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Incidence and predictors of attrition among children attending antiretroviral follow-up in public hospitals, Southern Ethiopia, 2020: a retrospective study

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ABSTRACT

Background It is a global challenge to enrol and retain paediatric patients in HIV/AIDS care. Attrition causes preventable transmission, stoppable morbidity and death, undesirable treatment outcomes, increased cost of care and drug resistance. Thus, this study intended to investigate the incidence and predictors of attrition among children receiving antiretroviral treatment (ART).

Method A retrospective follow-up study was conducted among children <15 years who had ART follow-up in Gedeo public hospitals. After collection, data were entered into Epi-data V.4.6, then exported to and analysed using STATA V.14. Data were described using the Kaplan-Meier statistics, life table and general descriptive statistics. The analysis was computed using the Cox proportional hazard regression model. Covariates having <0.25 p values in the univariate analysis (such as developmental stage, nutritional status, haemoglobin level, adherence, etc) were fitted to multivariable analysis. Finally, statistical significance was declared at a p value of <0.05.

Results An overall 254 child charts were analysed. At the end of follow-up, attrition from ART care was 36.2% (92 of 254), of which 70 (76.1%) were lost to follow-up, and 22 (23.9%) children died. About 8145.33 child-months of observations were recorded with an incidence attrition rate of 11.3 per 1000 child-months (95% CI: 9.2 to 13.9), whereas the median survival time was 68.73 months. Decreased haemoglobin level (<10 g/dl) (adjusted HR (AHR)=3.1; 95% CI: 1.4 to 6.9), delayed developmental milestones (AHR=3.6; 95% CI: 1.2 to 10.7), underweight at baseline (AHR=5.9; 95% CI: 1.6 to 21.7), baseline CD4 count ≤200 (AHR=4.4; 95% CI: 1.6 to 12.2), and poor or fair ART adherence (AHR=3.5; 95% CI: 1.5 to 7.9) were significantly associated with attrition.

Conclusion and recommendation Retention to ART care is challenging in the paediatrics population, with such a high attrition rate. Immune suppression, anaemia, underweight, delayed developmental milestones and ART non-adherence were independent predictors of attrition to ART care. Hence, it is crucial to detect and control the identified predictors promptly. Serious adherence support and strengthened nutritional provision with monitoring strategies are also essential.

What is known about the subject?

► Retaining patients receiving antiretroviral treatment (ART) in care is critical for successful ART outcomes. However, it is challenging to enrol and retain paediatric patients on ART care where about 20%–36% of children attrite from ART care. Studies also revealed that attrition from ART service is higher among children than in adults and is higher in resource-constraint settings. Different studies and organisations suggested some strategies and interventions intended to prevent attrition from HIV care programmes.

What this study adds?

► More than a quarter (27%) of children were lost to follow-up.
► Immunosuppression, anaemia, underweight, delayed developmental milestones and ART non-adherence were independent predictors of attrition to ART care.

INTRODUCTION

Despite the improvement in the survival of children infected with the virus following the introduction of highly active antiretroviral treatment (ART), AIDS is one of the world's most serious public health challenges.[1] According to the Joint United Nations Programme on HIV/AIDS(UNAIDS) report, in Ethiopia, by 2018, 690 000 people were living with HIV, 23 000 people newly infected with HIV and 11 000 people died from AIDS-related illnesses.[2]

Attrition refers to the interruption of ART care and is a composite variable which includes patients lost to follow-up, died and those who stopped ART.[3] Retention in ART care is essential to prevent HIV-related morbidity and deaths through early detection and treatment of opportunistic infections.

It also helps for early ART initiation, prevention and early detection of treatment failure. Moreover, retaining patients receiving ART in care is critical for successful ART outcomes.[4–7] Different studies and organisations suggested some strategies and interventions intended to prevent attrition from HIV care programmes such as nutrition support, ensuring uninterrupted drug supplies, consideration of simple, non-toxic ART regimens, decentralisation of ART care, engaging family role in ART care, strengthening the tracing mechanism and a reduction of indirect costs.[8 9]

However, it is challenging to enrol and retain paediatric patients in ART care.[7 10] ART follow-up interruption following an HIV diagnosis is associated with avoidable morbidity and death, increased cost of care, and preventable HIV transmission and drug resistance.[6] Attrition occurred in a speckled incidence ranging from 20% to 36%.[11–15] Studies also revealed that attrition from ART service is higher among children than in adults[6 16] and is higher in resource-constraint settings.[11 17–19]

