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Original Research

Early Mortality among HIV-positive Children Initiated Anti-retroviral Therapy in Eastern Ethiopia: A Retrospective Cohort Study

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Abstract

About 1,400 children under the age of 15 years are infected with HIV every day and more than 90% of them live in sub-Saharan African countries. The speed of disease progression and death in HIV-infected children in poor countries is highly alarming. Therefore, the aim of this study was to assess incidence of early mortality and identify the factors associated with it in HIV-infected children who began ART. A retrospective cohort study was conducted on 305 children receiving ART in Hiwot Fana Specialized University Hospital and Jugol Hospital, Ethiopia. All children enrolled into HIV care from September 2010 to March 2013 were included. Data were analyzed using SPSS, Version 20. Kaplan Meier was used to estimate the probability of survival and death of the children. Additionally, Cox regression analyses were undertaken to adjust for covariates. Out of the 305 cohort of children on ART, 255(83.6%) were alive, 28(9.2%) were deceased, and 22(7.2%) were lost to follow-up. The total follow-up time was 7,312 child-months. Out of the 28 death, 18 [2.46 per 1000 child-months (95% CI, 1.5 - 3.8)] died within 6 months of the ART initiation. Children with baseline bed-ridden functional status (aRR 8.8; 95% CI 1.4 - 53.8); baseline CD4 value <350 cells/mm^3 (aRR 3.8; 95% CI 1.2 -12.7); adherence to ART <85% (aRR 8.9; 95% CI 3.5 - 22.4); and developing AIDS-defining illnesses (aRR 4.8; 95% CI 1.4 - 16.4) were factors which increased the likelihood of early mortality. There was a high rate of early mortality in our cohort. Baseline functional status; CD4 value ≤ 350 cells/mm^3; adherence to ART <85%, and developing AIDS-defining illness were factors associated with early mortality. Hence, education and early ART initiation before CD4 values fall below 350 cells/mm^3 could optimize treatment outcomes of HIV-infected children

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INTRODUCTION

The Human Immunodeficiency Virus (HIV) epidemic has brought a huge challenge to the survival of mankind (UNAIDS, 2009). According to the World Health Organization (WHO), there were approximately 35 million people worldwide living with HIV/AIDS in 2013. Of these, 3.2 million were children (<15 years old) (WHO/UNAIDS 2014). Sub-Saharan African countries remain most severely affected, accounting for 69% of the people living with HIV (PLHIV) worldwide (WHO, 2012). About 1,400 children under the age of 15 years are infected with HIV every day and more than 90% of the children who are HIV-positive live in sub-Saharan African countries (WHO/UNAIDS/UNICEF, 2011; WHO, 2012). The speed of disease progression and death among HIV-infected children in poor countries is alarming (Taha T. Graham *et al.,* 2000). In addition, the questions of durability of the treatment response and its long-term effect on mortality have remained unanswered (Renaud-Théry *et al.*, 2007). Consequently, in resource limited settings, there is a pressing need for research to further refine HIV treatment strategies among the children (Zanoni, Phungula *et al.,* 2011). In Ethiopia, there are very few research reports on the factors associated with early mortality among children who follow ART. This study, therefore, tries to explore the extent of early mortality and the clinical factors associated with the early mortality among the children on ART.

MATERIALS AND METHODS

Study Area and Period

The study was done in the ART clinics of Hiwot Fana Specialized University Hospital (HFSUH) and Jugol Hospital (JH), Harar, Eastern Ethiopia. Harar, the capital city of Harari Regional State, is about 526Km from Addis Ababa. In the town, there are two government hospitals (HFSUH and JH); one federal police hospital; one Army hospital; two private general hospitals; one Fistula hospital; eight government health centers; and nineteen health posts that provide health care services. The total health service coverage of the region is about 100%. The study was done in June, 2014.

Study Design and Study Population

A retrospective cohort study was employed on all the children (N=305) enrolled into the chronic HIV care follow up from September 11, 2010 to March 31, 2013 at Hiwot Fana Specialized University Hospital and Jugol Hospital. Participants were HIV-positive children (≤ 15 years).

Data Collection and Quality Control

To obtain complete data, the medical records of the study subjects were abstracted using a customized data collection form, which was pre-tested on 16 (5%) study participants' medical records. The data abstractors were trained. Every day, after data collection, each datum was reviewed and checked for completeness by the supervisor and the principal investigator, and the necessary feedback was given to the data collectors the next day.

