1, 2017, and December 30, 2021, at selected health facilities and took first-line ART for at least six months were included, while children with incomplete medical records (those records lacking information on the date of ART initiation, age, or those records missing more than 20 % independent variables) were excluded from the

study.

2.3. Sample size determination

In this study sample size for the primary objective was determined by using Open Epi statistical software version 3.01 with the following assumptions under consideration; the total number of source population 932, desired degree of precision of 4 %, and 95 % of confidence interval and by taking 22.6 % proportion from a previous study in TASH, Ethiopia [10]. It provided 290 and with the consideration of 10 % incomplete documents, it resulted in 319.

The sample size for the secondary objective (predictors variables) is determined by using double population proportion formula for predictor variables taking a confidence limit of 95 %, power of 80 %, and a ratio of exposed to non-exposed of 1:1. A predictor, the caretaker's HIV status, from the study conducted at TASH, Ethiopia [10] resulted in 425 after considering 10 % for the incomplete document. Since the sample size for the secondary objective was larger than the sample size calculated for the primary objective, 425 is taken as the final sample size for this study.

2.4. Sampling procedure

From 20 health facilities that provide ART services, 9 health facilities (5 hospitals and 4 health centers) were selected randomly based on their number of pediatric ART users. According to the data from the zonal health department, the number of children less than 15 years of age on ART were: Wolaita Sodo Comprehensive Specialized Hospital (76), Dubo St. Mary Hospital (97), Bombe Primary Hospital (60), Tebela Primary Hospital (62), Bittena Primary hospital (58), Areka Health center (56), Boditi health center (61), Sodo health center (72), and Bedessa health center (48). Sample size allocation was based on the formula for proportional allocation ni = (Ni/N)*n. Accordingly, the sample size allocated for WSUCSH = 55; Dubo St. Mary Hospital = 70; Bombe Primary Hospital = 43; Tebela Primary Hospital = 45; Bittena Primary Hospital = 42; Sodo health center = 52; Boditi health center = 44; Areka health center = 40; and Bedesa health center = 34. (Fig. 1).

2.5. Operational definitions

Children: refers to HIV-positive children aged less than 15 years, and initiated cART at ART center [33,34].

ART failure: If any child in the study has one of the three categories of treatment failure (clinical, immunological, and virological failure) [4,26].

Clinical failure: is after 6 months of treatment, when the child has a new or recurrent clinical event indicating WHO clinical stage 3 and 4 clinical conditions except for tuberculosis [4,26].

Immunological failure: when CD4 level is below 100 cells/mm^3 for ≥5 years and below 200 cells/mm^3 for children younger than 5 years at least 2 of CD4 measurements [4,26].

Virological failure: is when the viral load is above 1000 copies/mL following two consecutive viral load tests in three months, with adherence support after the first viral load test [3,4,17].

Anemia: is identified if the hemoglobin level of a child is below 10 mg/dl whereas ≥10 mg/dl is considered non-anemic [35].

Event: occurrence of treatment failure after starting ART.

Censored: children who do not experience the event (treatment failure) at the end of the follow-up period, transferred out, lost to follow-up, and dead.

WHO clinical stage: WHO clinical stage in this study was categorized as non-advanced (WHO stage I and II) and advanced (WHO stage III and IV) [4].

First-line ART regimens: In Ethiopia, the preferred first-line ART regimen for children younger than 3 years is ABC or AZT + 3 TC + LPV/r or as an alternative ABC or AZT + 3 TC + NVP. For children 3 years to less than 10 years and adolescents <30 kg, the regimen

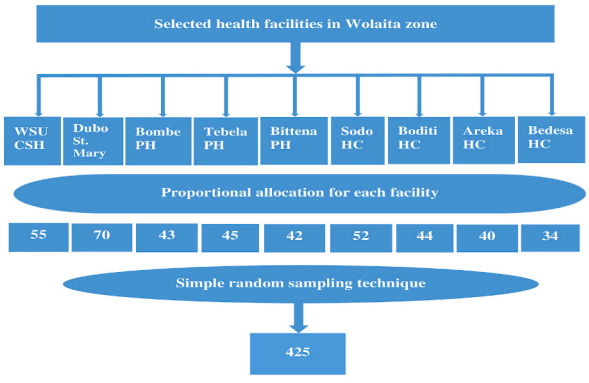

Fig. 1. Schematic presentation of sampling procedure.

AZT/ABC + 3 TC + EFV is the preferred first-line, while ABC or AZT + 3 TC + NVP or TDF + 3 TC + EFV/NVP are alternative first-line regimens, and adolescents (10–19 years) ≥30 kg receive TDF + 3 TC + EFV(FDC) as first-line ART therapy [36].

