BMJ Open Incidence and risk factors of first-line antiretroviral treatment failure among human immunodeficiency virus-infected children in Amhara regional state, Ethiopia: a retrospective follow-up study

Malede Mequanent Sisay,¹ Tadesse Awoke Ayele,¹ Yalemzewod Assefa Gelaw,¹ Adino Tesfahun Tsegaye,¹ Kassahun Alemu Gelaye,¹ Melkitu Fentie Melak²

To cite: Sisay MM, Ayele TA, Gelaw YA, *et al.* Incidence and risk factors of first-line antiretroviral treatment failure among human immunodeficiency virus-infected children in Amhara regional state, Ethiopia: a retrospective follow-up study. *BMJ Open* 2018;**8**:e019181. doi:10.1136/bmjopen-2017-019181

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-019181>).

Received 23 August 2017
Revised 19 December 2017
Accepted 6 February 2018

¹Department of Epidemiology and Biostatistics, Institute of Public Health, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

²Department of Human Nutrition, Institute of Public Health, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

Correspondence to

Malede Mequanent Sisay;
maledecsa@gmail.com

ABSTRACT

Objective This study aimed to assess the incidence and risk factors of treatment failure among HIV/AIDS-infected children who were on antiretroviral therapy (ART) in Amhara National Regional State, Ethiopia.

Methods A retrospective follow-up study was conducted from January 2010 to March 2016. A total of 824 children under the age of 15 who had started ART were included in the study. Data were collected from children's medical charts and ART registration logbook using a standard checklist. A Weibull regression model was used to identify the risk factors of treatment failure. Adjusted HRs (AHRs) with 95% CIs were used to declare statistical significance.

Results The mean ($\pm$ SD) age of the children was 6.4 ± 3.6 years, with a median (IQR) follow-up of 30.5 (14.6–51.4) months. Sixty-three children (7.7%, 95% CI 5.8 to 9.5) developed treatment failure, 17 (27.0%) of whom were immunological and 46 (73.0%) were clinical failures. The incidence rate of treatment failure was 22.1/10 000 person-months. The cumulative probability of failure was 0.4, with 28 562.5 person-month observations. Lack of disclosure (AHR=4.4, 95% CI 1.8 to 11.3), opportunistic infections during initiation of ART (AHR=2.3, 95% CI 1.3 to 4.1) and prolonged follow-up (AHR=0.06, 95% CI 0.02 to 0.18) were the main predictors of treatment failure.

Conclusion This study revealed that the incidence of treatment failure remains a significant public health concern in Ethiopia. Undisclosed HIV status to children, the presence of opportunistic infections during initiation of ART and prolonged follow-up were found to be the main predictors of treatment failure. Hence, early detection of treatment failure and further studies on viral monitoring need to be considered.

BACKGROUND

Globally, the HIV pandemic has affected over 36.9 million people. Of these, 2.6 million were children under 15 years of age. About 90% of new HIV infections among children and 150 000 (5.8%) of child death were in

Strengths and limitations of this study

- The study included the antiretroviral therapy centres of six public hospitals, along with prolonged follow-ups.
- Data were collected from routine medical care records and there were limited data on possible predictors of failure, such as laboratory assessment and prevention of maternal to child transmission.
- There might be an underestimation of treatment failure. Data mainly depended on clinical and immunological criteria. Virological failure was not used to detect treatment failure.

Sub-Saharan Africa.¹ In Ethiopia, 134 586 children were living with HIV/AIDS in 2014.² A previous report showed that one in four (25%) of the HIV-infected children die without treatment before their fifth birthday due to AIDS-related diseases.³ The incidence of HIV infection has been reduced, and AIDS-related deaths in Sub-Saharan Africa declined by 48% between 2004 and 2014^{1 4} due to the scale-up of antiretroviral therapy (ART).

Globally, a lot of progress has been made over the past few years towards the prevention of the incidence and access to treatment.² Hence, globally, 32% of HIV-infected children were on ART; 41% of them were in Sub-Saharan Africa, while 23.5% lived in Ethiopia.^{1 5}

The increment of the utilisation of ART raised the issue of drug resistance⁶ and subsequent treatment failure presenting as one or more of clinical, immunological or virological failure in middle-income and low-income countries.⁶ The benefit of first-line

antiretroviral drugs (ARVs) could be greatly compromised by ART failure in children.