A study subjects' follow-up time would end either at his/her last visit to the HIV clinic or on March 31, 2014, the administrative censoring day. For a child who died or lost to follow-up during the follow-up period, the day he or she last visited the clinic was considered, as we could not know the exact day of the event.

Study Variables

Independent Variables: In this study, the independent variables were age, sex, weight, date of HIV diagnosis, previous history of TB or other opportunistic illnesses (OIs), WHO clinical stages, new diagnoses of WHO stage III/IV or persisting stage IV, AIDS-defining illnesses and adverse drug events (ADEs), rate of adherence to the therapy during the follow-up, results of diagnostic tests (including CD4 cell counts), Liver Function Tests (LFTs), Blood Urea Nitrogen (BUN), and Creatinine (Cr) level.

Dependent Variable: In this study, the outcome variable was death. The time to death was also considered as an endpoint.

Data Processing and Analysis

The data were entered into EpiData software and analyzed with SPSS Version 20.0. The baseline demographic and clinical characteristics of the study subjects were summarized using descriptive statistics: frequency, percent, and measures of central tendency and of dispersion. In addition, chi-squared (X^2) tests were used to identify the covariates of early mortality. The covariate for which the p-value was less than 0.20 by the bivariate analysis was retained for the subsequent multivariate analysis. The survival probability and the time to death of the study participants were determined by Kaplan Meier. Moreover, Cox regression analyses were used for adjusting covariates. In all of the analyses, levels of significance were determined via two-sided p-values (P) and 95% confidence intervals (95% CI).

Ethical Consideration

The study was approved by the School of Pharmacy of Haramaya University, and to use the data from the clinical records, we obtained permission of the hospital's administration.

RESULTS

Baseline Characteristics of the Cohort

Data were retrospectively collected from the medical records of 305 cohorts of HIV-positive children aged ≤15 years. More than half of the children were female (52%). At ART initiation, of all study participants, 44.6% of them were 0 – 5 years of age, the functional status of 52.5% of them was ambulatory, and 56.4% of them had CD4 values < 350 cells/mm^3. About 15% of the children had history of documented tuberculosis and 49.3% of them were underweight at ART initiation. The mean haemoglobin of the cohort was 10.96 g/dl (SD±1.98) at initiation of ART. More than half of the children (53%) had anaemia, which was mild or moderate to severe (Table 1).

Table 1: Baseline socio-demographic and clinical characteristics of children on ART at HFSUH and JH, Sep 2010 – March 2013, Harar, Eastern Ethiopia

Variable	Characteristics	Frequency	Percent (%)
Sex	Male	146	47.9
	Female	159	52.1
Age	0 -5 years	136	44.6
	6 -12 years	148	48.5
	13 -15 years	21	6.9
Educational status	Under age	179	58.7
	Primary	98	32.1
	Secondary	28	9.2
Baseline health condition	Working	134	43.9
	Ambulatory	160	52.5
	Bed-ridden	11	3.6
CD4 cell count	<350 cells/mm^3	172	56.4
	350-500 cells/mm^3	35	11.5
	>500 cells/mm^3	98	32.1
Clinical WHO Stage	Stage I	52	17
	Stage II	115	37.7
	Stage III	118	38.7
	Stage IV	20	6.6
Previous TB history at baseline	No	259	85
	Yes	46	15
Documented other OIs history at baseline	No	43	14.4
	Yes	262	85.6
Developmental cornerstone	Appropriate	76	24.9
	Delayed	217	71.7
	Regression	12	3.9
Nutritional status at baseline	Normal	131	43.0
	Underweight	149	48.9
	Stunted	18	5.9
	Wasted	5	1.6
	Kwashiorkor	2	0.7
Baseline anemia status	No anemia	143	47
	Mild anemia	55	18
	Moderate to severe anemia	107	35

During the follow-up period, of all the study participants, 80.9% adhered to ART more than 95%, 9.2% were died, and 44.3% and 28.9% developed new AIDS-defining illnesses and new WHO stage III/IV or persisting stage IV, respectively (Table 2). Eighteen of the 28 deceased cases occurred within 6 months of the ART initiation.

