Time to Detection of Anemia and Its Predictors Among Children Receiving Antiretroviral Therapy at Debre Tabor Referral Hospital and University of Gonder Compressive Specialized Hospital, 2020: A Multicenter Retrospective Follow-Up Study

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Abstract

Background: Although antiretroviral therapy access for HIV infected children increased dramatically, anemia have been continued as a challenge regardless of cluster of differentiation (CD4) count and viral load. Hence, this study aimed to assess the time to detection of anemia and its predictors among children receiving antiretroviral therapy at Debre Tabor referral hospital and University of Gonder Compressive Specialized hospital, 2020.

Methods: A retrospective follow-up study was conducted from January 2010 to December 2018. A total of 372 children under the age of 15 who had received ART were included in the study. Data were collected from children's medical charts and ART registration logbook using a standard checklist. Besides, the data were entered into EPI data 4.2.2 and then exported to Stata 14.0 for further analysis. The Cox regression model, the variables having P-value $\leq .05$ with 95% CIs in multivariable analysis were declared as a statistically significant for anemia

Result: The mean ($\pm$ SD) of follow-up periods were 56.6 ± 1.7 SD months. The overall median survival time free from anemia was 137 months, and the incidence rate of anemia was 6.9 per 100 PYO (95% CI: 5.3, 7.8). Moreover, WHO clinical staging of III/IV [AHR: 4.2, 95% CI: 1.80, 11.1], low CD4 count below threshold [AHR: 1.9, 95% CI: 1.09, 3.37], cotrimoxazole preventive therapy non-users, and poor level of adherence [(AHR: 2.4, 95% CI: 1.20, 4.85)] were the main predictors of anemia.

Conclusion: The incidence rate of anemia was found to be high. Monitor hemoglobin levels routinely with concurrently CD4 cell count levels, WHO clinical stage, and level of adherence. Hence, preventing and correcting of those predictors in a systematic manner in ongoing basis is crucial. Moreover, strategies need to be strengthened cotrimoxazole preventive therapy supplementation

Background

Hematological abnormalities are a common and independent poor prognostic marker of HIV disease^{1,2}, which worsens quality of life³, and decreased survival⁴. Moreover, hematological abnormalities, mainly anemia has been continued as a challenge in resource limited setting⁵.

Anemia is the commonest disorder which is seen among HIV infected children⁶. WHO estimates that over 2 billion people are anemic worldwide, of these, more than 100 million of anemic children were living in Africa⁷. Even though ART access for HIV infected children increased dramatically, side effects have been continued after the initiation of therapy predominantly in resource-limited setting³. Besides, anemia has been a strong risk factor for disease progression and subsequent death regardless of cluster of differentiation (CD4) count and viral load^{4,8}.

Hematological abnormalities have been documented as the second cause of morbidity and mortality in HIV-infected children living in resource-limited countries⁹. Indeed, anemia is a common¹⁰. Anemia is the leading hematologic complication of HIV infection occurring in approximately 30% of patients with asymptomatic infection and as many as 75–80% of those with Acquired immunodeficiency disease (AIDS)¹¹, particularly in children whose immune systems are not yet fully developed¹². Additionally, children are the most vulnerable population for anemia, it is responsible for a high proportion of HIV-related deaths each year⁷, up to 90% of children develop anemia during HIV infection¹³.

Anemia is a leading cause of hospital admission, reduced cognitive development, growth, and poor immune function in children⁷, since the etiology and pathogenesis of anemia are complex¹⁴, caused by a multifactorial of factors. such as cancer; micronutrient deficiencies; infections, such as malaria and tuberculosis(TB)¹⁵. In HIV-infected children, the virus can infect parts of the bone marrow responsible for manufacturing red blood cells and erythropoietin, which is required

to stimulate red blood cell production¹⁶. Besides, a certain antiretroviral medication causes and exacerbates the anemia due to bone marrow suppression¹⁷.

Giving attention to the young age of children¹⁸ and children with unemployment parent¹⁹, children with viral load > 1000 copies/ml^{9,20}, low CD4 count < 200cells/ul^{21,22}, and WHO stage III/IV)^{7,20,23}, have been recommended to reduce the impact of HIV associated anemia in the previous era.

Despite the above prevention and management approach has been implemented in Ethiopia, the burden of anemia in HIV infected children is still intolerable. Besides, it attracts the attention of the government and researchers since there has been no prior evidence about the time to detection of anemia and its predictors among HIV infected children in the country in general and in the study area in particular. Hence, this study aims to assess time to detection of anemia and its predictors among children receiving Antiretroviral Therapy at Debre Tabor referral Hospital and University of Gonder Compressive specialized Hospital.

