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Predictors of first-line antiretroviral treatment failure among children on antiretroviral therapy at the University of Gondar comprehensive specialised hospital, North-west, Ethiopia: a 14-year long-term follow-up study

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ABSTRACT

Objective To determine the incidence and predictors of first-line human immune deficiency virus treatment failure among human immune deficiency virus-infected children at the University of Gondar comprehensive specialised hospital in Ethiopia.

Design A retrospective follow-up study.

Setting University of Gondar comprehensive specialised hospital, North-west, Ethiopia.

Participants Children were among the HIV infected from January 2005 to December 2018. There were 336 children included in the study. The data were entered into EPi Info V.7.2 and then exported to STATA V.14.0 Software for analysis. Both bivariable and multivariable analyses with Cox proportional hazards models were used to identify the predictors of treatment failure.

Primary outcome measures Predictors of first-line antiretroviral treatment failure among children on antiretroviral therapy (ART) during 14 years long-term follow-up study.

Result A total of 336 human immunodeficiency virus-infected children participated in this study with 27 058 child years of observation. The overall incidence rate was 2.1 (95% CI 1.57 to 2.78) per 100 child years. Poor adherence (adjusted HR (AHR); 6.5 (95% CI 2.03 to 21.39)), fair adherence (AHR; 6.55 (95% CI 2.64 to 16.53), the presence of opportunistic infection (AHR; 4.22 (95% CI 1.44 to 12.30), clinical staging of III/IV (AHR; 3.08 (95% CI 1.17 to 8.08) and a baseline CD4 count less than 200 cells/mm^3 (AHR; 3.61 (95% CI 1.12 to 11.54)).

Conclusion The incidence of first-line ART failure was found to be high. Baseline opportunistic infection, poor and fair adherence, advanced WHO clinical staging III/IV and a CD4 count less than 200 cells/mm^3 were all predictors of first-line treatment failure. Early identification of associated factors and monitoring treatment failure has to be important for the optimal management of HIV-infected children who are receiving ART and to prevent further complications.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was conducted in a long-term follow-up study that can provide a reliable estimate of predictors of first-line antiretroviral treatment failure among children.
⇒ This study used virological failure in addition to clinical failure and immunological failure as outcome variable (treatment failure), which is not mainly conducted in Ethiopia before.
⇒ Some variables, such as children's educational status, family economic status, caregivers' awareness levels, were not accessible in the medical records and, therefore, were not included in this study, which may affect the outcome variable.

INTRODUCTION

According to a recent global survey, 37.9 million people were living with HIV in 2021, with 1.7 million being children under the age of 15, 27.4 million on antiretroviral therapy (ART) and 940 000 dying.[1] An estimated 738 976 Ethiopians are living with HIV, 44 000 of whom are children and all of them require antiretroviral medication. However, only 390 400 people have access to ART, with 23 400 of them being children under the age of 15.[1 2] When compared with high-income countries, the rate of ART failure is higher in low-income ones, and according to a recent study conducted in six African countries, the rate of transmitted antiretroviral drug resistance has increased by 38%.[1 2]

Patients who have failed antiretroviral medication have an increased number of side effects and are more likely to develop drug

resistance.[3] If this virus spreads throughout the population, drug-resistant virus types may emerge as a problem.[4] A multicentre cohort study conducted in Mozambique and Uganda reported that 29% of children experienced treatment failure, with a crude incidence of 20.0 events per 100 person-years.[5]

Recommend first-line ART regimens for adolescents and children, for adolescents (10–19 years) weight ≥30 kg (including those with tuberculosis (TB)/HIV coinfection) (TDF+3TC + DTG (FDC), AZT+3TC + EFV, AZT+3TC + NVP, TDF+3TC + NVP and ABC+3TC + EFV). For children 3 years to less than 10 years and adolescents weight (AZT or ABC+3TC + EFV, AZT+3TC + NVP, TDF+3TC + EFV, TDF+3TC + NVP and ABC+3TC + NVP). For children <3 years (ABC or AZT+3TC + LPV/r, ABC+3TC + NVP and AZT+3TC + NVP).[6]