Table 3 shows that 56.4% of female participants had CD4 ≤ 350 cells/ mm^3 at ART initiation. About two-thirds of the participants (65.7%) aged 6 to 15 years had CD4 ≤ 350 cells/ mm^3. Compared to their counterparts, of all the participants who had a CD4 < 350 cells/ mm^3 at ART initiation, 11% were in the WHO clinical stage IV, 18.6% had previous history of TB, 91.9% had previous history of other OIs, 79% were in regressed developmental status, 9.3% were stunted, 9.9% adhered to ART less than 85%, and 50.6% had one or more new AIDS-defining illness diagnosis.

Table 2: Cohort characteristics during follow-up period at HFSUH and JH, Sep 2010 – March 2013, Harar, Ethiopia

Variable	Characteristics	Frequency	Percent (%)
Adherence to ART	>95% adherence	243	80.9
	85-95% adherence	18	5.1
	<85% adherence	22	7.2
	Lost to follow-up	22	7.2
	Alive	255	83.6
	Diseased	28	9.2
Mortality within 6 months	No	265	93.7
	Yes	18	6.3
TB diagnosed in the follow-up	No	266	87.9
	Yes	39	12.1
New stage III/IV or persisting stage IV	No	217	71.1
	Yes	88	28.9
Documented adverse event in the follow-up	No	235	77
	Yes	70	23
Any AIDS-defining illness in the follow-up	No	170	55.7
	Yes	135	44.3

Table 3: Characteristics of patients exposed to baseline lower or higher CD4 values at HFSUH and JH, September 2010 – March 2013, Harar, Ethiopia

Characteristics	CD4 ≤ 350 cells/ mm^3—No (%)	CD4 > 350 cells/ mm^3—No (%)
Sex		
Male	75 (43.6)	71 (53.4)
Female	97 (56.4)	62 (46.6)
Age (Years)		
0 – 5 years	59 (34.3)	77 (57.9)
6 – 15 years	113 (65.7)	56 (42.1)
Educational level		
Under age for education	87 (50.6)	92 (69.2)
Primary education	66 (38.4)	32 (24.1)
Secondary education	19 (11)	9 (6.8)
Health Condition		
Working	71 (41.3)	63 (47.4)
Ambulatory	94 (54.7)	66 (49.6)
Bed-ridden	7 (4.1)	4 (3)
WHO clinical stage		
Stage I	17 (9.9)	35 (26.3)
Stage II	62 (36)	53 (39.8)
Stage III	74 (43)	44 (33.1)
Stage IV	19 (11)	1 (0.8)
Previous history of TB		
No	140 (81.4)	119 (89.5)
Yes	32 (18.6)	14 (10.5)
Previous history of other OIs		
No	14 (8.1)	29 (21.8)
Yes	158 (91.9)	104 (78.2)
Developmental Cornerstone		
Appropriate	28 (16.3)	48 (36.1)
Regression	136 (79)	81 (60.9)
Delayed	8 (4.7)	4 (3)
Nutritional status		
Normal	64 (37.2)	67 (50.4)
Underweight	87 (50.6)	62 (46.6)
Stunted	16 (9.3)	2 (1.5)
Wasted	3 (1.7)	2 (1.5)
Kwashiorkor	2 (1.2)	0 (0)
Adherence Status		
> 95%	127 (73.8)	116 (87.2)
85-95%	16 (9.3)	2 (1.5)
< 85%	17 (9.9)	5 (3.8)
Lost to follow-up	12 (7)	10 (7.5)
Anemia status		
No anemia	78 (45.3)	65(48.9)
Mild anemia	28 (16.3)	27 (20.3)
Moderate-severe anemia	66 (38.4)	41 (30.9)
New AIDS-defining illness diagnosis		
No	85 (49.4)	84 (63.6)
Yes	87 (50.6)	48 (36.4)