Children may attrite from ART care for several reasons, including limited socioeconomic status, inadequate educational levels (lack of understanding of the need for lifelong care), living away from the ART facility and lack of transport. It may also be associated with providers' negative attitudes, long waiting times, drug side effects and delayed defaulter-tracing systems, suboptimal adherence and social support (stigma and disclosure-related issues).[3 6 11 20 21]

While several studies had been conducted on adults taking ART,[22–25] we have a paucity of evidence about attrition in children receiving ART, especially in resource-limited settings like Ethiopia. Besides, the definitions used by available studies to declare attrition were inconsistent. For instance, some studies considered only lost to follow-up cases and excluded deaths and defaulters. Some other studies included subjects with no follow-up after the diagnosis of HIV/AIDS, which could be challenging to declare attrition. Hence, it is difficult to draw a generalised country figure though having this problem at the back of paediatric ART. Identifying predictors of attrition could aid for focused planning and implementation of suggested strategies to improve retention. Therefore, this study intended to investigate the incidence and predictors of attrition among children receiving ART.

METHODS
Study setting and period
The study was conducted among children aged under 15 years who were attending ART follow-up at ART centres in public hospitals of Gedeo, Ethiopia, by reviewing 6 years (January 2013–December 2019) of ART follow-up data. Gedeo zone is located 1765 m above sea level and 394 km away from Addis Ababa. Gedeo has four hospitals, 36 health centres and 146 health posts. All four hospitals had access to paediatric ART services. The study was conducted from November 2019 to June 2020.

Study design
A hospital-based retrospective follow-up study was employed.

Study population
The study population comprised all HIV/AIDS-infected children less than 15 years of age who were attending ART follow-up at selected hospitals of Gedeo zone, Southern Ethiopia. Those children who had no at least one follow-up visit after confirmation of HIV/AIDS infection and charts with incomplete records were excluded.

Sample size determination and sampling procedure
The required sample size was estimated using the log-rank test according to the assumptions of the Cox proportional hazard model by using STATA V.13. Child aged <3 years at the initiation of ART follow-up was identified as a predictor variable from a previous study,[21] which yields the maximum sample size. After considering a 95% CI, 80% power, HR=5.3 and probability of failure among the control group (aged 3–8 years)=0.0423, the required sample size was 262. Thus, 262 charts were needed to be incorporated for review to conduct this study. A cluster sampling technique was applied after adjusting the four public hospitals providing ART services as clusters. Then, the three hospitals (Dilla University Referral Hospital, Bule Primary Hospital and Yirga Chefe Primary Hospital) were selected randomly using the lottery method. Afterwards, all charts that had been recorded from January 2013 to December 2019 were included for review. The details of steps and procedure of study participants' selection were described in the flow chart (figure 1).

Operational definitions and measurements
Survival time was measured from the beginning of ART follow-up until the time of the event or censoring. Children who had follow-up interruption either due to loss from ART follow-up, death or defaulters were considered as events (attrition),[3 6] whereas children who were active on ART follow-up, transferred out to other health institutions and those who exceed 15 years during the follow-up period were recorded as censored. Children were recorded lost if they did not return to the ART visit within 90 days or more after their last scheduled appointment.[6 26] Adherence was assessed based on the 2017 national ART score system.[6 27] The time scale in this study was in months. Nutritional status was assessed by weight-for-age (WFA) and height-for-age (HFA) using z-score and then classified as underweight (WFA ≤-2 z-score), stunting (HFA ≤-2 z-score) and normal (z-score >2). Severe immunodeficiency was defined as CD4 <200 for children under 5 years of age and CD4 <100 for those aged above 5 years.[26 27] The developmental milestone (<5 years) was determined as delayed where the child fails to achieve the expected milestone for age; regression in which the child loses what has been attained for age; and otherwise normal.[6 26]
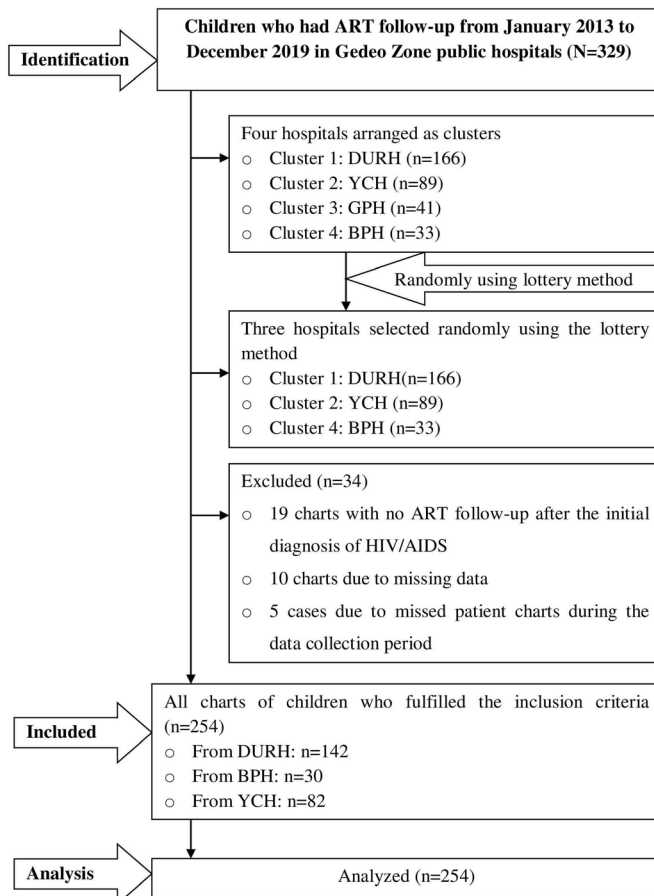
Figure 1 A flow chart of recruitment methods among HIV/AIDS-infected children who had ART follow-up at ART clinics of Gedeo public hospitals, Southern Ethiopia, 2020 (N=254). ART, antiretroviral treatment; BPH, Bule Primary Hospital; DURH, Dilla University Referral Hospital; GPH, Gedeb Primary Hospital; YCH, Yirga Chefe Hospital.