Methods

Study design and period

A retrospective follow-up study was conducted from January1, 2009–December 30, 2018 at Debre Tabor referral Hospital and university of Gonder Compressive specialized Hospital.

Study setting

Debre Tabor referral Hospital is the largest hospital in South Gondar Zone which provide in outpatient, inpatient and operation theatre department. The Hospital has been provided service for 2.4 million populations' including ART service. Besides, University of Gondar Hospital is a 400-bed university hospital, which acts as the referral centre for four district hospitals in the area. It has a range of. The hospital services about four million across the region²⁵.

Source population

All children < 15 years received Antiretroviral therapy at university of Gondar comprehensive specialized hospital

Study population

All children < 15 years received antiretroviral therapy from January1, 2010–December 30, 2018, at Debre Tabor referral hospital and university of Gonder Compressive specialized hospital

Inclusion criteria

All children < 15 years received Antiretroviral therapy from January1, 2010–December 30, 2018, at Debre Tabor referral hospital and university of Gonder Compressive specialized hospital

Exclusion criteria

Medical charts and ART registration logbook of the study participants with incomplete outcome (i.e. hemoglobin status not recorded) variables were excluded.

Sample size and sampling Procedure

The sample size was calculated by using Log-rank survival data analysis of the two-population proportion formula based on the following important assumptions- 95% confidence level, 80% optimum statistical power, and taking type one error 5%. By considering a study was conducted in eastern Ethiopia²⁶, by taking sex as a predictor variable (on

male as exposed group denoted by q1 (0.38) and female group denoted by q0 (0.53), and then the total sample size, after adding 10% as incomplete medical records, and the final sample size was 372.

A total of 372 children who started ART during the study period were identified in the pediatric ART clinics, the investigator assigned the registration numbers from January 1, 2010, to May 30, 2020 in a chronological order. Of these, the investigator drew 357 samples which fulfilled the inclusion criteria after reviewing the medical charts and ART registration logbook; and then 15 medical records did not fulfill the inclusion criteria were excluded (Fig. 1).

Variables of the study

The dependent variable of this study is time to anemia, whereas age, sex, educational status, marital status, occupation, religion, residence, relationship to the child, ART regimen, duration of ART, level of adherence, OI prophylaxis (IP& CPT), developmental milestone/Functional status, treatment failure, history of TB, WHO clinical stage, CD4 count/percent, nutritional status (WGT-Age, WGT-H & HT-Age), and history of OI were independent variables.

Operational definitions

Time to anemia: - The time from children ART initiation to the occurrence of the event (i.e. anemia) during the follow-up period. Anemia was defined based on the WHO cut-off point (hemoglobin less than 10 g/dl) for children below 15 years ^{27,28}.

Censored: A study participants who were lost to follow-up, transfer to another service, and end of the study period before developing anemia were considered as censored.

Data collection tools and procedures

Data extraction tool was derived from a standard national HIV follow-up form of Ethiopia. Data were extracted from medical charts and ART registration logbook in terms of socio-demographic variables of the children and parents/caregivers. Likewise, clinical and treatment related variables were extracted from medical charts and ART registration logbook. The three nurses who are experience in ART clinic were collecting the data. Besides, the data collectors have a qualification of university degree.

Data quality control

A Pretest was conducted among 19(5%) medical records to check the consistency of the abstraction tools from 2008, to 30, 2009 at University of Gondar comprehensive specialized hospital. Two-days training were given about the objectives, significance, and variables of the research for data collectors and supervisors. Besides, all data collectors and supervisors were taken basic ART training and mentorship. The filled formats were checked for completeness by the supervisor, data cleaning and double data entry were carried out to check for any inconsistencies, coding errors, missing values, and out of range.

Data processing and analysis

Data was entered into Epi data 4.2.2 then exported to Stata version 14 for further analysis. A categorical data was presented as frequency and continuous data as median and interquartile range (IQR). The incidence rate of anemia was calculated with children with anemia as the numerator divided by total child-months. The cumulative probability of anemia was estimated using Kaplan-Meier failure method and the survival curves were compared between the predictor variable by the log-rank test. In Cox regression analysis, variables having a p-value ≤ 0.25 were enter into multivariable and the variables having $\leq .05$ in multivariable were declared as a statistically significant for anemia. Besides, the model and the variable were tested via graphic and numerical assessment (global test = 0.644).