OIs, Opportunistic illnesses; HFSUH, Hiwot Fana Specialized University Hospital

Survival Pattern of the Cohort

Out of the 305 cohort of children on ART, 255(83.6%) were alive, 28 (9.2%) died, and 22 (7.2%) were lost to follow-up. After initiation of ART, the median time of survival the cohort was 30 months [Interquartile ranges (IQR) 18 - 30 months]. The cohort contributed to a total of 7, 312 person-months (609 child-years) of follow up. For all the death cases, the median time of death was 4 months (IQR 0.9 - 7 months). The mortality rate of the cohort was 3.8 per 1000 child-months (95% CI, 2.6 - 5.4). Out of the 28 mortality cases, 18 [2.46 per 1000 child-months (95% CI, 1.5 - 3.8)] died within 6 months of the ART initiation. Tuberculosis infections and other opportunistic infections were the causes of 32% and 25% of the deaths, respectively; whereas the causes of the remaining deaths were not recorded. The cumulative survival probabilities of the cohort were 0.91 at six months, 0.88 at twelve months, and 0.86 at twenty four months (Figure 1). However, children with CD4 > 350 cells/mm^3 at ART initiation had higher probability of survival compared to that of the children with CD4 ≤ 350 cells/mm^3 (Figure 2).

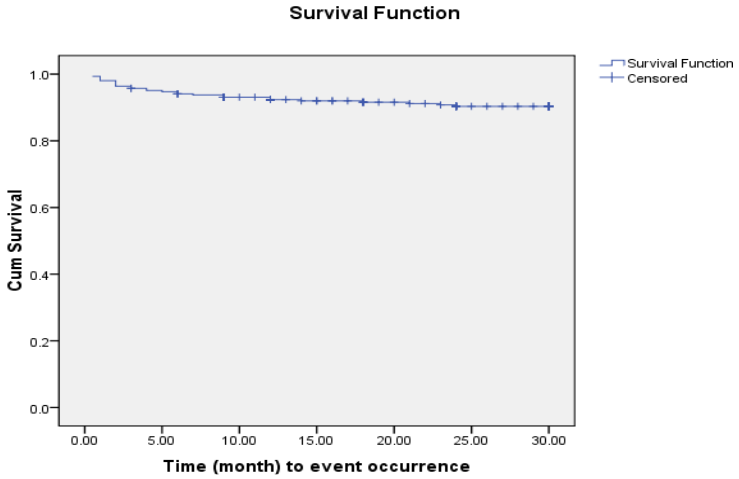

Figure 1: Kaplan Meier survival curve among HIV –infected children on ART at HFSUH and JH, September 2010 – March 2013

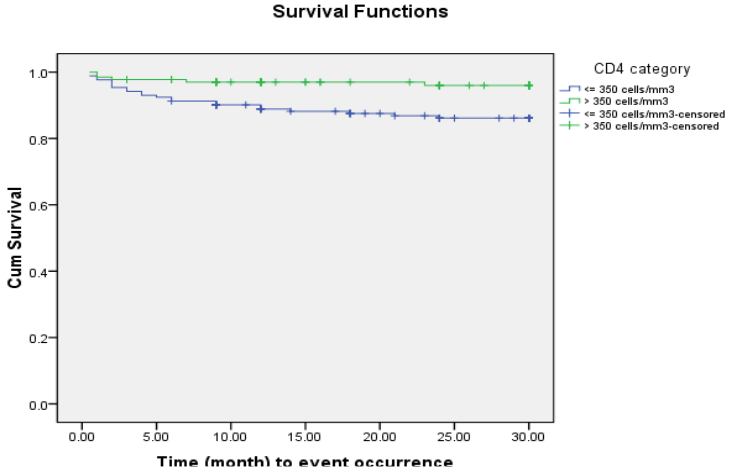

Figure 2: Kaplan Meier survival curve among HIV –infected children on ART with CD4 values > 350 cells/mm^3 versus CD4 values ≤ 350 cells/mm^3 at HFSUH and JH, September 2010 – March 2013

Factors Associated with Early Mortality

In the bivariate analyses, the factors associated with increased likelihood of early mortality were baseline bed-ridden functional status, CD4 ≤ 350 cells/mm^3, WHO stage IV, less than 95% adherence to ART, being under age for education, and developing AIDS-defining illness. The bed-ridden study subjects at the treatment initiation were 13.3 times more likely to die early than those who were working (cRR 13.3; 95% CI 4.7 – 37.7). The children whose baseline CD4 was ≤ 350 cells/mm^3 were 3.6 times more likely to die early compared to the children whose CD4 count was > 350 cells/mm^3 (cRR 3.6; 95% CI 1.4 – 9.5). Similarly, the children who adhered to ART < 85% were 8.4 times more likely to die early than the subjects who did so > 95% (Table 4).