Data collection tools and procedures

The authors initially observed patient records and designed an appropriate data extraction checklist in English after reviewing different literature, ART-monitoring chart and the national comprehensive HIV treatment guideline.[6] The tool comprised of sociodemographic, clinical, and disease-related and treatment-related variables. The lists of study participants were obtained from the ART data clerk, and charts were selected from the hospital card room using a medical record number. Three data collectors (ART-trained BSc) and one supervisor (MSc fellow) completed the data collection within 4 weeks, from 15 April to 15 May 2020.

Data quality assurance

A week before starting the actual data collection, the principal investigator conducted a pretest on 14 (5%) randomly selected charts at Yirgalem Primary Hospital to assure the consistency and clarity of the tool. Data collectors and supervisors had trained for 1 day regarding the information to be collected and how to collect relevant information. Appraisal of the collected data was conducted daily by the principal investigator and

supervisor for completeness. Charts with incomplete data during data collection were excluded.

Data processing and analysis

After data collection, data were checked via paper-wise observation, entered into Epi-data manager V.4.6, and exported to STATA V.14 for cleaning, edition, coding, and analysis. Exploratory analysis was performed before data description to determine the normality nature and presence of outliers. Then, categorical data were described using frequency tables and percentages, and continuous data were described using median with IQR and minimum and maximum values since the data were not normally distributed. Kaplan-Meier's curve was constructed to estimate median time to attrition during the follow-up period and log-rank tests to compare survival curves among different categories of predictor variables. A life table was constructed to estimate the cumulative probability of attrition at different time intervals.

The univariate analysis was performed using Cox proportional hazard regression to identify the association between attrition and each independent variable in which variables with $p \leq 0.25$ were included in the multivariable analysis, to identify independent predictors of attrition. Multicolinearity was checked using the variance inflation factor (VIF) (mean VIF=1.36). Moreover, proportional hazard assumptions were checked using the Schoenfeld residual test ($p > \chi^2 = 0.852$). Harrell's C was also computed (C=0.8359), which indicates that this study can correctly order survival times for pairs of children 83.6% of the time based on observations of fitted variables in the model. The Cox regression model for its fitness to the data was checked using the Cox-Snell residuals. Generally, we could conclude that the model fits successfully. In the final Cox proportional hazard model, statistical significance was declared at $p < 0.05$, and the presence and strength of associations were summarised using an adjusted HR (AHR) with 95% CIs. Finally, texts, tables and graphs were used to present the study findings.

Patient and public involvement

It is not applicable for this study since patients were not directly involved. The study was conducted via patient chart review without contacting patients.

RESULTS

From January 2013 to December 2019, an overall 288 (166 charts from Dilla Referral Hospital, 89 from Yirga Chefe Hospital and 33 from Bule Hospital) children less than 15 years started ART follow-up. Of those, 254 children under 15 years who fulfilled the inclusion criteria were reviewed, and 34 charts were excluded from the analysis.