Routes of transmission: HIV can be transmitted to children either by vertical (perinatal) or horizontal (secondary) transmissions. In vertical transmission, a child can be born with HIV or contract it soon after birth. HIV transmission can happen during gestation, delivery, or while breastfeeding. Horizontal transmission involves contact with semen, vaginal fluid, or blood containing HIV [37–40].

ART Adherence: described as good adherence (≥95 % adherence that is, missing only ≤2 out of 30 doses or missing ≤3 from the 60 doses), fair adherence (85–94 % adherence that is, missing 3 to 5 doses out of 30 tabs or 3 to 9 tablets from 60 doses) and poor adherent (less than 85 % adherence that is, missing ≥6 tablets out of 30 tabs or >9 tabs from 60 tabs) [6,14].

Nutritional status: was categorized as undernutrition for children under 5 years of age, if the weight for age of a child is below −2SD, the standard WHO weight for age z-score. Body mass index (BMI) was used for children ≥5 years, and BMI less than 16 kg/m^2 was categorized as undernutrition otherwise normal [28,41].

Immunization Status: is categorized as appropriate for the age when immunized at the recommended age and up to one month, not appropriate for age if lagged more than one month, and finally as not immunized if delayed for 48 months and above [42].

3. Data collection method

Data extraction tool was prepared after evaluating standard ART monitoring charts, HIV patient medical records, ART registrations, and reviewing certain related literature. Five clinical nurses and two public health officers who had earlier experience were assigned as data collectors and supervisors respectively.

3.1. Data quality assurance

To assure the quality of data, the data collection checklist was pretested on 5 % of the sample size at Gesuba primary hospital. One day of training was given to data collectors and supervisors on the general objective of the study and the contents of the checklist. The collected data were reviewed and checked for completeness before entry. Finally, data completeness reassurance and data cleaning

Table 1
Socio-demographic characteristics of children with HIV at the initiation of ART in Wolaita zone ART providing health facilities from January 2017 to December 2021 (n = 388).

Variables	Category	Frequency	Percentage
Health facility	Hospital	202	52.1
	Health center	186	47.9
Sex	Male	204	52.6
	Female	184	47.4
Age categories	<5	95	24.5
	5–9	151	38.9
	10–14	142	36.6
Residence	Urban	219	56.4
	Rural	169	43.6
Parent status	Both alive	193	49.7
	One parent alive	116	29.9
	Both dead	35	9.1
	Unknown	44	11.3
Caregiver relationship with the child	Parents	300	77.3
	Relatives	41	10.6
	Orphanage	41	10.6
	Guardians/neighbors	6	1.5
Caregiver's marital status	Married	270	69.6
	Widowed	74	19.1
	Single	37	9.5
	Divorced/separated	7	1.8
Caregiver's occupation	Housewife	70	18.1
	Governmental employed	68	17.5
	Farmer	66	17.0
	Non-governmental employed	53	13.6
	Daily laborer	53	13.6
	Merchant	49	12.6
	Unemployed	28	7.3
	Others	1	0.3
Caregiver's educational status	Can't read and write	57	14.7
	primary school (1–8)	134	34.5
	Secondary school (9–12)	86	22.2
	Tertiary	111	28.6
Caregiver's HIV status	Positive	286	73.7
	Negative	90	23.2
	Unknown	12	3.1

were done.

3.2. Data processing and analysis

Data was declared as survival and median survival time with incidence rate was computed. The Kaplan-Meier survival curve with the log-rank test was applied to estimate the median time to treatment failure and to compare survival curves between different categories of explanatory variables respectively.

The proportional hazard assumption was checked graphically (parallel plot of survival) and Schoenfeld residual (global test = 0.142). The magnitude of the association between the predictive factors and treatment failure was estimated in terms of the hazard ratio, at a 95 % confidence interval by using Cox Proportional hazard model. In the bi-variable analysis, the variable with a p-value <0.2 became eligible for multivariable analysis. Finally, variables with p-value less than 0.05 in the multivariable Cox regression were considered independent predictors. Multi-collinearity was also checked and no independent variable was found multi-collinear in terms of tolerance, and variance inflation factor (mean VIF = 1.72). The overall model fitness was checked by the Cox-Snell residual.

4. Results

4.1. Baseline characteristics

4.1.1. Socio-demographic characteristics

The total number of 388 records of children with HIV registered between January 1, 2017, and December 30, 2021, were reviewed, and the rest 37 records of children were excluded due to incompleteness. The median (IQR) age in years of the client at ART initiation was 8(6). About 39 % of the clients were in the age group between 5 and 9 years, and more than half 204(52.6 %) were males.