In Ethiopia, first-line ART regimens are advised, which are simpler and less toxic, and more convenient regimens as fixed-dose combinations are available. The first-line ART regimen is a combination of two nucleoside reverse-transcriptase inhibitors (NRTIs) and onenon-nucleoside reverse transcriptase inhibitor. Protease inhibitors-based regimen is recommended for children under the age of 3 (AZT or ABC plus 3TC plus LPV/r (lopinavir). If LPV/r is not feasible, treatment should be initiated with an NVP (nevirapine)-based regimen.[2]

Treatment failure is defined as the progression of disease and replication of HIV despite treatment. Viral failure can be tracked virologically (plasma viral load above 1000 copies/mL after 3 months with compliance support), immunologically (a drop in CD4 cell counts to baseline (or below), a 50% reduction from one treatment peak value or the presence of persistent CD4 cell counts below 100 cells/mm^3) and clinically (new or recurrent WHO stage 4 or some stage 3 conditions).[7–9]

For the purpose of discovering clinical and laboratory indicators of virological treatment failure, the Ethiopian Paediatric HIV Cohort was established in order to develop a clinical-immunological prediction rule that could predict failure of first-line antiretroviral medication with an area under the curve exceeding 0.80. A number of studies have shown that highly active ART improves children's clinical and immunological outcomes. In addition, as the use of HAART increases, there is an increasing risk of drug resistance and subsequent treatment failure manifesting as clinical, immunological, or virological ART failure.[10 11]

Despite the expansion of ART in resource-constrained countries, the development of first-line antiretroviral treatment failure remains a significant concern. Treatment failure among the ART population in Ethiopia is a public health problem because patients who fail treatment have an increased risk of morbidity, mortality, increased transmission and the build-up of drug resistance mutations. Currently, in Ethiopia, although medication is fully provided by the government, treatment failure and frequent medication substitution are major barriers in disease control.[12–14]

The previous literature used immunological and clinical failure criteria to identify first-line ART failure, but this study also used virological failure criteria. Because of this, relying solely on immunological and clinical failure criteria understates the incidence of failure. As a result, the purpose of this study was to determine the incidence of first-line antiretroviral treatment failure and its predictors among children at the University of Gondar compressive and specialised hospital. The findings will be useful to programme planners and decision-makers at various stages of the HIV/AIDS care and support programme in order to increase the efficacy of HAART in children.

METHODS

Study design and period

A retrospective follow study was conducted among HIV-infected children on ART from January 2005 to December 2018.

Study setting

The study was conducted at the University of Gondar comprehensive and specialised hospital; Gondar town is located in the central Gondar administrative zone, Amhara National Regional State. Based on a 2007 national census conducted by the Central Statistical Agency of Ethiopia, Gondar had a total population of 207 044, of whom 98 120 were men and 108 924 were women. The University of Gondar's comprehensive specialised hospital serves more than five million people in the central Gondar zone and the people of the neighbouring zones and districts. The HIV care service of the hospital was initiated in 2005 and has three clinics, namely: the Adult ART clinic, the Paediatric ART clinic and the Voluntary Counselling and Testing clinic.

Study participants

The study included all HIV-positive children under 15 years of age who were receiving ART in the University of Gondar comprehensive specialised hospital from January 2005 to December 2018. Participants whose data were incomplete (that means charts without outcome variables and major explanatory variables) were excluded from the study.

Operational definition

ART teatment failure: When an antiretroviral regimen is unable to control HIV infection. ART treatment failure is diagnosed if one of the following is satisfied and defined as follows:[2]

Clinical failure: New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical condition with exception of TB) after 6 months of effective treatment.[2]

Immunological failure: Adolescents-CD4 count at or below 250 cells/mm^3 following clinical failure or persistent CD4 levels below 100 cells/mm^3.