Results

Socio-demographic characteristics

Out of 372 records, 357 of pediatric ART records with the completeness response rate of 95.9% were reviewed and 15 of the medical records were excluded from study. The median age of children and caregivers were 7.3(SD+0.28) and 34.9(SD +0.37) years respectively. More than half the children 184(51.5%) were male, whereas 193(54.1%) caregivers were female. About 285(79.8%) of the caregiver's were urban residences and 249(69.7%) were married. Majority of the caregivers 302(84.6%) were orthodox Christian; likewise, 330 were Amara ethnic group. Moreover, 147(41.2%) and 193(54.1%) of the caregivers were uneducated and unemployed respectively, and 203(56.9%) of the children were enrolled before test and treat strategies (Table 1).

Table 1
Socio demographic characteristics among children receiving Antiretroviral Therapy at Debre Tabor referral Hospital and university of Gondar Compressive Specialized Hospital, 2020 (n=357)

Exposure variable	Responses	Frequency (n = 202)	Percent (%)
Age of the Caregiver's	≤ 34 years	216	60.5
	> 34 years	141	39.5
Sex Caregiver's	Male	164	45.9
	Female	193	54.1
Age of the child (years)	≤ 7	178	49.9
	> 7	179	50.1
Sex	Male	184	51.5
	Female	173	48.5
Residence	Rural	72	20.2
	Urban	285	79.8
Caregiver's Marital status	Married	249	69.7
	Widowed	37	10.4
	Divorced	71	19.9
Ethnicity	Amhara	338	94.7
	Tigray	17	4.8
	Others	2	0.6
Religion	Orthodox	302	84.6
	Muslim	49	13.7
	Other*	6	1.7
Caregiver's educational status	No education	147	41.2
	Primary education	92	25.8
	Secondary education	96	26.9
	Tertiary education	22	6.2
Caregiver's Occupation	Non employed	193	54.1
	Employed	164	45.9

Clinical and treatment related characteristics

A total of 70(19.6%) and 111(31.1%) of children were CD4 counted below the threshold level and WHO clinical III and IV respectively. Besides, 41(11.5%) had tuberculosis and 181 (50.7%) had a history of opportunistic infection in the follow-up period. The majority 309(86.6%) of children were zidovudine regimen contain, and 291(81.5%) had taken Cotrimoxazole preventive therapy. whereas, only 109(30.5%) had taken isoniazid preventive therapy. Regarding to

nutritional status, 182(59.1%) and 146(40.9%) of the children were underweight and stunted respectively. 36(10.15) of the children had treatment failure, and 199(55.7%) of the children were < 60 months on ART (Table 2).

Table 2
Clinical and treatment related characteristics among children receiving Antiretroviral Therapy at Debre Tabor referral Hospital and university of Gondar Compressive Specialized Hospital, 2020 (n=357)

Exposure variable	Responses	Frequency (n = 202)	Percent (%)
Weight for height	Normal	175	49.0
	Underweight	182	59.1
Height for age	Normal	211	59.1
	Stunted	146	40.9
CD4 counts or %	Below threshold	70	19.6
	Above threshold	287	80.4
WHO stages	Stage I&II	244	68.3
	Stage III&IV	111	31.1
Hx of OIs	Yes	181	50.7
	No	176	49.3
Regimen at baseline	AZT-based	309	86.6
	d4T-based	48	13.4
Cotrimoxazole preventive therapy (CPT)	Yes	291	81.5
	No	66	18.5
Isoniazid preventive therapy (IPT)	Yes	109	30.5
	No	248	69.5
ART adherence	Good	278	77.9
	Fair	31	8.7
	Poor	48	13.4
Treatment failure	Yes	36	10.1
	No	321	89.9
TB status	Yes	41	11.5
	No	316	88.5
HAART duration	< =5 years	199	55.7
	> 5 years	158	44.3
Follow-up status Anemia	Yes	58	16.2
	No	299	83.8

The median survival time to develop anemia during follow-up period

The mean follow-up periods were 56.6 ± 1.7 SD months, overall yielding 20,191 child-month observations. At the end of follow-up, 58[16.5%, 95% CI: 12.8–20.4%] of the children were anemia while 299(83.8%) of children were non-anemic. The incidence rate of anemia was 6.9 per 100 PYO (95% CI: 5.3, 7.8). The overall median survival time of children free from anemia was 137 months (Fig. 2). The median survival time free from anemia among children who had CD4 count below the threshold level were 62 months, while 125 who had CD4 count above the threshold level. Besides, 70 months among children who had WHO stage III and IV, and 107 months for those WHO stage I and II to develop anemia in the follow-up period. The median survival time free from anemia among children who had who had zidovudine regimen were 60 months, while 140 months for those non-zidovudine regimens contained to in the follow-up period (Fig. 3). Log rank survival curve comparisons of the associated predictor's variables were estimated. Besides, Cox-Snell residual Nelson- Alen cumulative hazard graph for the goodness of model fitness also evaluated (Fig. 4).