Sociodemographic characteristics of HIV/AIDS-infected children

The finding revealed that among 137 (54%) male participants, 46 (33.6%) interrupted ART visits, whereas 50

Table 1 Distribution of sociodemographic characteristics among HIV/AIDS-infected children who had follow-up at ART centres of Gedeo public hospitals, Southern Ethiopia, 2020 (N=254)

Covariates	Category	Outcome status		Total (%)
		Attrition (%)	Censored (%)	
Child age	≤3 years	24 (48)	26 (52)	50 (19.7)
	3–9 years	46 (35.7)	83 (64.3)	129 (50.8)
	≥9 years	22 (29.3)	53 (70.7)	75 (29.5)
Sex	Female	46 (39.3)	71 (60.7)	117 (46.1)
	Male	46 (33.6)	91 (66.4)	137 (53.9)
Religion of the caregiver	Orthodox	31 (33)	63 (67)	94 (37.0)
	Muslim	12 (28.6)	30 (71.4)	42 (16.5)
	Protestant	46 (41.4)	65 (58.6)	111 (43.7)
	Catholic	3 (42.9)	4 (57.1)	7 (2.8)
Residence	Rural	50 (41.3)	71 (58.7)	121 (47.6)
	Urban	42 (31.6)	91 (68.4)	133 (52.4)
Caregiver's marital status	Single	10 (41.7)	14 (58.3)	24 (9.4)
	Married	58 (33.9)	113 (66.1)	171 (67.3)
	Divorced	8 (42.1)	11 (57.9)	19 (7.5)
	Widowed	16 (40)	24 (60)	40 (15.8)
Parent status	Both alive	71 (36.8)	122 (63.2)	193 (76)
	Either died	19 (37.3)	32 (62.7)	51 (20.1)
	Both died	2 (20)	8 (80)	10 (3.9)
Caregiver's HIV status	Reactive	60 (35.9)	107 (64.1)	167 (65.8)
	Non-reactive	32 (36.8)	55 (63.2)	87 (34.2)
Occupation of caregiver	Governmental employee	3 (18.7)	13 (81.3)	16 (6.30)
	Housewife	46 (38.3)	74 (61.7)	120 (47.24)
	Self-employee	41 (38)	67 (62)	108 (42.52)
	Others	2 (20)	8 (80)	10 (3.94)
Educational status of the caregiver	Illiterate	45 (34.6)	85 (65.4)	130 (51.2)
	Read and write	18 (40.9)	26 (59.1)	44 (17.3)
	Grade 1–8	21 (43.8)	27 (56.2)	48 (18.9)
	Grade 9–12	3 (27.3)	8 (72.7)	11 (4.3)
	College and above	5 (23.8)	16 (76.2)	21 (8.3)

ART, antiretroviral treatment.

(41.32%) of the 121 (47.6%) study participants living in rural areas interrupted their follow-up. The median age of the study participants at the initiation of ART follow-up was 6 years. About 129 (50.8%) children started ART follow-up at the age of 4–8 years. Among those children who lost from ART follow-up, 76.1% started follow-up below 9 years of age. One hundred eighty-six (73.2%) respondents were living with their parents. Of whom, 67 (36.0%) did not return to ART visits. Similarly, 21 (34.4%) of 61 (20.1%) children who lost either one or both parents failed to retain ART care. The study also showed that 171 (67.3%) caregivers of children were married, of which 58 (33.92%) children discontinued their follow-up (table 1).

Clinical and disease-related characteristics of HIV/AIDS-infected children

The median CD4$^+$cell count at baseline was 606 cells/µL. From the overall 254 subjects, more than two-thirds of study participants (69.3%) had baseline CD4 cell count greater than 350 cells/µL, of which 45 (25.6%) experienced attrition while 9% of those who had CD4$^+$ counts of ≤200 cells/µL attrited from ART follow-up. Among those children who started ART with an advanced clinical stage (WHO III or IV), 15.4% interrupted ART follow-up. Furthermore, 51 (68.9%) of the 74 (29.1%) children who had <10 mg/dL at the initial HIV/AIDS diagnosis were found to be absent sometime after initiation of ART follow-up. Among those children below

Table 2 Clinical and disease-related characteristics of HIV/AIDS-infected children who had follow-up at ART centres of Gedeo public hospitals, Southern Ethiopia, 2020 (N=254)