Table 2
Clinical, immunological, and laboratory characteristics of children with HIV at the initiation of ART in Wolaita zone ART providing health facilities from January 2017 to December 2021.

Variables	Category	Frequency	Percentage
Baseline nutritional status	WFA z-score ≥ −2	67	70.5
	WFA z-score < -2	28	29.5
	BMI ≥16	195	66.6
	BMI <16	98	33.4
Baseline	Non-advanced stage	266	68.6
WHO clinical stage	Advanced stage	122	31.4
Baseline CD4 Count[a]	>200	307	80.2
	≤200	76	19.8
Access to viral load	Yes	354	91.2
	No	34	8.8
Baseline VL[a]	≤1000	187	52.2
	>1000	171	47.8
OI at baseline	No	264	68.0
	Yes	124	32.0
Baseline diarrhea	No	347	89.4
	Yes	41	10.6
Baseline TB	No	350	90.2
	Yes	38	9.8
Baseline meningitis	No	382	98.4
	Yes	6	1.6
Baseline pneumonia	No	336	86.6
	Yes	52	13.4
Baseline candidiasis	No	371	95.6
	Yes	17	4.4
URTI	No	375	96.6
	Yes	13	3.4
Skin disorders	No	351	90.5
	Yes	37	9.5
SAM	No	358	92.3
	Yes	30	7.7
Anemia	No	358	92.3
	Yes	30	7.7
Baseline functional status for ≥5 years children	Working	133	45.1
	Ambulatory	160	54.2
	Bedridden	2	0.7
Baseline developmental status for <5 years children	Normal range	47	51.6
	Delayed	36	39.6
	Regressed	8	8.8

[a] Number of respondents for baseline CD4 count and viral load is less than the total number of respondents (388) due to incomplete data.

Regarding residence, 219(56.4 %) of the participants were from urban areas. Among the participants, the majority 309(80 %) had lived at least with one of their parents. Most of the caregivers 270(69.6 %) were married. Regarding HIV status majority of the caregivers, about three-fourths 286(73.7 %) were HIV-positive (Table 1).

4.1.2. Clinical, immunological, and laboratory characteristics

About two-thirds, 266(68.6 %) of the participant were in non-advanced WHO clinical stage (stage I and II) at the baseline. The majority of participants 307(80.2 %) had baseline CD4 count greater than 200 cells/mm^3. The median (IQR) CD4 count at baseline for the participants was 671(851). More than half of the participants 187(52.2 %) had ≤1000 copies/mL viral load at baseline. About two-thirds, 264(68 %) had no opportunistic infection at baseline (Table 2).

4.1.3. ART and other medication-related characteristics

Among 388 participants, 167(43.0 %) were on a combination AZT-3TC-NVP regimen at cART initiation. More than two third of the participants 303(78.1 %) had good adherence. The majority 377(97.2 %) received CPT prophylaxis, and more than half 228(58.8 %) had received isoniazid prophylaxis. About two-thirds of the patients 261(67.3 %) had changed the first-line regimen and of these, the majority 250(95.8 %) were due to new drug availability. Among the participants, 43(11.1 %) had a history of anti-TB treatment (Table 3).

4.2. Incidence of treatment failure

During the follow-up period, participants were followed for a minimum of 6 months and a maximum of 62 months with a total of 13,136 person-months of observation. The median (IQR) follow-up period in months was 33 (25). 42(10.8 %) had developed treatment failure, from those 1(2.4 %) were clinical, 4(9.5 %) were immunological 10(23.8 %) were virological and 27(64.3 %) were combined. Of those, only 16(38.1 %) changed the regimen (Table 3).

There were 42 incident cases of treatment failure within 13,136 person-months or 1094.7 person-years of observation with an incidence density rate of 3.2 (95 % CI: 2.4, 4.3) per 1000 person-months or 38 per 1000 person-years of observation. The cumulative probabilities of survival at 12, 24, 36, 48, and by the end of the study were 0.99, 0.94, 0.90, 0.85, and 0.77 respectively (Table 4).

The Kaplan-Meier survival curve shows the decline in survival probability was constant across follow-up times (Fig. 2).

To test the equality of survival curves of different categorical explanatory variables, the Mantel Log-rank test was performed. The test statistics showed that there was a significant difference in survival function for different categorical variables (Table 5).

In this study participants who had baseline CD4 count ≤200 had low survival time than their counterparts (Fig. 3).