In Cox proportional hazard model bivariable analysis including sex of caregivers, occupation of caregivers, test and treat strategies, weight for age, height for age, TB status, regimen type, CPT, CD4 count threshold level, level of adherence, WHO clinical staging and OI status were having P value less than 0.25 for the occurrence of anemia and enter into multivariable analysis. Besides, in multivariable models, test and treat strategies, WHO clinical staging, CD4 count threshold level, CPT, and level of adherence were associated with anemia.

The hazards of anemia in children enrolled before test and treat strategies (Pre ART) were 2.0 times higher than those after test and treat strategy [AHR: 2.0(95% CI: 1.13, 3.57)]. The hazard of anemia in children who had WHO staging III and IV were increased a risk of anemia by 4.2 times as compared with WHO staging I and II [AHR: 4.2 (95% CI: 1.80, 11.1)]. Besides, Children who had CD4 count below the threshold level were increased a risk of anemia by 1.9 times as compared with CD4 count above the threshold level [AHR: 1.9 (95% CI: 1.09, 3.37)]. Moreover, children who had cotrimoxazole preventive therapy non-users were 2.2 times higher than those who those cotrimoxazole preventive therapy users [AHR: 2.2 (95% CI: 1.23, 3.82)], and children with poor level of adherence were increased a risk of anemia by 2.4 times [(AHR: 2.4 (95% CI: 1.20,4.85))] (Table 3).

Table 3

Bivariable and multivariable Cox-regression analysis of predictors for anemia among children receiving Antiretroviral Therapy at Debre Tabor referral Hospital and university of Gonder Compressive Specialized Hospital, 2020 (n=357)

Characteristics		Anemic		OR (95% CI)		
		Yes (58)	No (299)	COR	AOR	P-value
Age of the Caregiver's	≤ 34 years	34	182	0.9(0.55–1.57)	-	
	> 34 years	24	117	Ref	-	
Sex Caregiver's	Male	30	134	1.4(0.83–2.32)	1.3(0.82–2.38)	0.220
	Female	28	165	Ref	Ref	
Age of the child (years)	≤ 7	25	153	0.8(0.45–1.28)	-	
	> 7	33	146	Ref	-	
Sex	Male	29	155	1.0(0.59–1.66)	-	
	Female	29	144	Ref	-	
Residence	Rural	10	62	0.8 (0.45–1.75)	-	
	Urban	48	237	Ref	-	
Marital status	Married	39	210	0.9(0.49–1.70)	-	
	Divorced	5	32	0.7(0.27–2.09)	-	
	Widowed	14	57	0.8(0.34–2.41)	-	
Religion	Orthodox	49	253	1.4(0.18–10.8)	-	
	Muslim	8	41	1.3(0.16–11.3)	-	
	Other*	1	5	Ref	-	
Caregiver's educational status	No education	25	122	0.7(0.28–1.89)	-	
	Primary education	15	77	0.6(0.23–1.77)	-	
	Secondary education	13	83	0.6(0.20–1.55)	-	
	Tertiary education	5	17	Ref	-	

b

Occupation of the caregiver	Non employed	37	156	1.6(0.94–2.76)	2.1(0.97–3.89)	0.056
	Employed	21	143	Ref	Ref	
<i>b</i>						

Table 3
(continued): Bivariable and multivariable Cox-regression of predictor variable