The WHO recommended the use of regular virological monitoring for both developed and resource-limited settings.⁷ Due to cost implications, currently clinical and immunological criteria are used to monitor treatment failure in resource-limited settings,⁸ although the WHO clinical and CD4 criteria have poor sensitivity and specificity in detecting virological failure.^{9–11}

Treatment failure and drug toxicity are critical in the national ART programme. Public health leaders consider the availability of financial, human and other essential resources, as well as access for the most at-risk populations.¹² But treatment failures are not well-documented, while there is a large scale-up of ARV supplies in resource-limited countries like Ethiopia. Studies done in Africa showed that the rate of treatment failure among children was heterogeneous geographically. For example, 18.8% of children in Nigeria¹³ and 26%–34% in Uganda^{14 15} reported treatment failure. Out of the 29% failure in Mozambique and Uganda, 46% and 53% were immunological and clinical failures, respectively.¹⁶ In Thailand the regimen was changed in 17.1% of children due to treatment failure.¹⁷

A study conducted in Addis Ababa showed that 14.1% of children had treatment failure. Of these, 5.9% were clinical, 6.7% were immunological, and 1.5% were both clinical and immunological failures.¹⁸ In Adama 69.8% were switched to second-line treatment due to treatment failures.¹⁹ There has been limited evidence on the effects of clinical and sociodemographic factors on poor treatment outcomes in the study setting.

This study investigated the incidence of treatment failure and risk factors among children below 15 years of age who were on ART in the public hospitals of the Amhara National Regional State.

METHODS

Study design and setting

A retrospective follow-up study was conducted at six public hospitals, namely the University of Gondar Teaching Hospital, Debre Tabor Hospital, Felege Hiwot Specialized Hospital, Debre Markos Hospital, Dessie Referral Hospital and Debre Berhan Referral Hospital, from January 2010 to March 2016.

Amhara National Regional State is the second largest region in Ethiopia, with great climatic, geographical and cultural diversity. According to the Central Statistical Agency of Ethiopia, Health and Health Related Indicators published by Federal Ministry of Health (FMoH), Amhara has 19 hospitals, 520 health centres and 2941 health posts. The Amhara National Regional State has an estimated population of 18 167 982, with 9 110 481 men and 87.4% rural inhabitants.¹²

Since 2005, the Amhara referral hospitals have been providing free ART services as part of the National AIDS Control Programme. The hospitals provide clinical care, including laboratory and pharmacy services.

Study participants

The inclusion criteria for the children were aged below 15 years, initiation into ART and follow-up of at least 6 months, plus availability of required information such as age, CD4 count and at least two visits after the initiation of ART. Of 11865 registered children, 824 were included in the study.

Sample size and sampling technique

The sample size was calculated based on a log-rank test with the assumption of the proportional Cox hazard model.²⁰ In a previous study, chronic diarrhoea after initiation of ART was taken as a significant predictor of failure, with an HR of 3.44.¹⁸ An assumption of significance level $\alpha=0.05$ ($z_{\alpha/2}=1.96$) and power $1-\beta=0.8$ ($z_{\beta}=0.84$) were considered. Additionally, a 10% difference in favour of lost to follow-up (incomplete information) was considered. Finally, a total sample of 824 was obtained.

A systematic random sampling technique was used to select the participants. The sample size was proportionally allocated to each randomly selected hospital in order to obtain fair or proportional size of study participants in all hospitals for the sake of representativeness.

Data collection tools and procedures

A structured data abstraction checklist was adopted from the HIV care/ART intake forms of the Federal Ministry of Health of Ethiopia.³ Training was given to data collectors on how to review registration logbooks and medical charts and maintain confidentiality of the data. ART nurses working in the ART clinics were recruited as data collectors.

The primary outcome was treatment failure, defined as clinical or immunological failure. We used the standard definition of clinical failure as occurrences of new opportunistic infections (OIs) or malignancies, or failure to sustain growth rate in a child who had responded initially, or loss of neurodevelopmental milestones having excluded other causes like inadequate nutrition and tuberculosis (TB) after 6 months of effective treatment. Immunological failure was also defined according to the national guidelines. That is, a child younger than 5 years should have persistent CD4 levels below 200 cells/mm³ or <10%, and a child older than 5 years should have persistent CD4 levels below 100 cells/mm³. Virological criteria were not used because of the complexity of defining ART failure in children using viral load and the unavailability of regular virological tests in Ethiopia.^{3 21} In addition, all other outcomes such as death and lost to follow-up are defined as censored events, unless there is a clear indication of treatment failure. Time to the first occurrence of any of these outcomes was calculated by subtracting the date of Highly active antiretroviral therapy (HAART) regimen initiation from the date the event occurred.