Children younger than 5 years: Persistent CD4 level below 200 cells/mm^3 or <10%.

Older than 5 years: Persistent CD4 levels below 100 cells/mm^3.[2]

Virological failure: The client's viral load is found to be >1000 copies/mL on a routine or need-based viral load test, providers should identify adherence barriers and provide enhanced adherence support for 3 months. Viral load testing must be performed once again after 3 months of improved adherence support. If the second viral load test findings are 1000 copies/mL or more, the patient should be continued on the first-line regimen with ongoing adherence support. But if the viral load is greater than 1000 copies/mL in two evaluations conducted back-to-back within a 3-month time frame with adherence support in between, the results will show that the current treatment approach has failed.[2]

In Ethiopia, during all HIV clinic visits, the healthcare provider assesses adherence to ART by pill counts at visits and records adherence appropriately as 'GOOD' (the children took ≥95% of the medication) or FAIR (the children took 80%–95% of the medication), while POOR adherence is they took less than 80% of the medication. Missing doses in the last 3 days or missing >15 doses since the last visit was defined as poor adherence[2]

Events The event of this study was first line antiretroviral treatment failure.

Survival: If the children free from the event until the end of the follow-up period.

Censored: A child considered as 'censored' if the child is lost, drop-out and transfer out to other service before developing the event or if the child not develop treatment failure until the end of the study period.

Underweight: Weight for age ≤2 SD of the WHO Child Growth Standards median.[15]

Stunting: Height for age ≤2 SD of the WHO Child Growth Standards median.[15]

Opportunistic infections (OIs): Are diseases that cause infections in individuals whose immune systems are compromised.[16]

Regimen change: Any alteration/switching or discontinuation of at least one antiretroviral drug from the triple ART regimen.[17]

Disclosure of HIV status: When children are told the name of the illness (HIV and/or AIDS disease-specific information) and how they acquired the disease.[18]

Sample size determination

Log-rank survival data analysis of the two-population proportion formula was used to determine the sample size. In addition, the assumptions—95% CI, 80% optimum statistical power and taking type 1 error 5% were taken with baseline CD4 count as the exposed group denoted by q1 (0.237) and the baseline CD4 count as the non-exposed denoted by q0 (0.115) from a study that was conducted at Amhara regional state hospitals[19] and the final total sample size, after adding 10% as incomplete or inconsistent data were 336.

Sampling procedure

A simple random sampling technique via computer generated system was used to select the study participants from January 2005 to December 2018.

Data collection tools and procedures

A data abstraction checklist was used to obtain data from medical records. The checklist was developed from the Ethiopian Federal Ministry of Health's HIV care and ART intake forms. The data abstractors were three bachelor's degree nurses with prior experience working in an ART clinic and ART training, and the supervisor was a master's degree nurse. Data abstractors combed through patient charts and extracted information. A main investigator assessed the quality of the data collected by data collectors every day. The pretest was carried out on 19 medical records to ensure that the data extraction check list was consistent.

Data management and analysis

The data entered in Epi Info V.7.2 were examined for uniformity, coding errors, accuracy and incomplete data after being processed by STATA V.14.0 Software. The median, mean, percentage and frequency were employed to calculate the descriptive and summary statistics. Tables and graphics were used to present the data. The incidence of antiretroviral treatment failure was estimated by dividing the total number of children who experienced antiretroviral treatment failure during the follow-up period by the total number of child person-years of observation. The Kaplan-Meier curves were used to determine the overall median survival rates. Furthermore, the Kaplan-Meier curve was used to compute the median survival time for distinct categories. A log-rank test was applied to investigate at the variation between the predictors and the p value.

Assumptions about the Cox proportional hazard model and the goodness of fitness were evaluated using the Schoenfeld residual (global test=0.95800) and the stphplot-Log-Log parallel plot of survival, respectively. The Cox proportional hazard model was fitted to bivariate and multivariate data to discover predictors of ART failure. The variables that had a bivariate analysis p value of up to 0.25 were added to the multivariate model to determine their relevance. For the purpose of calculating an adjusted HR (AHR) with a 95% CI, variables with a pvalue of less than 0.05 in the multivariable analysis were assumed to be significantly linked with the dependent variable.