| Covariates | Category | Outcome status | | Total (%) |
		Attrition (%)	Censored (%)	
Developmental status (<5 years)	Appropriate	32 (36)	57 (64)	89 (87.2)
	Delayed	10 (76.9)	3 (23.1)	13 (12.8)
Functional status (>5 years)	Working	25 (29.8)	59 (70.2)	84 (55.3)
	Ambulatory	18 (30.5)	41 (69.5)	59 (38.8)
	Bedridden	7 (77.8)	2 (22.2)	9 (5.9)
WFA	Z-score >−2	72 (32.1)	152 (67.9)	224 (88.2)
	Z-score ≤−2	20 (66.7)	10 (33.3)	30 (11.8)
HFA	Z-score >−2	75 (32.8)	154 (67.2)	229 (90.2)
	Z-score ≤−2	17 (68)	8 (32)	25 (9.8)
Baseline haemoglobin	<10 mg/dL	51 (68.9)	23 (31.1)	74 (29.1)
	≥10 mg/dL	41 (22.8)	139 (77.2)	180 (70.9)
Baseline CD4$^+$ count	≤200	23 (65.7)	12 (34.3)	35 (13.8)
	>200–350	24 (55.8)	19 (44.2)	43 (16.9)
	≥350	45 (25.6)	131 (74.4)	176 (69.3)
WHO clinical stage	I and II	53 (30.5)	121 (69.5)	174 (68.5)
	III and IV	39 (48.8)	41 (51.2)	80 (31.5)
Disclosure status	Disclosed	52 (34.4)	99 (65.6)	151 (59.45)
	Not disclosed	40 (38.8)	63 (61.2)	103 (40.55)
Opportunistic infections	No	66 (33.2)	133 (66.8)	199 (78.35)
	Yes	26 (47.3)	29 (52.7)	55 (21.65)
Tuberculosis	No	82 (35.2)	151 (64.8)	233 (91.7)
	Yes	10 (47.6)	11 (52.4)	21 (8.3)

ART, antiretroviral treatment; HFA, height-for-age; WFA, weight-for-age.

the age of 5 years (102), 13 (12.8%) had delayed developmental status at baseline. Fifty-five (21.7%) respondents developed an opportunistic infection, of which 25 (45.5%) had diarrhoea and 12 (21.8%) had pneumonia. Almost 50% of participants who had tuberculosis coinfection discontinued their follow-up. Only 87 (34.3%) children knew their serostatus at ART follow-up initiation. Among children who started ART follow-up with non-disclosed serostatus, 33 (36.7%) had discontinued ART visits (table 2).

Treatment-related characteristics of HIV/AIDS-infected children

Fifty-nine (23.3%) participants had poor or fair adherence. Among those, 47 (79.7%) lost from follow-up. Of the total 254 participants, 32 (12.6%) children had not received cotrimoxazole preventive therapy (CPT), and 17 (53.1%) of them had attrited from follow-up. Regarding the baseline ART regimen, 195 (76.8%), 39 (15.4%) and 20 (7.9%) study subjects started with nevirapine-based (NVP), efavirenz-based and other regimens correspondingly. The majority (83.7%) of children who initiated ART with the NVP-based regimen had failed to retain care. Moreover, 78 (30.7%) respondents suffered drug side

effects while 74 (29.1%) children changed their initial ART regimen. More than half (56.4%) of children who experienced drug side effects had exhausted attending ART visits (table 3).

Comparison of survival status using Kaplan-Meier and log-rank test

The Kaplan-Meier failure curve increased stepwise as the follow-up time increased, and it crossed the survival function at the survival probability of 0.5 (figure 2).

Survival function and incidence of attrition

We have retrospectively followed children for a minimum of 29 days and a maximum of 84 months with a median follow-up of 26.4 months. Ninety-two (36.2%, N=254) children had attrited from ART follow-up, of which 70 (76.1%, n=92) were lost to follow-up and 22 (23.9%, n=92) children died. The rest, 162 (64.8%) participants, were considered censored. Among those, 127 (78.4%) were active on follow-up; and the rest, 35 (21.6%) cases, had transferred out to other health facilities. Fifty-seven (48%) of attrition cases occurred after 60 months of the follow-up.

Table 3 Distribution of treatment-related characteristics among HIV/AIDS-infected children who had follow-up at ART centres of Gedeo public hospitals, Southern Ethiopia, 2020 (N=254)