The study participants who had a shorter follow-up duration (<36 months) had lower survival time compared with children with

Table 3
ART and other medication-related characteristics of children with HIV at the initiation of ART in Wolaita zone ART providing health facilities from January 2017 to December 2021.

Variables	Category	Frequency	Percentage
CPT at initiation	Yes	377	97.2
	No	11	2.8
INH at initiation	Yes	228	58.8
	No	160	41.2
PMTCT intervention	Yes	50	12.9
	No	253	65.2
	Unknown	85	21.9
Duration of follow-up in months	<36	210	54.1
	≥36	178	45.9
Baseline HAART regimen	Non-NVP based	221	57.0
	NVP based	167	43.0
Adherence	Good	303	78.1
	Fair	48	12.4
	Poor	37	9.5
ART side effects	Yes	11	2.8
	No	377	97.2
Drug substitution	Yes	261	67.3
	No	127	32.7
TB treatment history	Yes	43	11.1
	No	345	88.9
Last status	Still on treatment	295	76.0
	Transfer out	44	11.3
	Lost to follow up	36	9.3
	Died	13	3.4
Treatment failure detection	Virologically	10	23.8
	Immunologically	4	9.5
	Clinically	1	2.4
	Combined	27	64.3

Table 4
Life table for treatment failure among HIV-positive children receiving ART at health facilities in Wolaita zone, January 2017 to December 2021.

Interval in months	Number Entering Interval	Number Withdrawing during Interval	Number Exposed to Risk	Number of Terminal Events	Proportion Terminating	Probability of Surviving	Cumulative Probability Surviving at the end of Interval	95 % CI
[0–12)	388	31	372.5	2	0.01	0.99	0.99	0.97, 0.99
[12–24)	355	75	317.5	18	0.06	0.94	0.94	0.90, 0.95
[24–36)	262	80	222	9	0.04	0.96	0.90	0.85, 0.93
[36–48)	173	79	133.5	8	0.06	0.94	0.85	0.78, 0.88
[48–60)	86	61	55.5	5	0.09	0.91	0.77	0.68, 0.83
[60–72)	20	20	10	0	0.00	1.00	0.77	0.68, 0.83

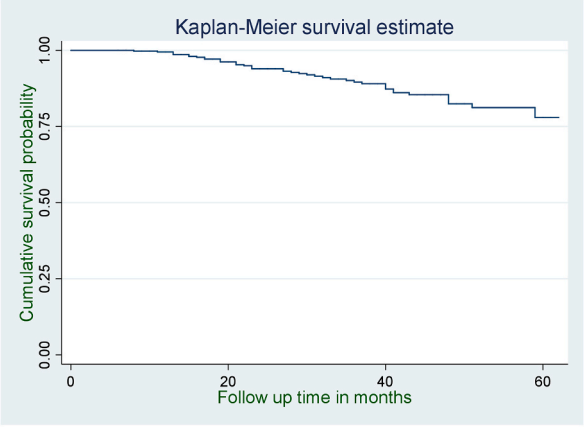

Fig. 2. The overall Kaplan-Meier survival estimate curve of HIV-positive children receiving ART at health facilities in Wolaita zone, January 2017 to December 2021.

Table 5
Log-rank test for equality of survivor functions between categories of covariates.

Variables	Chi-square (X^2)	P value
Parent status	9.31	0.025
Caregiver marital status	16.98	0.001
WHO clinical stage	27.82	<0.001
Baseline CD4 count	45.70	<0.001
Baseline VL	11.96	0.001
OI at baseline	14.37	<0.001
ART adherence	31.19	<0.001
Drug substitution	6.98	0.008
TB treatment history	21.37	<0.001
Follow-up duration	30.74	<0.001

prolonged follow-up duration found statistically significant (Fig. 4).

4.3. Predictors of treatment failure

In the bi-variable Cox regression sex, parent status, caregiver marital status, OI at baseline, ART adherence, drug side effect, drug substitution, treatment with the anti-TB drug, WHO clinical stage, viral load at baseline, baseline CD4 count, and follow-up duration were found statistically significant candidates for multivariable cox regression with p-value <0.2 (Table 6).