Patient and public involvement

The study report was shared with all the stakeholders (University of Gondar comprehensive specialised hospital, technical and financial partners, non-governmental organisations, etc).

The inputs and recommendations from different parties have been incorporated into the final report. The recommendations made by this implementation

Table 1 Sociodemographic characteristics among HIV-infected children in the University of Gondar compressive specialised hospital, North West, Ethiopia

Variable	Frequency (n=336)	Percentage (n=100%)
Age at enrolment		
<5 years	101	30.1
5–9 years	114	33.9
≥10 years	121	36
Sex		
Male	177	52.7
Female	159	47.3
Residence		
Urban	282	83.9
Rural	54	16.1
Parental status of the child		
Both alive	211	62.8
Mother alive, but father dead	75	22.3
Mother dead, but father alive	19	5.7
Both dead	31	9.2
Relation of the caregiver to the child		
Parent	285	84.82
Sister/brother	23	6.84
Uncle/aunt	11	3.27
Grandparent	13	3.87
Orphan	6	1.2
Marital status of the caregiver		
Single	12	3.6
Married	219	65.2
Divorced	13	39
Widowed	92	27.4
HIV status of the mother/caregiver		
Reactive	299	89
Non-reactive	27	8
Unknown	10	3

research have been taken into account in the University of Gondar comprehensive specialised hospital to reduce the burden of treatment failure among HIV-infected children.

RESULTS

Sociodemographic characteristics

A total of 336 HIV-infected children who were on a first-line ART regimen were included in the study, of which 177 (52.7%) of them were males. The mean age of the study participants was 7.75 (3.68 SD) years. Nearly one-third (30.1%) of the children were under 5 years old. The majority (83.9%) of the respondents were from urban areas and 296 (88.1%) of those children live with their parents. Eighty-nine per cent of the children's caregivers were HIV positive (table 1).

Clinical characteristics, treatment side effects and regimen change

A total of 39 (11.60%) children had baseline WHO clinical stage IV and 97 (28.86%) children had baseline WHO clinical stage III. In 53 (15.8%) of the children, the CD4 count was less than 200 cells/mm^3 at baseline, with a median CD4 count of 326 (IQR; 212–532). Regarding prophylaxis use, 274 (81.5%) of the respondents were on co-trimoxazole preventive therapy and 37 (11%) were on isoniazid preventive therapy. Almost one-third (27.1%) of children had an initial regiment change during the follow-up period. Of these, 47 (14%) children had ART treatment failure. Nineteen (5.7%) were due to drug toxicity, and seven (2.1%) were due to drug out of stock (table 2). In terms of frequency, TB was found in 33% of the children, followed by bacterial pneumonia (14.1%).

Incidence of first-line antiretroviral treatment failure during follow-up period

Children were followed for a minimum of 9 and a maximum of 168 months. The median follow-up period was 81 months (IQR 51–116 months) with a total person-time observation of 27 058 person-months. About 47 (14%) children developed treatment failure. Of those, 13 (27.65%) were immunological, 14 (29.3%) were clinical failures, 11 (23.35%) were virological failures and 9 (19.4%) were both clinical and immunological failures. At the time of establishing treatment failure, all the children had been on ART for at least 6 months, and 33 (70%) were switched to second-line drugs. The overall incidence rate was 2.1 (95% CI 1.57 to 2.78) per 100 child years. The ART failure-free survival probability at the end of 20 months was 0.99 (95%CI 0.97 to 0.99); at the end of 3 years was 0.97 (95% CI 0.95 to 0.98); at the end of 6 years was 0.91 (95% CI 0.87 to 0.94); at the end of 9 years was 0.82 (95% CI 0.75 to 0.86) and at the end of 14 years was 0.71 (95% CI 0.62 to 0.79) (figure 1). During the follow-up period, TB was the most common opportunistic illness (33%).