Covariates	Category	Outcome status		Total (%)
		Attrition (%)	Censored (%)	
Baseline ART regimen	D4T-3TC-NVP	14 (42.4)	19 (57.6)	33 (12.99)
	AZT-3TC-NVP	56 (37.1)	95 (62.9)	151 (59.45)
	TDF-3TC-EFV	3 (20)	12 (80)	15 (5.91)
	ABC-3TC-EFV	2 (28.6)	5 (71.4)	7 (2.76)
	AZT-3TC-EFV	7 (41.2)	10 (58.8)	17 (6.69)
	ABC-3TC-NVP	7 (63.6)	4 (36.4)	11 (4.33)
	Others	3 (15)	17 (85)	20 (7.87)
Adherence	Good	45 (23.1)	150 (76.9)	195 (76.77)
	Fair	4 (66.7)	2 (33.3)	6 (2.36)
	Poor	43 (81.1)	10 (18.9)	53 (20.87)
CPT	Given	75 (33.8)	147 (66.2)	222 (87.4)
	Not given	17 (53.1)	15 (46.9)	32 (12.6)
Drug side effect	Yes	44 (56.4)	34 (43.6)	78 (30.7)
	No	48 (27.3)	128 (72.7)	176 (69.3)
Drug substitution	Yes	22 (29.7)	52 (70.3)	74 (29.1)
	No	70 (38.9)	110 (61.1)	180 (70.9)
Last outcome	Active/on follow-up	0 (0)	127 (100)	127 (50.0)
	Transfer out	0 (0)	35 (100)	35 (13.8)
	Attrition/interrupted	92 (100)	0 (0)	92 (36.2)

ABC, abacavir; ART, antiretroviral treatment; AZT, zidovudine; CPT, cotrimoxazole preventive therapy; D4T, stavudine; EFV, efavirenz; NVP, nevirapine; 3TC, lamivudine; TDF, tenofovir.

The total child-month observation was 8145.33 child-months or 678.775 child-years with an incidence attrition rate of 11.3 (95% CI: 9.21 to 13.86) per 1000 child-month observations or 13.5 (95% CI: 11 to 16.6) per 100 child-year observations. The median survival time was 68.73 months. The cumulative probabilities of attrition were

Figure 2 An overall Kaplan-Meier failure estimate among HIV/AIDS-infected children who had ART follow-up at ART clinics of Gedeo public hospitals, Southern Ethiopia, 2020 (N=254). The Y-axis represents the probability of failure, whereas the X-axis indicates the analysis time in months. ART, antiretroviral treatment.

0.14, 0.35, 0.47, and 0.62 at the end of 12, 36, 60, and 84 months of follow-up in that order.

Predictors of attrition among children who were on ART
In the univariate analysis, variables such as child age, residence, parent's marital status, WFA, HFA, developmental milestone, baseline haemoglobin, baseline WHO clinical stage, baseline CD4 count, opportunistic infection, presence of tuberculosis, CPT, adherence to ART, ART drug side effect and drug substitution were found to have a p value less than 0.25 and included in the multivariable analysis. On the other hand, variables that contain less than 20% events per cell, such as parents' status, occupation, parents' education and functional status, were excluded from the final model. Likewise, the duration of ART follow-up violated the proportional hazard assumptions and thus further excluded from the multivariable analysis.

Finally, Cox proportional hazard model (multivariable analysis) showed that being underweight, baseline low CD4 count, suboptimal ART adherence, delayed developmental stage at follow-up initiation and a haemoglobin level of <10 mg/dL were significantly associated with attrition at 5% level of significance (table 4).

Those children having low haemoglobin levels (<10 mg/dL) were 3.12 times (AHR=3.12; 95% CI: 1.41 to 6.93) at an increased hazard of attrition than their
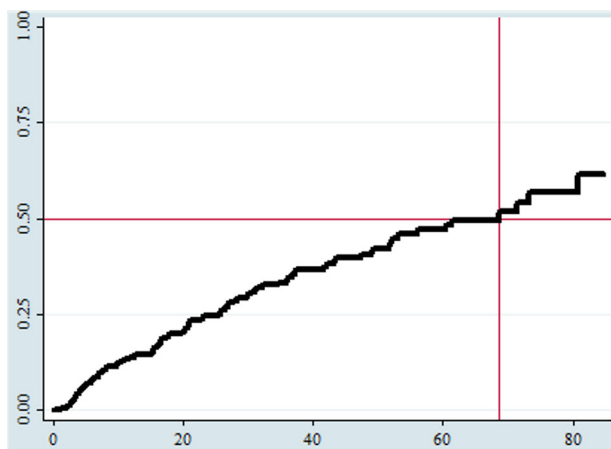
Table 4 Cox proportional hazard regression analysis output for predictors of attrition among HIV/AIDS-infected children in Gedeo public hospitals, Southern Ethiopia, 2020 (N=254)