In multivariable Cox regression caregiver marital status, follow-up duration, and baseline CD4 count were found to be independent predictors of treatment failure among children with HIV on first-line ART. Accordingly, children with single caregivers were 4.86 times more likely to develop antiretroviral treatment failure as compared to those children who live with married caregivers (AHR = 4.86,

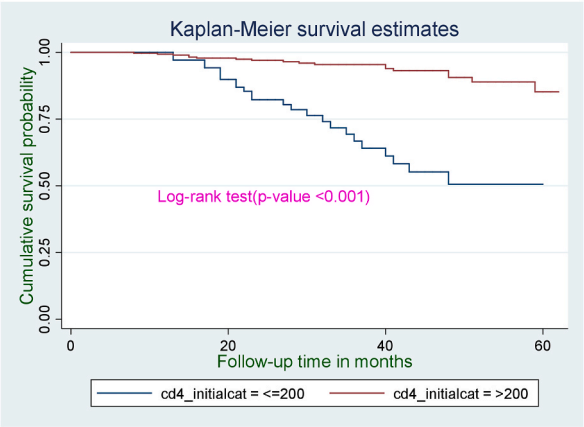

Fig. 3. Kaplan-Meier survival estimate for baseline CD4 count among HIV-positive children receiving ART at health facilities in Wolaita zone, January 2017 to December 2021.

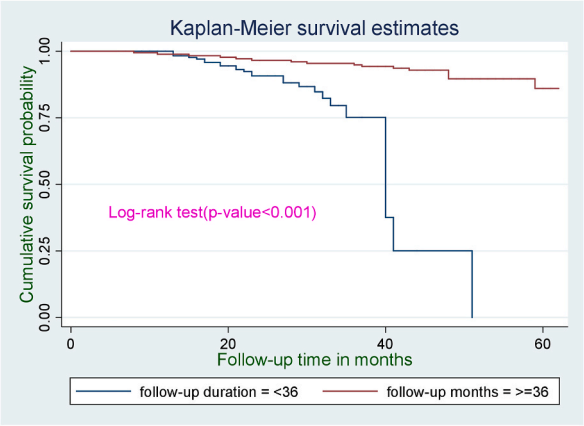

Fig. 4. Kaplan-Meier survival estimate for follow-up duration among HIV-positive children receiving ART at health facilities in Wolaita zone, January 2017 to December 2021.

95 % CI: 1.52, 15.60). Moreover, the risk of antiretroviral treatment failure is 3.75 times higher among children with HIV who live with widowed caregivers than children who live with married caregivers (AHR = 3.75, 95 % CI: 1.16, 12.11). Duration of follow-up on ART is also another significant predictor. Those children who had been on ART for less than 36 months were at a 4.95 times higher hazard for treatment failure than those who stayed for 36 months and longer on ART (AHR = 4.95, 95 % CI: 1.81, 13.54). Moreover, baseline CD4 count ≤200 were 4.7 times at higher risk of antiretroviral treatment failure (AHR = 4.70, 95 % CI: 1.68, 13.14) compared to their counterparts (Table 7).

5. Discussions

The objective of this retrospective cohort study was to assess the incidence and predictors of antiretroviral treatment failure among children with HIV on first-line ART at health facilities in Wolaita zone. The overall incidence density of antiretroviral treatment failure was found 3.2 per 1000 person-months (38 per 1000 person-years) of observation. The finding of the current study is in line with the report from Amhara region referral hospitals (37.7 per 1000 person-years of observation) [14]. It is slightly higher than the study conducted in Myanmar (25 per 1000 person-years of observation) [43]. Similarly, other studies conducted in the Amhara region and Shashemene town showed 26 per 1000 person-years of observation and 19.2 per 1000 person-years of observation respectively [25, 28]. However, it is lower than the finding from a study conducted in Tigray (104.4 per 1000 person-years of observation) [26]. The possible reason for the difference might be due to the difference in person-time of observation, duration of follow-up, and study setting.

The median survival time was 60 months with a cumulative survival probability of 0.77 at the end of the study. This finding was in line with a previous study conducted in Tigray with a survival time of 57.7 months [26]. It is higher than the results of studies conducted in the Ethiopian town of Shashemene, in Uganda, a cohort from Mozambique and Uganda, which found that the median survival times were 30, 26.4, and 12.6 months, respectively [21,24,28]. The fact that the survival time of this study is longer than that

Table 6
Bi-variable Cox regression for predictors of treatment failure among HIV-positive children receiving ART at health facilities in Wolaita zone, January 2017 to December 2021.