The indicated statistically significant differences in survival curves were observed among groups such as children with level of ART adherence, OIs, WHO clinical staging III/IV and CD4 count (figure 2).

Predictors of treatment failure during follow-up period

In the bivariate Cox proportional hazard model fitted, residence, disclosure of HIV status of the child, duration of follow-up, initial regimen initiation, baseline CD4 count, WHO clinical staging, weight for age, height for age, adherence and baseline OI occurrence were significant at a p<0.25. In the multivariable models, four variables were predictors of first-line ART treatment failure at the 95% significance level. According to the analysis, children who had fair and poor ART adherence had a 6.5 and 6.6 times higher risk of developing treatment failure than children who had good ART adherence, respectively.

This study found that participants with baseline advanced WHO clinical staging III/IV had a 3.0 increased

Table 2 Clinical, immunological and treatment characteristics, among HIV-infected children in the University of Gondar compressive specialised Hospital, North West, Ethiopia

Variable	Response	ART failed	Not ART failed	Frequency/(percentage)
WHO clinical staging at baseline	Stage I /II	7	193	200 (59.5)
	Stage III / IV	40	96	136 (40.5)
CD4 count or CD4% at baseline	<200 cells/mm^3	23	30	53 (15.8)
	200–350 cells/mm^3	6	106	112 (33.3)
	350–500 cells/mm^3	6	67	73 (21.7)
	>500 cells/mm^3	5	93	98 (29.2)
Haemoglobin level at baseline	<10 g/L	15	6	21 (6.3)
	>10 g/L	32	283	315 (93.8)
BMI	Normal	32	251	283 (84.2)
	Underweight	18	35	53 (15.8)
Height/age	Normal	29	267	296 (88.1)
	Stunting	18	22	40 (11.9)
Opportunistic infection	No	5	173	178 (53)
	Yes	42	116	158 (47)
Past TB treatment	No	17	254	271 (80.7)
	Yes	30	35	65 (19.3)
Opportunistic infection prophylaxis given	Not given	6	4	10 (3)
	Co-trimoxazole	23	251	274 (81.5)
	INH	10	20	37 (11)
	Both co-trimoxazole and INH	8	7	15 (4.5)
ART adherence	Good	8	230	238 (70.8)
	Fair	6	25	31 (9.2)
	Poor	33	34	67 (19.2)
Disclosure status	Disclosed	22	150	172 (51.2)
	Non disclosed	25	139	164 (48.8)
Drug side effect	Yes	27	25	72 (21.4)
	No	20	244	264 (78.6)
Does the regimen change	Yes	34	57	91 (27.1)
	No	13	232	245 (72.9)

ART, antiretroviral therapy; BMI, body mass index; INH, Isoniazid; TB, tuberculosis.

risk of having ART treatment failure. Similarly, children who had a baseline CD4 count less than 200 cells/mm^3 had 3.61 times higher risk of developing treatment failure than children who had a baseline CD4 count of >200 cells/mm^3. This study found that children who had baseline OIs were 4.2 times more likely to develop ART treatment failure than children who had no OIs (table 3).

DISCUSSION

The cumulative incidence of treatment failure in this study was 14% (95% CI 10.4% to 18.5%), which was comparable with studies conducted in Addis Ababa (14.1%),[20] Chennai and Mumbai clinics in India (11% and 14%, respectively)[21] and a multicentre study in the UK and Ireland (18%).[22]