Covariates	Category	Outcome status		P>|z|	Crude HR (95% CI)	P>|z|	Adjusted HR (95% CI)
		Attrited	Censored				
Child age		92	162	0.205	0.96 (0.90 to 1.02)	0.131	0.82 (0.63 to 1.06)
Residence	Rural	50	71	0.088	1.43 (0.95 to 2.16)	0.348	1.50 (0.64 to 3.47)
	Urban	42	91	—	—	—	—
Caregiver's marital status	Single	10	14	0.204	1.55 (0.80 to 3.03)	0.730	1.29 (0.31 to 5.38)
	Married	58	113	0.287	1.49 (0.71 to 3.13)	0.399	1.71 (0.49 to 5.99)
	Divorced	8	11	0.569	1.17 (0.67 to 2.05)	0.380	1.62 (0.55 to 4.75)
	Widowed	16	24	—	—	—	—
Developmental status (for <5 years)	Appropriate	32	57	—	—	—	—
	Delayed	10	3	0.002	3.15 (1.53 to 6.49)	0.021*	3.60 (1.22 to 10.66)
WFA	Normal	72	152	—	—	—	—
	Underweight	20	10	<0.001	3.28 (1.98 to 5.45)	0.007*	5.91 (1.61 to 21.71)
HFA	Normal	75	154	—	—	—	—
	Stunted	17	8	<0.001	2.88 (1.69 to 4.89)	0.215	0.39 (0.09 to 1.74)
Baseline haemoglobin	<10mg/dL	51	23	<0.001	3.87 (2.56 to 5.85)	0.005*	3.12 (1.41 to 6.93)
	≥10mg/dL	41	139	—	—	—	—
Baseline CD4$^+$ count	≤200	23	12	<0.001	2.53 (1.57 to 4.06)	0.004*	4.43 (1.62 to 12.18)
	>200	69	150	—	—	—	—
WHO stage	Early	53	121	—	—	—	—
	Advanced	39	41	0.015	1.67 (1.11 to 2.53)	0.068	2.29 (0.94 to 5.59)
OIs	No	66	133	—	—	—	—
	Yes	26	29	0.161	1.38 (0.88 to 2.18)	0.395	1.44 (0.62 to 3.40)
Presence of TB	No	82	151	—	—	—	—
	Yes	10	11	0.148	1.63 (0.84 to 3.15)	0.240	0.51 (0.17 to 1.57)
Adherence	Good	45	150	—	—	—	—
	Suboptimal	47	2	<0.001	5.55 (3.65 to 8.46)	0.004*	3.45 (1.50 to 7.94)
CPT	Given	75	147	—	—	—	—
	Not given	17	15	0.019	1.88 (1.11 to 3.18)	0.290	1.81 (0.60 to 5.40)
ARV drug side effect	Yes	44	34	0.009	1.73 (1.15 to 2.61)	0.125	0.51 (0.21 to 1.21)
	No	48	128	—	—	—	—
ARV drug substitution	Yes	22	52	—	—	—	—
	No	70	110	0.007	1.96 (1.20 to 3.19)	0.153	1.90 (0.79 to 4.61)

*Significant at 5% level of significance.

ARV, antiretroviral drugs; CPT, cotrimoxazole preventive therapy; HFA, height-for-age; OIs, opportunistic infections; TB, tuberculosis; WFA, weight-for-age.

counterparts. Children with delayed developmental milestones had a 3.6 increased risk of attrition (AHR=3.60; 95% CI: 1.22 to 10.66) when compared with those with an appropriate developmental milestone. Likewise, underweight children at baseline had a sixfold increased hazard of follow-up interruption than those having ideal weight (WFA z-score ≥−2) (AHR=5.91; 95% CI: 1.61 to 21.71). Furthermore, children who had CD4 count ≤200 cells/µL at the beginning of ART follow-up were 4.43 times (AHR=4.43; 95% CI: 1.62 to 12.18) at an increased hazard of follow-up interruption compared with their counterparts. Moreover, patients who had suboptimal adherence at baseline were three and a half times at a higher risk of experiencing attrition compared with those who had good adherence (AHR=3.45; 95% CI: 1.50 to 7.94).

DISCUSSION

This study aimed to determine the incidence and predictors of attrition among HIV/AIDS-infected children on ART follow-up. In this study, the overall incidence rate of attrition was 13.5 per 100 child-year observations (95% CI: 11 to 16.6). Moreover, decreased baseline haemoglobin level, low baseline CD4 level, poor/fair ART adherence, delayed developmental stage at baseline and being underweight were found to predict children's attrition from follow-up.

The current study showed that the overall incidence of attrition was 13.5 per 100 child-years of observation (95% CI: 11 to 16.6) which was higher than the findings of previous studies conducted in Thailand,[28] Myanmar,[3] Asian Pacific countries[29] and Addis Ababa.[21] This discrepancy could be due to the variation in access and quality of healthcare services among those countries. The level of awareness towards healthcare-seeking behaviour among those populations may vary as well. The length of follow-up would also contribute to the variation in the incidence rate where the previous study[21] used only 2 years of follow-up data compared with 7 years in this study.