Variables	Category	Failure status		CHR (95 % CI)	p-value
		Event	Censored		
Type of health facility	Hospital	24(11.9)	178(88.1)	1.19 (0.64, 2.19)	0.578
	Health center	18(9.7)	168(90.3)	1.00	
Sex	Male	27(13.2)	177(86.8)	1.56 (0.83, 2.94)	**0.167**[a]
	Female	15(8.2)	169(91.8)	1.00	
Age	<5	13(13.7)	82(86.3)	1.20 (0.57, 2.53)	0.627
	5–9	14(9.3)	137(90.7)	0.73 (0.35, 1.51)	0.397
	10–14	15(10.6)	127(89.4)	1.00	
Residence	Urban	27(12.3)	192(87.7)	1.45 (0.77, 2.73)	0.248
	Rural	15(8.9)	154(91.1)	1.00	
Parent status	Both alive	15(7.8)	178(92.2)	1.00	
	one parent alive	16(13.8)	100(86.2)	2.14 (1.05, 4.35)	**0.036**[a]
	Both dead	7(20.0)	28(80.0)	3.46 (1.40, 8.52)	**0.007**[a]
	Unknown	4(9.1)	40(90.9)	1.45 (0.48, 4.37)	0.510
Caregiver's marital status	Single	7(18.9)	30(81.1)	4.74 (1.98, 11.32)	**<0.001**[a]
	Married	21(7.8)	249(92.2)	1.00	
	Divorced	1(14.3)	6(85.7)	1.31 (0.17, 9.87)	0.793
	Widowed	13 (17.6)	61(82.4)	2.49 (1.24, 4.99)	**0.010**[a]
Caregiver's relationship with the child	Parents	31(10.3)	269(89.7)	1.00	
	Relatives	6(14.6)	35(85.4)	1.62 (0.67, 3.89)	0.280
	Guardians/neighbors	1(16.7)	5(83.3)	1.24 (0.17, 9.08)	0.834
	Orphanages	4(9.8)	37(90.2)	1.09 (0.38, 3.09)	0.869
Caregiver's educational status	Can't read & write	3(5.3)	54(94.7)	0.52 (0.14, 1.88)	0.316
	Primary school	17(12.7)	117(87.3)	1.42 (0.65, 3.12)	0.376
	Secondary school	12(14.0)	74(86.0)	1.57 (0.68, 3.64)	0.294
	Tertiary	10(9.0)	101(91.0)	1.00	
Caregiver HIV status	Positive	30(10.5)	256(89.5)	1.00	0.411
	Negative	11(12.2)	79(87.8)	1.34 (0.67, 2.67)	0.825
	Unknown	1(8.3)	11(91.7)	0.80 (0.11, 5.87)	
Disclosure	Disclosed	14(8.5)	151(91.5)	1.00	
	Not disclosed	28(12.6)	195(87.4)	1.43 (0.75, 2.72)	0.273
WFA z-score (<5 years)	Normal	8(11.9)	59(88.1)	1.00	
	Undernourished	5(17.9)	23(82.1)	1.79 (0.58, 5.50)	0.308
BMI (≥5 years)	Normal	17(8.7)	178(91.3)	1.00	
	Undernourished	12(12.2)	86(87.8)	1.33 (0.63, 2.78)	0.454
WHO clinical stage	Non-advanced stage	16(6.0)	250(94.0)	1.00	
	Advanced stage	26(21.3)	96(78.7)	4.67 (2.49, 8.77)	**<0.001**[a]
Baseline CD4 count	≤200 cells/mm^3	24(31.6)	52(68.4)	6.38 (3.44, 11.83)	**<0.001**[a]
	>200 cells/mm^3	18(5.9)	289(94.1)	1.00	
Baseline VL	≤1000 copies/mL	11(5.9)	176(94.1)	1.00	
	>1000 copies/mL	26(16.4)	133(83.6)	3.13 (1.54, 6.36)	**0.002**[a]
Baseline OIs	Yes	23(18.5)	101(81.5)	3.06 (1.66, 5.62)	**<0.001**[a]
	No	19(7.2)	245(92.8)	1.00	
PMTCT intervention	Yes	5(10)	45(90.0)	1.00	
	No	26(10.3)	227(89.7)	1.09 (0.42, 2.86)	0.852
	Unknown	11(12.9)	74(87.1)	1.41 (0.49, 4.08)	0.524
Baseline CPT	Yes	41(10.9)	336(89.1)	1.00	
	No	1(9.1)	10(90.9)	1.12 (0.15, 8.14)	0.913
Baseline INH	Yes	21(9.2)	207(90.8)	1.00	
	No	21(13.1)	139(86.9)	1.48 (0.81, 2.72)	0.202
Baseline regimen	NVP based	20(12.0)	147(88.0)	1.03 (0.56, 1.89)	0.928
	Non-NVP based	22(10)	199(90.0)	1.00	
ART adherence	Good	24(7.9)	279(92.1)	1.00	
	Fair	9(18.8)	39(81.3)	3.15 (1.46, 6.82)	**0.004**[a]
	Poor	9(24.3)	28(75.7)	6.58 (3.00, 14.42)	**<0.001**[a]
ART side effect	Yes	3(27.3)	8(72.7)	2.41 (0.74, 7.82)	**0.144**[a]
	No	39(10.3)	338(89.7)	1.00	
Regimen change	Yes	25(9.6)	236(90.4)	1.00	
	No	17(13.4)	110(86.6)	2.26 (1.21, 4.21)	**0.010**[a]
TB treatment history	Yes	13(30.2)	30(69.8)	4.13 (2.15, 7.95)	**<0.001**[a]
	No	29(8.4)	316(91.6)	1.00	
Duration of follow-up	<36	26(12.4)	184(87.6)	8.59 (3.76, 19.65)	**<0.001**[a]
	≥36	16(9.0)	162(91.0)	1.00	