However, this study showed a lower incidence of failure rate than a study conducted in Adama regional hospital (69.8%).[23] This difference may be explained by differences attributed to the study area, study period and follow-up period. Similarly, this study indicated a lower rate than the studies conducted in Uganda (34%),[24] Mozambique-Uganda (29%),[5] Nigeria (33.3%),[25] Malaysia (54.9%)[26] and Thailand (33.7%).[27] This difference may be explained by differences in sociodemographic characteristics and differences in the diagnostic criteria for treatment failure. Hence, the above studies were assessed using viral load to diagnose treatment failure earlier than clinical and immunological indicators. In Ethiopia, diagnosis and treatment failure using viral load started recently; it may influence the rate of treatment failure compared with other countries. On the other hand, a higher failure rate has been observed in this study than in a study conducted by Amhara regional hospitals (7.7%).[19] This difference may be explained by

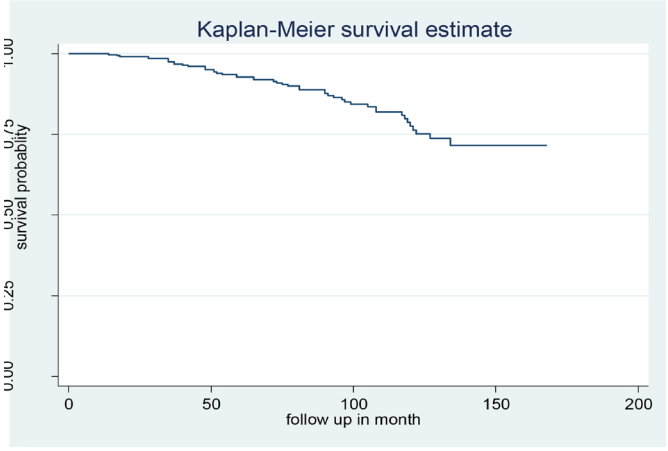

Figure 1 Survival plot of predictors for treatment failure among children on ART by opportunistic infection, level of adherence, WHO clinical staging and CD4 count, respectively, at University of Gondar compressive specialised hospital, North West, Ethiopia from January 2005 to December 2018. ART, antiretroviral therapy.

differences in the study period and the diagnostic criteria for treatment failure, because the above study uses only two WHO criteria. This study indicated a higher rate than a study conducted in India (5.1%).[28] This difference may be explained by differences in sociodemographic characteristics, differences in sample size, the difference in the follow-up period and differences in healthcare service.

The incidence rate of this study was 2.1 (95% CI 1.5708 to 2.7844) per 100 person-years of observation, which was comparable with a study conducted in Amhara regional hospitals (2.64 per 100 person-years).[19] This consistency could be because the previous study was conducted on

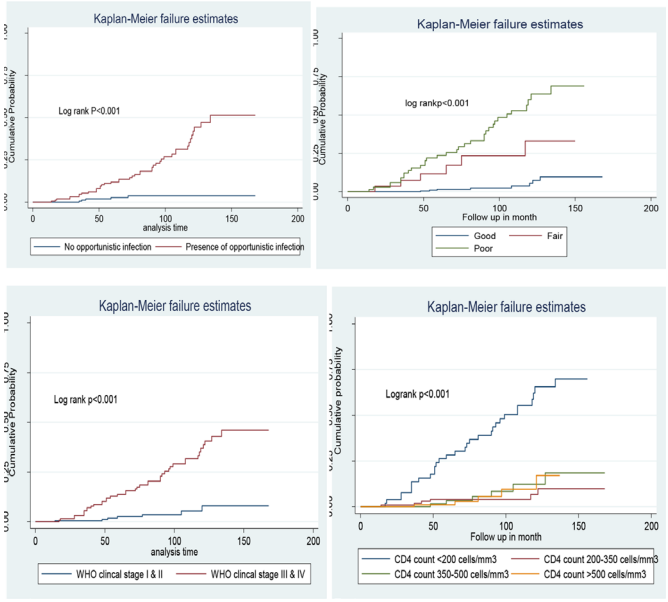

Figure 2 Kaplan-Meier survival curve showing the probability of treatment failure of HIV-positive children on first-line antiretroviral therapy at University of Gondar compressive specialised hospital, North West, Ethiopia from January 2005 to December 2018.