Several studies have shown that there is no perfect way to measure adherence; however, it can be assessed at each visit through ARV pill count or pharmacy records, and

missed or late clinic visits in resource-poor countries.^{21–24} 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’ ($\geq 95\%$ adherence) or FAIR (80%–95%), while POOR adherence is less than 80%.²¹ Thus adherence to ART was assessed using retrospective records review. Missing doses in the last 3 days or missing >15 doses since last visit was defined as poor adherence.

We also extracted data on sociodemographic characteristics (age and sex), clinical characteristics (WHO clinical staging, CD4 count at initiation of ART, change in weight, presence of OIs and calendar year of starting ART) and treatment-related factors (drug regimen, OI prophylaxis, history of first-line modification, treatment duration and drug side effects).

Data processing and analysis

The data were checked for inconsistencies, coding errors, completeness, accuracy, clarity and missing values before they were entered. The data were entered using Epi Info V.7 and then exported to R V.3.2.0 statistical software for further data cleaning and statistical analysis.

Summary measures such as counts, percentages, medians, IQRs, means and SD were computed. A Kaplan-Meier curve method and log-rank test were applied to estimate the probability of treatment failure at a given time and to compare survival probability between categorical variables, respectively.

The assumptions of log-rank test and proportional hazards (ie, probability of treatment failure occurring at any time point is the same for each population) were checked²⁵ using graphical and statistical tests for time to treatment failure and to identify the potential predictors.

Weibull and exponential models were used to identify the predictors of treatment failure by considering heterogeneity between hospitals, and hence frailty model was also used.^{26–27} The factors significantly associated with first-line ART failure in the univariate models at P value less than 0.2 were included in the multivariable survival model and were further examined in frailty models. A default enter selection procedure was used to adjust models, with a variable being included in the model fitted. A more parsimonious hazard model was chosen by means of the likelihood ratio test and Akaike information criterion (AIC). The proportional hazard model assumption was tested.

RESULTS

Baseline characteristics

A total of 1006 samples were screened, of which 52 (5.2%) were excluded following the inclusion criteria. However, 130 (13.6%) were further excluded because of incomplete recording. Finally, a total of 824 children were included in the analysis. More than half (445, 54.1%) were female. The mean ($\pm$ SD) age at initiation of ART and the average duration of follow-up were 6.4 ± 3.6 years

and 34.7 ± 21.3 months, respectively. About 34 (4.15%) of the participants had history of use of PMTCT (prevention of maternal to child transmission) service. Of whom, 8 (23.5%) received only nevirapine (NVP) ARV during PMTCT, whereas 37.50% received both NVP and zidovudine (AZT). At initiation of treatment, 294 (35.8%) were in WHO clinical stages III and IV. Majority (588, 71.5%) of the children were initiated with NVP-based regimen with d4T-3TC-NVP and AZT-3TC-NVP, whereas efavirenz-based regimens were used in 218 (26.5%) of the patients. More than half (62.6%) had CD4 count above 350 cells/ mm^3 .

The median z -scores for weight and height were -1.53 (IQR: -2.49 to -0.25) and -0.77 (IQR: -2.36 to 0.09), respectively. During the initiation of ART, 218 (26.4%) had OIs. The most common OIs were unexplained persistent diarrhoea (>14 days) (14.2%), followed by pulmonary TB (13.3%). After the initiation of ART, 99 (12.0%) of the children developed OIs. During follow-up, the main (17.2%) OI was pulmonary TB. On the level of treatment adherence, 447 (54.9%) had good adherence ($>95\%$). Furthermore, the overall full disclosure status (age 7 years and older) of HIV to children was 182 (22.1%) (table 1).

Treatment failure

Children were followed for a minimum of 6 and a maximum of 77.83 months. The median (IQR) follow-up period was 30.5 months (14.6–51.4 months). The total person time observation was 28562.5 person-months.

A total of 63 (7.7%) children developed treatment failure. Of these, 17 (27.0%) failures were reported within the first 24 months of follow-up. Of the failures, 17 (27.0%) were immunological and 46 (73.0%) were clinical failures. Only 15 (23.8%) children were switched to second-line drugs after first-line treatment failure, confirmed by virological failure (plasma viral load above 1000 copies/mL). At the time of establishing treatment failure, all the children had been on ART for at least 6 months.

The main reasons for modifying the baseline drug regimen for 299 (36.3%) of the children were drug stockout, drug side effects, clinical failure and new TB case for 145 (54.3%), 72 (27.0%), 24 (9.0%) and 8 (3.0%), respectively (figure 1).