In the multivariate analyses, however, the factors associated with the early mortality were bed-ridden health status at ART initiation (adjusted risk ratio [aRR] 8.8; 95% CI 1.4 -53.8), CD4 values ≤ 350 cells/mm^3 at ART initiation (aRR 3.86; 95% CI 1.17 -12.7), <85% adherence to ART (aRR 8.9; 95% CI 3.52-22.4), and developing AIDS-defining illness in the follow-up (aRR 4.8; 95% CI 1.4- 16.4).

Table 4: Factors associated with early mortality among HIV-infected children initiated with ART, Harar, Eastern Ethiopia, September 2010-March 2013

Factor	cRR (95% CI)	aRR (95% CI)
Sex		
Male	1	1
Female	1.24 (0.48 – 3.22)	1.4(0.56 - 3.58)
Age		
≤ 5 years	1	1
6 – 15 years	1.03(0.81-1.31)	0.7(0.19-2.54)
Health Condition		
Working	1	1
Ambulatory	0.92 (0.31 – 2.72)	1.24 (0.47 -3.30)
Bed-ridden	13.3 (4.7 – 37.7)*	8.8(1.4 -53.8)*
Baseline CD4 cell counts		
≤ 350 cells/mm3	3.6 (1.4 – 9.5)	3.86 (1.17-12.7)*
> 350 cells/mm3	1	1
WHO clinical stage		
Stage I	1	1
Stage II	0.15 (0.04 – 0.62)	0.17 (0.03 -1.05)
Stage III	0.15 (0.05 – 0.46)	0.17 (0.03 -0.94)
Stage IV	0.27 (0.12 – 0.71)*	0.40 (0.04 -3.85)
Previous history of TB		
No	1	1
Yes	2.23 (0.74 – 6.70)	1.34(0.45 -4.04)
History of OIs other than TB		
No	1	1
Yes	3.25 (0.42 – 25.29)	3.2 (0.26 -38.5)
Adherence to ART		
> 95%	1	1
85 – 95%	3.86 (1.07 – 13.8)*	1.6 (0.35-7.2)
< 85 %	8.4 (3.8 – 18.5)*	8.9 (3.52-22.4)*
Educational status		
Under age	1	1
Primary or Secondary	0.36 (0.15-0.89)*	0.40 (0.14-1.13)
AIDS-defining illness		
No	1	1
Yes	7.8 (2.7 - 22.6)*	4.8 (1.4- 16.4)*

Asterisk (*) shows significant association; cRR, Crude Risk Ratio; aRR, Adjusted Risk Ratio; TB, Tuberculosis; OIs, Opportunistic Illnesses

DISCUSSION

The finding of this study indicated that there were 28 deaths in 609 child-years of follow up, providing an incidence density of 46 deaths per 1000 child-years. Many of the deaths (18) occurred early, within the first 6 months of the ART initiation. The rate of early mortality was 2.46 deaths per 1000 child-months, whereas that of the overall was 3.83 deaths per 1000 child-months. The factors associated with the early mortality were baseline bed-ridden functional status, baseline CD4 values ≤ 350 cells/mm^3; less than 85% adherence to ART, and developing AIDS-defining illness during follow up.

The overall mortality rate found in this study (46 deaths per 1000 child-years; 3.83 deaths per 1000 child-months) is almost similar to the rate reported from a study in Kenya (47 deaths per 1000 child-years) (Wamalwa DC, Farquhar C *et al.,* 2007), but it is higher than the ones from Central Ethiopia (2.06 deaths per 100 child-years), and from Northern Ethiopia (16.85 deaths per 1000 child-years) (Gebremedhin *et al.,* 2013; Kedir *et al.,* 2014). Moreover, in our study, the early death rate was nearly as high as the rates found by similar studies done in Ethiopia (Koye Ayele *et al.,* 2012; Gebremedhin *et al.,* 2013; Kedir *et al.,* 2014) and sub-Saharan African countries (Moore *et al.,* 2011; Steele *et al.,* 2011; Zanoni *et al.,* 2011; Carolyn *et al.,* 2007). At baseline, 15% of the children had TB history, and like in other studies (Moore *et al.,* 2011; Zanoni *et al.,* 2011), it was a major (32%) contributing factor for the death. From the usual clinical experience, there was a delayed presentation for HIV diagnosis and treatment, as well.