similar study participants and similar cultural, social and economic aspects of the study participants, and also because both studies had a longer follow-up period. However, it has a lower incidence rate than a study conducted in Addis Ababa (3.0 per 100 person-years),[29] Mozambique and Uganda (20.0 events per 100 person-years (95% CI 17.5 to 22.9),[5] Uganda (8.6 per 100 person-years)[24] and South Africa (4.5 per 100 person-years).[30] The difference might be due to the variations in the study area, the duration of time on ART and the follow-up periods, since a shorter follow-up period is likely to find a higher probability of failure when compared with a study with a longer follow-up period. Also, there may be differences in the diagnostic criteria for treatment failure, like different viral load cut-off points, and this may be due to improvements in healthcare services in the later periods of follow-up as compared with earlier periods.

This study shows that the incidence and rate of failure vary over the years. ART failure-free survival probability at the end of 20 months was 0.99 (95% CI 0.97 to 0.99); at the end of 3 years was 0.97 (95% CI 0.95 to 0.98); at the end of 6 years was 0.91 (95% CI 0.87 to 0.94); at the end of 9 years was 0.82 (95% CI 0.75 to 0.86) and at the end of 14 years was 0.71 (95% CI 0.62 to 0.79). This difference could be due to the fact that outcome definition criteria (diagnostic criteria) or guideline National Guidelines for Comprehensive HIV Prevention, Care and Treatment are revised from time to time, as well as when children and caregivers gain knowledge about the importance of ART medication and how to take it correctly throughout the year.

During the follow-up period, TB was the most common opportunistic illness (33%). This finding is congruent with research undertaken in Ethiopia (29.8%) and India (34.6%).[31 32] In contrast, a study conducted in North America, discovered that pneumonia is a prevalent OI.[33]

In this study, it was found that children who had fair or poor adherence to ART drugs had a higher risk of treatment failure than children who had good adherence to ART drugs. Similar findings were reported in other studies conducted in Gondar, Ethiopia,[34] Fiche and Kuyu hospitals, Oromia region, Ethiopia[35] and Uganda.[36] This may be due to adherence to ART drugs, which suppress viral replication, and when viral replication is suppressed, the CD4 cell count increases. However, poor adherence allows more viral replication, which in turn increases infection of more CD4+cells and ultimately depletes their numbers. Furthermore, children will face several problems such as treatment failure, drug resistance and the occurrence of OIs that could lead to poor treatment outcomes. Thus, it would be helpful to provide treatment adherence counselling to the parents and caregivers of the child at the start of treatment and during the follow-up periods.

We also found that children who had baseline advanced WHO clinical staging III or IV were three times more likely to experience ART treatment failure than children who had WHO clinical stage I or II. Similar results have been reported from Gondar,[34] Kuyu hospital, Oromia

Table 3 Predictors of first-line antiretroviral treatment failure among children on ART at the University of Gondar comprehensive specialised Hospital, Ethiopia