The incidence of treatment failure during first-line regimen was 22.1 (95% CI 17.2 to 28.2) per 10000 person-months of observation. The incidence of immunological failure was 5.96 (95% CI 3.7 to 9.6) per 10000 person-months and clinical failure was 16.1 (95% CI 12.1 to 21.5) per 10000 person-months. The cumulative probabilities of failure at 20, 40, 60 and 80 months were 0.02, 0.06, 0.15 and 0.43, respectively (figure 2).

Both the estimated survival curve and the log-rank tests showed that there was no overall difference among the survival curves of the hospitals (log-rank $\chi^2(5)=7$, $P=0.2$). According to the log-rank test, sex of the child ($\chi^2(1)=4.15$, $P>\chi^2=0.042$), disclosure status

Table 1 Sociodemographic, clinical and immunological characteristics of HIV-positive children on first-line HAART in public hospitals in north-west Ethiopia, January 2010–March 2016

Variable	Category	Frequency (n)	%
Age	<5	283	34.68
	5–9	347	42.52
	≥10	186	22.79
Sex	Female	445	54.07
	Male	378	45.93
WHO clinical stage at initiation	T stage I	257	31.19
	T stage II	273	33.13
	T stage III	238	28.88
	T stage IV	56	6.80
Baseline CD4 count (cells/mm ³)	<200	145	17.60
	200–350	166	20.14
	351–500	323	39.20
	≥500	190	23.06
Duration of follow-up in months	≤34	448	54.57
	≥35	373	45.43
Weight to age z-score	<–2 SD	327	40.42
	–2 SD to 2 SD	423	52.29
	>2 SD	59	7.29
Height to age z-score	<–2 SD	245	29.91
	–2 SD to 2 SD	469	57.26
	>2 SD	105	12.82
Adherence	Poor (<95%)	368	45.15
	Good (≥95%)	447	54.85
Year of initiations	2010–2012	443	53.76
	2013–2016	381	46.24
Last status	Alive	640	77.67
	Die	17	2.06
	Lost to follow-up	27	3.28
	Transfer to	125	15.17
	Switch to second-line	15	1.82
Baseline NNRTI regimen	EFV	588	71.36
	NVP	218	26.46
	LPV/r	12	1.46
	ABC+3TC+AZT	6	0.73
Side effects	No	755	91.63
	Yes	69	8.37
Baseline opportunistic infections	No	606	73.54
	Yes	218	26.46

3TC, Lamivudine; ABC, Abacavir; AZT, zidovudine; EFV, efavirenz; HAART, Highly active antiretroviral therapy; NNRTI, Non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; LPV/r, Lopinavir/ritonavir.

($\chi^2(1)=5.12$, $P>\chi^2=0.024$), year of initiation ($\chi^2(1)=41.38$, $P>\chi^2=0.0000$), initial regimen code ($\chi^2(3)=9.09$, $P>\chi^2=0.0281$) and duration of follow-up ($\chi^2(1)=63.20$,

$P>\chi^2<0.0001$) indicated statistically significant differences of survival curve observed among groups (figures 3 and 4).

Predictors of treatment failure

Before we fit the final model, we assessed the model adequacy and chose the most parsimonious model. According to Schoenfeld global test, the overall full model satisfies the proportional hazard assumption ($\chi^2(11)=4.44$, $P>\chi=0.9554$).

Based on AIC, the Weibull (AIC=343.1636) model was more efficient than Cox proportional hazard (AIC=651.5), parametric exponential model (AIC=440.5) and frailty models (table 2). Thus, the inclusion of a frailty effect estimated a not statistically significant variance and indicates the absence of a heterogeneous or unobserved variability among hospitals (table 2).

In the univariate Weibull proportional hazard model fitted, sex of children, disclosure of HIV status of the child, duration of follow-up, initial regimen initiation, baseline CD4 count, drug substitutions, weight for age z-score, adherence, baseline OI occurrence and calendar year of treatment initiations were significant at a P value less than 0.2. In the multivariable models, the covariate not disclosing their HIV status, baseline OI presence and long duration of follow-up in months were predictors of the time to treatment failure of the first-line regimen at the 5% significance level. The HR for the presence of OIs during initiations of ART was 2.3 times higher than the hazard for the absence of OIs (adjusted HR (AHR)=2.3, 95% CI 1.3 to 4.0). Similarly the hazard of children who did not disclose their HIV status was 4.5 times higher than those who disclosed their HIV status (AHR=4.5, 95% CI 1.8 to 11.5). Holding the other covariates constant, children who had less duration of follow-up in months had significantly high difference to fail the treatment. Thus, those who followed up for more than 34 months were 94% less likely to develop treatment failure compared with those whose follow-up time was less than or equal to 34 months (AHR=0.06, 95% CI 0.02 to 0.19) at any time (table 3).