The early mortality was significantly associated with the CD4 values of the study subjects. Like studies done on different cohorts of ART receiving participants (Puthanakit *et al.,* 2007; Zanoni *et al.,* 2011; Gebremedhin *et al.,* 2013; Kedir *et al.,* 2014), in this study the children with baseline CD4 values ≤ 350 cells/mm^3 were 3.86 times more likely to die early than the children with baseline CD4 values > 350 cells/mm^3. Recovery of immune status with ART in children has also been shown to be dependent on the baseline CD4 values at initiation of treatment (Newell *et al.,* 2006; Patel *et al.,* 2008). Initiation of ART in children with severe immune suppression is more likely to result in the development of immune reconstitution inflammatory syndrome (IRIS), which can be associated with potential mortality in the early months after initiation of ART (Puthanakit *et al.,* 2007). There was also greater proportion of the children with documented history of TB and other OIs among patients with CD4 values ≤ 350 cells/mm^3 that could contribute for early death compared to patients with CD4 values > 350 cells/mm^3.

The early mortality was also significantly associated with the presence of AIDS-defining illness (OIs) during follow up. The children who developed AIDS-defining illness during the follow up period were 4.8 times risker to

early mortality compared to their counter parts. This is consistent with other studies (Grinsztejn *et al.,* 2009; Brady *et al.,* 2010). About 45% of the children in our cohort started ART at advanced WHO clinical stage (III/IV), which could result in multi organ failure, progressive malnutrition due to lack of intake, increased metabolic rate, immune dysfunction, chronic infectious and non-infectious inflammatory complications (Brady, Oleske *et al.,* 2010). Late presentation and starting ART with advanced symptomatic disease may lead even to death (Janssen *et al.,* 2010; Koye *et al.,* 2012).

Furthermore, the early death was closely linked to the children's level of adherence to ART. The study subjects whose adherence to ART was < 85% were 8.9 times more likely to early mortality than those whose adherence to ART was ≥ 95%. A study in rural Uganda also revealed an 8.8 times increased hazard of death among individuals with adherence to therapy < 95% (Moore *et al.,* 2011). In addition, a study in Botswana provides an evidence that suboptimal early ART adherence as measured by pharmacy refill data and pill counts increases the risk of early mortality(Steele *et al.,* 2011). This could be due to low virologic suppression and subsequent AIDS progression in the setting of low levels of ART adherence.

At the initiation of the ART, although some of the study participants had moderate to severe anemia (35%) and few had mild (18%), unlike the reports from other studies (Janssen *et al.,* 2010; Koye *et al.,* 2012; Kedir *et al.,* 2014; Carolyn Bolton-Moore *et al.,* 2007), we found no association between the baseline anemia status and the early mortality. Similarly, more than half of the children were underweight (low weight-for-age). Several studies revealed that growth failure is a predictor of mortality (Wamalwa *et al.,* 2007; Koye *et al.,* 2012; Kedir *et al.,* 2014). However, this nutritional problem was also not significantly associated with the early mortality in our study. The small number of our study subjects might have contributed to the inconsistencies between our finding and the others'.

Though long duration of follow-up was made for reliable outcome, there were some limitations to this study. Firstly, the data were abstracted from the medical records and may suffer from variable deficiencies that could result into under- or over-estimations of early mortality. Secondly, early mortality might be underestimated since lost to follow-up might also include those who died without being reported. Thirdly, nearly half of the deaths were without diagnosed clinical cause (s) and measurement of specific disease-caused mortality was not complete. Therefore, any interpretation of the findings in this study should consider these limitations.

CONCLUSIONS

The present cohort study demonstrated that the overall mortality rate was 3.83 deaths per 1000 child-months. In addition, more than two-thirds of the total deaths (2.46 deaths per 1000 child-months) occurred in the first sixth months ART initiation. Bed-ridden functional status at ART initiation, CD4 values ≤ 350 cells/mm^3 at ART initiation, <85% adherence to ART, and developing AIDS-defining illness were independently associated with early mortality. Hence, early initiation of ART before the fall of CD4 values < 350 cells/mm3, and targeted interventions should be prepared to intensify support and care for children, especially during the first sixth months of ART initiation. Educating children or family on the importance of adherence to treatment could optimize the treatment outcome of HIV-positive.

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Conflict of Interest

The authors would like to declare that there is no conflict of interest.

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