	Survival status				
Variables	**Event (n=47)**	**Censored n=289**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**	**P value**
Age (years)					
<5	12	89	0.9 (0.45 to 2.02)	–	
5–9	19	95	1.4 (0.73 to 2.78)		
≥10	16	105	1		
Sex					
Male	28	149	0.6 (0.37 to 1.18)	–	
Female	19	140	1		
Residence					
Urban	248	34	0.39 (0.20 to 0.74)*	1.74 (0.48 to 6.25)	
Rural	13	41	1	1	0.35
Relation of the caregiver to the child					
Parent					
Sister/brother	21	256	1.5 (0.81 to 4.12)	–	
Uncle/aunt	9	18	0.4 (0.35 to 5.18)	–	
Grandparent	9	6	1.3 (0.26 to 7.16)	–	
Baseline CD4 count					
<200 cells/mm^3	23	30	8.6 (3.32 to 22.28)*	3.61 (1.12 to 11.54)†	0.03
200–350 cells/mm^3	6	106	0.7 (0.22 to 2.44)	1.60 (0.45 to 5.63)	0.46
350–500 cells/mm^3	6	67	1.2 (0.36 to 3.95)	1.74 (0.48 to 6.25)	0.39
>500 cells/mm^3	5	93	1	1	
Baseline WHO clinical staging					
I/II	7	193	1	1	
III/IV	40	96	7.1 (3.19 to 15.94)*	3.08 (1.17 to 8.08)†	0.02
Baseline OIS					
No	5	173	1	1	
Yes	42	116	9.7 (3.80 to 24.36)*	4.22 (1.44 to 12.30)†	0
BMI					
Normal	32	251	1	1	
Underweight	18	35	2.6 (1.32 to 4.34)*	0.91 (0.51 to 1.92)	0.07
Height for age					
Normal	29	267	1	1	
Stunting	18	22	4.0 (2.24 to 7.27)*	1.63 (0.69 to 3.81)	0.25
Disclosure status					
Disclosed	22	150	0.7 (0.41 to 1.30)	–	
Non disclosed	25	139	1		
Adherence					
Good	8	230	1	1	
Fair	6	25	6.8 (2.36 to 19.66)*	6.5 (2.03 to 21.39)†	0
Poor	33	34	15 (7.09 to 33.29)*	6.6 (2.64 to 16.53)†	0
Duration of follow-up					
<34 months	7	29	0.14 (0.06 to 0.32)*	0.8 (0.31 to 2.19)	0.71
>34 months	40	260	1	1	
Initiation regimen					
ABC or AZT or TDF+3TC + NVP	32	200	0.24 (0.10 to 0.58)*	0.99 (0.33 to 1.30)	0.66
ABC or AZT or TDF+3TC+EFV	9	78	0.22 (0.08 to 0.63)*	0.16 (0.04 to 1.57)	0.75
ABC or AZT+3TC +LVP/r	6	11	1	1	

*Variables p<0.2
†Variables having p<0.05
ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; BMI, body mass index; EFV, efavirenz; LPV/r, lopinavir based; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; OIS, opportunistic infections; TDF, tenofovir.

region, Ethiopia[35] and southern Ethiopia.[37] This may be due to having advanced WHO stage III and IV compromised children's immunity and can increase the replication of the virus. This may affect the response of children to the treatment.

This study showed that a baseline CD4 count <200 cells/mm^3 was a predictor of treatment failure. This finding was similar to other studies conducted in Gondar,[34] Wolidia,[38] Addis Ababa,[20] India[39 21] and Cambodia.[40] The possible explanation for this may be that patients with a very low CD4 count are more likely to have different OIs, and the added burden of these diseases further complicates their treatment response. Furthermore, as CD4 counts decline, virus replication accelerates, resulting in the rapid accumulation of drug resistance. The circulation of such resistant viruses can have a negative impact on treatment choice.

We also discovered that children with baseline OIs were four times more likely to fail ART treatment than children without opportunistic infections. This association was similar to studies conducted in Amhara regional state, Ethiopia[19] and India.[24] With the logical reasoning that baseline OIs lead to decreased CD4 count, disease progression and higher chances of associated ill health and lower compliance due to intolerance.

This study was conducted in a long-term follow-up study that can provide a reliable estimate of predictors of first-line antiretroviral treatment failure among children. Moreover, this study used virological failure in addition to clinical failure and Immunological failure as outcome variable (treatment failure), which is not mainly conducted in Ethiopia before. On the other hand, due to its retrospective nature, some variables, such as children's educational status, family economic status, caregivers' awareness levels, were not accessible in the medical records and, therefore, were not included in this study, which may affect the outcome variable.

CONCLUSION

The incidence of first-line ART treatment failure was found to be high. Baseline OIs, poor and fair adherence, advanced WHO clinical staging III/IV, and a CD4 count less than 200 cells/mm^3 were all predictors of first-line treatment failure. Early identification of associated factors and monitoring treatment failure has been necessary for the optimal management of HIV-infected children who are receiving ART and to prevent further complications.

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