DISCUSSION

This study investigated the incidence and risk factors of treatment failure to first-line regimen among HIV-infected children (<15 years of age) in Amhara National Regional State hospitals in north-west Ethiopia. In this study 7.7% treatment failure and 22.1/10 000 person-months were observed. None disclosed HIV status to the child, the presence of baseline OIs and ART follow-up of more than 35 months were predictors of treatment failure.

In the study, the incidence of treatment failure was 7.7% (95% CI 5.83% to 9.46%); clinical and immunological failure accounted for 27% and 73%, respectively. In all hospitals, only 15 (23.8%) children switched to a second-line regimen. This finding was lower than that of a study done in Addis Ababa (14.1%)¹⁸ and Adama

Figure 1 Reasons of drug modification among children's first-line antiretroviral therapy regimen at public hospitals in north-west Ethiopia, January 2010–March 2016. Keys: baseline drug modification: ■ clinical failure; ■ new drug; ■ drug side effects; ■ drug stockout; ■ new tuberculosis (TB) case; ■ virologic failure; ■ immunological failure; ■ no change in baseline drug; ■ others (such as risk of pregnancy, switch to second-line).

regional hospital (69.8%).¹⁹ Moreover, this study showed a lower failure rate than other studies done in Africa, for example Nigeria (18.8%),¹³ Uganda (34%),²⁸ a combined study from Mozambique-Uganda (29%)¹⁶ and Cambodia (8.6%).²⁹ However, the result was higher than the result in India of 5.1%.³⁰ This may be due to improvements of healthcare services in the later periods of follow-up as

compared with earlier periods. This means that there is a general consensus, in which countries encourage earlier HIV diagnosis and earlier antiretroviral treatment, and promote the use of less toxic regimens and more strategic laboratory monitoring. Furthermore, new evidence has also emerged on when to initiate ART, optimal ART regimens, the management of HIV coinfection and the

Figure 2 Kaplan-Meier survival curve showing the probability of treatment failure of HIV-positive children on first-line antiretroviral therapy at public hospitals in north-west Ethiopia, January 2010–March 2016. Key: — probability of failure of the first-line drug.

Figure 3 Survival probability plot by sex of follow-up for HIV-positive children on first-line antiretroviral therapy at public hospitals in north-west Ethiopia, January 2010–March 2016.

Figure 4 Survival probability plot by duration of follow-up for HIV-positive children on first-line antiretroviral therapy (ART) at public hospitals in north-west Ethiopia, January 2010–March 2016.

management of ART failure. Additionally, this may be explained by differences in sociodemographic characteristics, stage of the disease when ART was initiated and adherence of children, which readily affect the response to and effectiveness of ART. Another explanation may be differences in the diagnostic criteria for treatment failure. Hence the above-reported studies were assessed using viral load, which can diagnose treatment failure early and can overestimate the amount as compared with clinical and immunological indicators.

The crude incidence rate was 22.06 (95% CI 17.23 to 28.24) per 10000 person-months of observation, which was lower than the finding of the combined cohort study in Mozambique and Uganda, which reported 20.0 events per 100 person-years (95% CI 17.5 to 22.9).¹⁶ Because most failures occur soon after initiation of therapy, 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. The difference might be due to the variations in the study area and the higher number of failures in comparison with our study.

In our study, children who did not disclose their HIV status were more likely to experience treatment failure than those who did. This might be due to the fact that

disclosure tended to reduce anxiety and improve adherence in children.³ Only 22.1% of children knew their status, which is lower than the result of a cross-sectional study done at the University of Gondar (39.5%).³¹ This could be explained by differences in study designs. However, it is higher than that of a study conducted in Addis Ababa (17.4%).³² This might be due to the increase in awareness, adequate support and acceptance of people living with HIV in Addis Ababa than in the Amhara Region.

The proportion of children with treatment failure was significantly higher in the first 34 months of HAART follow-up than in the last ones. This was in contrast with the finding of a study done in Addis Ababa.³² Our study revealed 5 (3.45%) failures in the first 12 months and 21 failures (8.64%) in the last year of study. This was because the ART service provided before the universal increase of access to treatment for all children living with HIV was limited.³

The rate of OIs (26.46%) was higher than the rate of a study done in Addis Ababa (3.5%),¹⁸ which noted the common OIs were unexplained persistent diarrhoea (>14 days) (14.22%), followed by pulmonary TB (13.3%), severe recurrent pneumonia (11.47%), unexplained persistent ear discharge (12.39%), herpes zoster (10.55%) and unexplained persistent fever (≥ 30 days) (5.96%). However, this was lower than the finding of a study conducted in India, which reported 40%–49.7%.³⁰ Additionally, having advanced opportunistic disease may compromise immunity, and this may negatively affect response to treatment.