[a] p-value <0.2; CHR: crude hazard ratio; and CI: confidence interval.

Table 7
Multivariable Cox regression for predictors of treatment failure among HIV-positive children receiving ART at health facilities in Wolaita zone, January 2017 to December 2021.

Variables	Failure Status		AHR (95 % CI)	p-value
	Event	Censored		
Sex				
Male	27(13.2)	177(86.8)	1.46 (0.71, 3.00)	0.306
Female	15(8.2)	169(91.8)	1.00	
Parent status				
Both are alive	15(7.8)	178(92.2)	1.00	
one parent alive	16(13.8)	100(86.2)	0.39 (0.13, 1.22)	0.105
Both dead	7(20.0)	28(80.0)	1.30 (0.41, 4.10)	0.660
Unknown	4(9.1)	40(90.9)	1.83 (0.49, 6.85)	0.368
Caregiver marital status				
Single	7(18.9)	30(81.1)	4.86 (1.52, 15.60)	**0.008**[a]
Married	21(7.8)	249(92.2)	1.00	
Divorced	1(14.3)	6(85.7)	1.65 (0.12, 22.78)	0.709
Widowed	13(17.6)	61(82.4)	3.75 (1.16, 12.11)	**0.027**[a]
WHO clinical stage	16(6.0)	250(94.0)	1.00	
Non-advanced Advanced stage	26(21.3)	96(78.7)	1.16 (0.41, 3.31)	0.780
Baseline CD4 count				
≤200 cells/mm^3	24(31.6)	52(68.4)	4.70 (1.68, 13.14)	**0.003**[a]
>200 cells/mm^3	18(5.9)	289(94.1)	1.00	
Baseline OIs				
Yes	23(18.5)	101(81.5)	0.92 (0.39, 2.15)	0.857
No	19(7.2)	245(92.8)	1.00	
Baseline VL				
≤1000 copies/mL	11(5.9)	176(94.1)	1.00	
>1000 copies/mL	26(16.4)	133(83.6)	1.11 (0.42, 2.90)	0.831
ART adherence				
Good	24(7.9)	279(92.1)	1.00	
Fair	9(18.8)	39(81.3)	1.86 (0.69, 5.04)	0.219
Poor	9(24.3)	28(75.7)	1.33 (0.43, 4.04)	0.613
Drug side effect				
Yes	3(27.7)	8(72.3)	1.85 (0.37, 9.18)	0.450
No	39(10.3)	338(89.7)	1.00	
Regimen change				
Yes	25(9.6)	236(90.4)	1.07 (0.45, 2.51)	0.883
No	17(13.4)	110(86.6)	1.00	
TB Rx history				
Yes	13(30.2)	30(69.8)	2.13 (0.82, 5.59)	0.122
No	29(8.4)	316(91.6)	1.00	
Duration of follow-up				
<36	26(12.4)	184(87.6)	4.95 (1.81, 13.54)	**0.002**[a]
≥36	16(9.0)	162(91.0)	1.00	

[a] p-value <0.05; AHR: adjusted hazard ratio; CI: confidence interval.

of most previous studies may be attributable to developments in diagnosis and treatment technology, such as the development of dolutegravir (DTG), and the fact that, in contrast to other studies, the majority of study participants 266(68.6 %) started ART at an earlier non-advanced clinical stage.

In this study, baseline CD4 count was significantly associated with antiretroviral treatment failure. Those children with baseline CD4 count ≤200 were 4.7 times at higher risk of antiretroviral treatment failure compared to their counterparts. This finding was supported by the study conducted in Nigeria that reported children with baseline CD4 count <200 were 1.71 times more likely to develop ART failure than their counterparts [44]. The current finding is also consistent with prior studies conducted in Gondar, Fiche and Kuyu, and Addis Abeba, which found that children with low baseline CD4 counts had a 5.75-, 4.3-, and 2.3-times higher probability of ART failure than their counterparts respectively [20,23,30]. The likelihood that children with low baseline CD4 counts may develop opportunistic infections that weaken the immune system and increase the risk of ART failure, may account for the similarities in the findings.