On the contrary, higher figures were reported from studies conducted in West Africa,[14] Uganda,[30] sub-Saharan Africa[31] and East African countries.[32] The possible explanation could be the emergence of more potent and palatable ART drugs these days. Moreover, the current guideline recommends frequent visits with enhanced adherence support and family involvement in ART care.[6 26] The other possible reason might be the difference in sample size since previous studies conducted on larger sample sizes, N=17155 in East African study[32] and N=2170 in West African study.[14]

According to the study result, children who had low haemoglobin levels (<10 mg/dL) were 3.12 times at an increased hazard of attrition than their counterparts. This finding was in agreement with reports of other studies.[3 11 21 33–35] The possible justification could be anaemia is associated with reduced immune defence resulting in decreased tolerance and absorption of ART

drugs. Consequently, this may worsen the disease progression and retarding the response to standard therapy, and eventually, end up with exhaustion. Besides, some ART regimens were associated with anaemia that could further exacerbate the pre-existing condition.[26] Another explanation could be decreased ART tolerance because of decreased absorption and the effect of immune defence from anaemia. To strengthen this evidence, about two-thirds (66.1%) of participants in our study started with zidovudine-containing regimen, of that 38.1% of children had experienced attrition.

This study also showed that children who had CD4 count ≤200 cells/µL at the beginning of ART follow-up were 4.43 times at an increased hazard of follow-up interruption than their counterparts did. The findings of previous studies conducted in Asian and African countries were consistent with the current study result.[3 11 14 32 33 36–38] The explanation could be because immune suppression could expose children to further associated infections (opportunistic infections), contribute to rapid viral replication and HIV/AIDS progression, and hinder the desired therapeutic effect. As a result, the above mechanisms will result in exhaustion and non-compliance to ART follow-up leading to missed follow-up.

Moreover, HIV/AIDS-infected children who had suboptimal adherence at baseline were three and a half times at an increased hazard to experience attrition compared with those who had good adherence to ART drugs at initiation (AHR=3.45; 95% CI: 1.50 to 7.94). No statistically significant association was reported by earlier studies except the Addis Ababa study.[21] The rationale could be suboptimal adherence to ART regimens contributes to increased viral replication and poor immunological and clinical outcomes. Suboptimal adherence would also be associated with an increased risk of ART drug resistance. Consequently, HIV/AIDS-infected children might become hopeless and exhausted to follow their ART visits. On the other hand, children are dependent on others to attend their ART follow-up visits and to take medications timely and in recommended dosages. Thus, caretaker-related issues might also influence adherence. Additionally, children frequently encountered adherence issues for several reasons.[6 26 27]

Likewise, children who were underweight at baseline had sixfold increased hazard of follow-up interruption than those patients having ideal weight (WFA z-score ≥−2). This finding was in line with the study done in Myanmar,[3] Bali,[35] Côte d'Ivoire,[34] Uganda[30] and a combined report in East Africa.[33] The possible justification could be that undernutrition would lead to several undesired health effects, including compromised immunity, decreased effectiveness and response to ART drugs, and the emergence of complications and new coinfections. These in turn aid the further HIV replication and disease progression so that patients might prefer to interrupt their follow-up or lead to death.[6 39]

The other significantly associated factor in this study was a delayed developmental milestone. Children with

delayed developmental milestones had a 3.6 increased risk of attrition when compared with those with an appropriate developmental milestone. Children are dependent on their parents/caregivers to accomplish their needs and responsibilities, including attending follow-up visits and timely intake and dosage of ART drugs. It could be like adding fire on the chaff when there is a developmental delay. In resource-limited countries like Ethiopia, it is challenging to assign regular caregivers to attend and fulfil the requirements of children in such circumstances. Moreover, the developmental delay may also be associated with diminished immune capability, further complicating the immunological and clinical recovery, thus affecting retention at care.

Although this study reported pertinent findings by considering censored observations for analysis and used longer follow-up period to estimate cumulative incidence of attrition, it has some limitations. First, the study involves patient chart review so that the effects of some important variables such as laboratory findings (eg, viral load) were left unevaluated. Second, excluding charts absent during the data collection period and those charts with missing data may underestimate or overestimate the study findings.

CONCLUSION

Retention to ART care is challenging in the paediatric population with such a high attrition rate. The incidence of attrition was found to be high in this study. Immune suppression (CD4^{+} count <200), anaemia (<10 mg/dL), underweight (WFA z-score <−2), delayed developmental milestone and ART non-adherence were independent predictors of attrition from ART care. Hence, it is crucial to detect and control the identified predictors promptly. Serious adherence support and strengthened nutritional provision with monitoring strategies are also essential.

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