This study showed that the baseline CD4 count was not a predictor of treatment failure. This was in contrast with the result of studies done in Addis Ababa,¹⁸ Cambodia²⁹ and Thailand,³³ but consistent with the study conducted among Ugandan children.²⁸ This might be due to the high public health advocated approach to ART nowadays, which substantially increased the awareness of health-care providers and caregivers. In fact, 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. Additionally, this needs further exploration of changes in CD4 cell count using consecutive measurements.

Table 2 Summary of model comparison between semi-Cox proportional hazard models and parametric Cox regression models using AIC and other estimates

Parameter	Proportional hazard	Weibull	Exponential	Frailty	
				Exponential Gamma	Weibull Gamma
–2 log L	–289.0	–154.9	–205.4	–206.7	–154.9
AIC	602.0	339.7	438.9	443.4	341.7
BIC	658.2	409.9	504.4	513.7	416.6
LR χ^2	96.2	79.7	24.8	27.8	84.7
(P value)	(<0.0001)	(<0.0001)	(0.0248)	(0.001)	(<0.0001)

AIC, Akaike information criterion; BIC, Bayesian information criterion; LR, likelihood ratio.

Table 3 Multivariable analysis using the Weibull Cox regression model for predictors of first-line ART failure of HIV-positive children at public hospitals in north-west Ethiopia, January 2010–March 2016

	Survival status		Incidence density/10000	Crude HR (95% CI)	Adjusted HR (95% CI)
Variables	Censored	Event			
Sex of child					
Male	357	22	17	1	
Female	404	41	27	1.63 (0.97 to 2.74)	*
Disclosure status					
No	586	56	25	2.35 (1.07 to 5.16)	4.51 (1.78 to 11.45)
Yes	175	7	11	1	1
Duration of follow-up in months					
≤34	424	25	32	1	1
≥35	337	38	18	0.05 (0.02 to 0.10)	0.06 (0.02 to 0.19)
Baseline OIs					
No	567	39	19	1	1
Yes	194	24	30	1.47 (0.88 to 2.44)	2.27 (1.29 to 3.99)
Baseline CD4 count, cells/mm ³					
<200	130	15	27	1.45 (0.66 to 3.15)	*
200–350	158	8	15	0.88 (0.35 to 2.19)	*
351–500	294	29	26	1.41 (0.71 to 2.83)	
≥500	179	11	18	1	
Baseline NNRTI regimen					
NVP	544	44	20	1	
EFV	202	16	26	1.54 (0.87 to 2.72)	*
LVP/r	15	3	62	4.33 (1.34 to 13.99)	*
Year of initiations					
≤2013	402	41	19	1	
≥2014	359	22	30	7.33 (3.74 to 14.36)	*
Weight for age z-score					
<−2 SD	295	32	25	0.49 (0.17 to 1.40)	*
−2 SD to 2 SD	408	27	19	0.38 (0.13 to 1.11)	*
>2 SD	58	4	29	1	
Adherence					
Poor (<95%)	349	28	21	0.98 (0.60 to 1.63)	*
Good (≥95%)	412	35	23	1	
Drug substitutions					
No	494	31	22	1.44 (0.87 to 2.38)	*
Yes	267	32	22	1	

*Non-significant from the Weibull Cox regression model at 5% level of significance.

ART, antiretroviral therapy; EFV, efavirenz; LPV/r, Lopinavir; NNRTI, Non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; OIs, opportunistic infections.

The possible limitation of the study is that the data were collected from routine medical care records, which were limited in terms of information on possible key predictors of failures, such as PMTCT and laboratory assessments. Adherence was measured by pill count at last visit, even though the nature of the study design allowed for multiple measurements. It is because measurements abstracted from charts were

performed by different clinicians, some of whom do not adhere to the same rigorous quality control standards as the guideline. In Ethiopia, as in other low-income countries, the identification of treatment failure mainly depends on clinical and immunological criteria for the routine monitoring of patients on first-line ART. Therefore, we were unable to explore the virological failure that might have underestimated

the treatment failure. In Ethiopia, access to ART is expanding to all patients including children, and in this country HIV/AIDS care and treatment are carried out based on a guideline called the 'National Guidelines for Comprehensive HIV Prevention, Care And Treatment'. This study was carried out in Amhara Region hospitals, which provide services based on the above guidelines to patients coming from every corner of the region specifically and nationally in general, so this study can be generalised to the larger population since we have taken adequate sample size and strong study design. Therefore these findings may be generalisable to patients with treatment experience. Since our patients participated in a large multicentre study within the region and country, their experiences may not differ from that of patients accessing treatment in the remaining community-based setting because all hospitals follow the same guidelines and support. Future studies should be conducted to evaluate the best approaches to use HIV-RNA monitoring.