As revealed in this study caregiver marital status was significantly associated with antiretroviral treatment failure. Accordingly, the risk of developing antiretroviral treatment failure among single caregivers was 4.9 times higher as compared to those children who live with married caregivers. This finding is supported by a prior study conducted in Nigeria [44]. The possible reason might be explained by individual factors and fear of social stigmatization.

The result of this study revealed also the duration of follow-up had a significant association with ART failure among HIV-infected children. Children who had been on ART for less than 36 months were 4.9 times at high hazard than those who stayed for 36 months and longer on ART. This finding is consistent with studies from Mekelle and Southern zones of Tigray and another study at Amhara regional hospitals in which a long duration of follow-up was a protective effect on first-line ART failure [25,26]. This may be explained

by the effect of Immune Reconstitution Inflammatory Syndrome (IRIS) in the initial stages of ART. As ART progresses, children's levels of adherence may rise, resulting in a satisfactory response to the ART regimen and preventing ART failure.

In contrast, this finding contradicts two previous studies conducted in Gondar which found that children who had been on a long duration of follow-up were 1.47 and 2.64 times at higher risk of ART failure than their counterparts respectively [2,30]. Considering that this study covered both hospitals and health centers while the investigations in Gondar were carried out at specialized hospitals that have substantial patient flow may be one factor. Therefore, compared to hospitals, health clinics may provide patients with better follow-up and counseling. The difference in diagnostic capacity may also be the other reason.

In this study, WHO clinical stage, baseline OIs, ART adherence, and TB treatment history were not found as significant predictors of ART failure. The reason might be due to the difference in person-time observation and sample size.

5.1. Strength of the study

Children on first-line ART at health centers were included in the present investigation as they were given fewer considerations in prior research which mainly examined those in hospitals. Additionally, it included both public and private healthcare facilities.

5.2. Limitations of the study

As information was gathered from secondary sources, medical records had poor documentation. Given the limitations of the retrospective study design, some factors that influence treatment failure have not been evaluated. Due to a lack of documentation on patient cards and a large number of missing values, factors like immunization status, hemoglobin level, organ function test, and other laboratory results that may affect an outcome variable were not included in the analysis.

6. Conclusions

The incidence rate of antiretroviral treatment failure among children with HIV on first-line ART at health facilities in Wolaita zone was found significant. Low baseline CD4 count, being with single or widowed parents, and short follow-up duration on ART were significantly associated with antiretroviral treatment failure.

Recommendations

Governmental and non-governmental organizations involved in HIV/AIDS care programs must concentrate on identifying children with low CD4 counts early and subsequent initiation of ART. Healthcare professionals should pay special attention to and regularly monitor the treatment progress of children who have single or widowed caregivers, and those with shorter duration of follow-up.

Ethics statements

This study was reviewed and approved by the Institutional Ethical Review Committee (ERC) of the College of Health Sciences and Medicine, Wolaita Sodo University, with the approval number: CHSM/ERC/01/14. Informed consent was not required for this study because routinely collected data were used for this study. Authorities of selected health facilities granted permission to use data. There were no identifiable, personal, or sensitive data. Throughout the study, data were collected in an anonymous form and kept confidential and secured.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Zufan Berhanu: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Eskinder Wolka:** Conceptualization, Data curation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing, Formal analysis. **Tadele Dana:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing. **Getachew Asmare:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing. **Muluken Berhanu:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Temesgen Leka Lerango:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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Abbreviations

ART:Anti-Retroviral Therapy;
AZT:Zidovudine;
cART:Combination Anti-Retroviral Therapy;
CD4:Clusters of Differentiation 4;
CPT:Co-trimoxazole Preventive Therapy;
EFV:Efavirenz;
HC:Health Center;
HIV/AIDS:Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome;
NNRTI:Non-Nucleoside Reverse-Transcriptase Inhibitor;
NVP:Nevirapine;
PH:Primary Hospital;
PMTCT:Prevention of Mother-To-Child Transmission;
SNNPR:Southern Nation Nationalities and Peoples Region;
UNAIDS:Joint United Nations Program on HIV/AIDS;
WHO:World Health Organization;
WSUCSH:Wolaita Sodo University Comprehensive Specialized Hospital.

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