In conclusion, the incidence of treatment failure remains a significant public health concern in Ethiopia. Undisclosed HIV status of child, presence of OIs during initiation of ART and prolonged follow-up were found to be the predictors of treatment failure. Early detection of treatment failure is important for optimal management of HIV-infected patients receiving ART. Furthermore, future studies can examine underlying relevant factors, including repeat measurements such as CD4 count, for treatment failure.

Acknowledgements The University of Gondar Teaching Hospital, Debre Tabor Hospital, Felege Hiwot Specialized Hospital, Debre Markos Hospital, Dessie Referral Hospital and Debre Berhan Referral Hospital and data collectors deserve appreciation for their cooperation and assistance.

Contributors MMS, TAA and YAG developed the proposal, collected data, and did the analysis and write-up. TAA, YAG, ATT, KAG and MFM advised during proposal development, edited the proposal, advised during data analysis, and edited the manuscript and formatted it for publication. All the authors read and approved the final manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. However, the financial backing of this research was provided by the University of Gondar as a grant to staff. The University of Gondar Research and Community Services Directorate is acknowledged for financial support. The sponsor had no role in study design, data collection or analysis, manuscript writing, or submission for publication.

Competing interests None declared.

Patient consent Not required.

Ethics approval Ethical approval was obtained from the Institutional Review Board (IRB) of the University of Gondar. As the study was retrospective, the IRB waived that the research could be done based on record review without contacting patients. A letter of support was obtained from the Amhara Regional State Health Bureau. Permission letters were obtained from each hospital administration (University of Gondar, Felege Hiwot, Debre Tabor, Debre Markos, Debre Berhan and Dessie) and respective hospital ART coordinators. All information was kept confidential and no individual identifiers were collected.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Extra data can be accessed via the Dryad Data Repository at <http://datadryad.org/> with the doi: 10.5061/dryad.85t2hr9.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which

permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1. World Health Organization. *Global Fact Sheet 2014: World AIDS Day*, 2015.
2. Federal HIV/AIDS Prevention and Control Office (FHAPCO). *Country Progress Report on the HIV Response*: Addis Ababa, 2014.
3. Federal HIV/AIDS Prevention and Control Office Federal Ministry of Health. *Guidelines for Paediatric HIV/AIDS Care and Treatment in Ethiopia*, 2007.
4. Haberer J, Mellins C. Pediatric adherence to HIV antiretroviral therapy. *Curr HIV/AIDS Rep* 2009;6:194–200.
5. Ethiopian Ministry of Health. *For Comprehensive HIV Prevention, Care and Treatment*, 2014.
6. World Health Organization (WHO). *HIV Drug Resistance Report, HIV/AIDS Programme*. Geneva, Switzerland: Department of HIV/AIDS, 2012.
7. Gupta RK, Hill A, Sawyer AW, et al. Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:409–17.
8. World Health Organization. *Antiretroviral Therapy for HIV infection in Adults and Adolescents Recommendations for a public health approach*, 2010.
9. Mee P, Fielding KL, Charalambous S, et al. Evaluation of the WHO criteria for antiretroviral treatment failure among adults in South Africa. *AIDS* 2008;22:1971–7.
10. Castelnuovo B, Sempa J, Agnes KN, et al. Evaluation of WHO Criteria for Viral Failure in Patients on Antiretroviral Treatment in Resource-Limited Settings. *AIDS Res Treat* 2011;2011:1–6.
11. Emmett SD, Cunningham CK, Mmbaga BT, et al. Predicting virologic failure among HIV-1-infected children receiving antiretroviral therapy in Tanzania: a cross-sectional study. *J Acquir Immune Defic Syndr* 2010;54:368–75.
12. Central Statistical Agency [Ethiopia] and ICF International. *Ethiopia Demographic and Health Survey 2011*. Addis Ababa, Ethiopia and Calverton, Maryland, USA, 2012.
13. Oshikoya K, Lawal S, Oreagba I, et al. Adverse Events in HIV-infected Children on Antiretroviral Therapy at a Teaching Hospital in Lagos, Nigeria: A Retrospective Study. *Adv Pharmacoeconom Drug Safety* 2012;1.
14. Sebunya R, Musiime V, Kitaka SB, et al. Incidence and risk factors for first line anti retroviral treatment failure among Ugandan children attending an urban HIV clinic. *AIDS Res Ther* 2013;10:25.
15. Kanya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007;46:187–93.
16. Costenaro P, Penazzato M, Lundin R, et al. Predictors of Treatment Failure in HIV-Positive Children Receiving Combination Antiretroviral Therapy: Cohort Data From Mozambique and Uganda. *J Pediatric Infect Dis Soc* 2015;4:39–48.
17. Tsuchiya N, Pathipvanich P, Wichukchinda N, et al. Incidence and predictors of regimen-modification from first-line antiretroviral therapy in Thailand: a cohort study. *BMC Infect Dis* 2014;14:565.
18. Bacha T, Tilahun B, Worku A. Predictors of treatment failure and time to detection and switching in HIV-infected Ethiopian children receiving first line anti-retroviral therapy. *BMC Infect Dis* 2012;12:197.
19. Wilhelmson S, Reepalu A, Balcha TT, et al. Retention in care among HIV-positive patients initiating second-line antiretroviral therapy: a retrospective study from an Ethiopian public hospital clinic. *Glob Health Action* 2016;9:29943.
20. Chow S-C, Shao J, Wang H. *Sample Size Calculations in Clinical Research Biostatistics series*. Jones B, Lui J, eds. 2nd edn: Chapman & Hall/CRC Taylor & Francis Group, LLC, 2008.
21. Ministry of Health. *Federal Democratic Republic of Ethiopia, National guidelines for comprehensive HIV prevention, care and treatment*, 2014.
22. Ross-Degnan D, Pierre-Jacques M, Zhang F, et al. Measuring adherence to antiretroviral treatment in resource-poor settings: the clinical validity of key indicators. *BMC Health Serv Res* 2010;10:42.

23. Oyugi JH, Byakika-Tusiime J, Charlebois ED, *et al.* Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. *J Acquir Immune Defic Syndr* 2004;36:1100–2.
24. Chalker JC, Andualem T, Gitau LN, *et al.* Measuring adherence to antiretroviral treatment in resource-poor settings: the feasibility of collecting routine data for key indicators. *BMC Health Serv Res* 2010;10:43.
25. Germanaud D, Derache A, Traore M, *et al.* Level of viral load and antiretroviral resistance after 6 months of non-nucleoside reverse transcriptase inhibitor first-line treatment in HIV-1-infected children in Mali. *J Antimicrob Chemother* 2010;65:118–24.
26. Kleinbaum DG, Klein M. *et al.* Survival Analysis: A Self-Learning Text. In: Gail KKM, Samet A, Samet J, Tsiatis A, Wong W, . *Statistics for Biology and Health*. 2nd edn.
27. Machin D, Cheung YB, Parmar MK. *Survival Analysis a Practical Approach*. 2nd edn: John Wiley & Sons Ltd, 2005.
28. Sebunya R, Musiime V, Kitaka SB, *et al.* Incidence and risk factors for first line anti retroviral treatment failure among Ugandan children attending an urban HIV clinic AIDS Research and Therapy. 2013;10.
29. Barennes H, Virak K, Rouet F, *et al.* Factors associated with the failure of first and second-line antiretroviral therapies therapy, a case control study in Cambodian HIV-1 infected children. *BMC Res Notes* 2016;9:69.
30. Mukherjee A, Shah N, Singh R, *et al.* Outcome of highly active antiretroviral therapy in HIV-infected Indian children. *BMC Infect Dis* 2014;14:701.
31. Negese D, Addis K, Awoke A, *et al.* HIV-Positive Status Disclosure and Associated Factors among Children in North Gondar, Northwest Ethiopia. *Isrn Aids* 2012;2012:1–7.
32. Biadgilign S, Deribew A, Amberbir A, *et al.* Factors associated with HIV/AIDS diagnostic disclosure to HIV infected children receiving HAART: a multi-center study in Addis Ababa, Ethiopia. *PLoS One* 2011;6:e17572.
33. Bunupuradah T, Puthanakit T, Kosalaraksa P, *et al.* Immunologic and virologic failure after first-line NNRTI-based antiretroviral therapy in Thai HIV-infected children. *AIDS Res Ther* 2011;8:40.