Characteristics		Anemic		OR (95% CI)		
		Yes (58)	No (299)	COR	AOR	P-value
Weight for height	Normal	21	154	Ref	Ref	
	Underweight	37	145	1.9(1.10–3.24)	1.5(0.88–2.72)	0.127
Height for age	Normal	28	183	Ref	Ref	
	Stunted	30	116	1.5(0.92–2.59)	1.2(0.69–2.05)	0.543
CD4 counts or %	Below threshold	21	49	2.4(1.39–4.09)	1.9(1.09–3.37)	0.024
	Above threshold	37	250	Ref	Ref	
WHO stages	Stage I&II	24	220	Ref		
	Stage III&IV	34	77	4.3(2.50–7.24)	4.2(1.8–11.1)	0.001**
Hx of opportunistic infections	No	17	159	Ref	Ref	
	Yes	41	140	2.7(1.56–4.85)	1.1(0.45–2.85)	0.800
Regimen at baseline	AZT-based	52	257	1.4(0.60–3.24)	-	
	d4T-based	6	42	Ref	-	
Cotrimoxazole preventive therapy (CPT)	No	22	44	3.1(1.82–5.32)	2.2(1.23–3.82)	0.008**
	Yes	36	255	Ref	Ref	
Isoniazid preventive therapy (IPT)	No	40	208	1.0(0.55–1.72)	-	
	Yes	18	91	Ref	-	
ART adherence	Good	39	241	Ref	Ref	
	Fair	9	22	4.3(2.02–8.98)	2.0(0.88–4.79)	0.094
	Poor	12	36	2.8(1.45–5.37)	2.4(1.20–4.85)	0.016*
Treatment failure	Yes	5	31	1.0(0.38–2.42)	-	
	No	53	268	Ref	-	
TB status	Yes	11	30	2.6(1.34–5.00)	0.7(0.32–1.53)	0.369
	No	47	269	Ref	Ref	

Duration on ART	<=5 years	43	156	1.2(0.3-3.2)	-
	> 5 years	15	143	Ref	-
ART initiation	after test and treat	20	134	Ref	Ref
	before test and treat(pre-ART)	38	165	1.5(0.89–2.62)	2.0(1.13–3.57) 0.017*

*Significant at < 0.05; ** Significant at < 0.01; COR = Crude odds ratio; AOR = adjusted odds ratio; Ref = reference category; CI = confidence interval

Discussion

This study assessed the time to detection of anemia and its predictors among time to detection of anemia and its predictors among children receiving Antiretroviral Therapy at Debre Tabor referral Hospital and university of Gonder Compressive Specialized Hospital, Ethiopia, Northwest, Ethiopia; 2020. Almost one-in-six HIV infected children (16.5%, n = 58) with anemia were recorded in the follow-up period. The incidence rate of anemia was 6.9 per 100 child-years. Moreover, the median survival time was 137 months. WHO clinical staging III/IV, CD4 count below the threshold level, CPT non-user, poor adherence, and before test and treat strategies (pre-ART) were found to be the main predictors of anemia.

Our finding is comparable with a cohort study conducted in northwest Ethiopia in 2012 and 2017, were 19.8% and 12.26% respectively^{27,28}. Moreover, a cross sectional study in Addis Ababa, Ethiopia in 2016 was 17.59%²⁹. This could be justified in two ways. Firstly, cut-off value of Hgb to define anemia. Secondly, study participants having similar age group (i.e., children < 15 years). In addition to this, it may be due the data extraction tools of all studies were prepared from a standard HIV/AIDS Care and treatment guidelines ART service in Ethiopia.

However, this study showed a lower incidence rate of anemia than a cross sectional and prospective cohort in India were 21.9%³⁰ and 47.1%³¹ respectively. In Jimma, Ethiopia in 2007, was 21.9%³⁰, in Nigeria among aged between 5 and 12 years, was 54.2%³², in Cameroon from November 2012 to May 2013, was 49.6%¹², in South Africa, was 73%³³, in Gahan 2091 among under Five Years, was 53.8%³⁴, Malawi, was 45.7%⁹, in Mozambique among 6–59 months of children, was 88%⁷, in Kenya 2008, was 35.9%²³, and in Tanzania in 2015, was 27.7% respectively¹⁹. This difference could be due to the cut-off point of anemia, study design since most of the above studies were cross sectional, whereas our study was a cohort. In addition, the variations might be due to the difference in the study area, duration of time on ART, and differences in the follow-up periods. A shorter follow-up period is likely to find a higher probability of anemia when compared with a study with a longer follow-up period. Besides, the discrepancy may be due to monitoring of anemia in every three months in our study area whereas frequently in others settings. Likewise, the discrepancy may be due to the study participants (i.e. aged b/n 5–12 years and under five years).

On the other hand, the incidence rate of anemia has been observed in this study is higher than a study conducted in Hawassa Ethiopia, in 2018, which was 11.4%³⁵. In Asia-Pacific region, between January 2003 and September 2013, severe anemia was 5.5%³⁶, a study conducted from November 2007 to June 2009 in the region of Africa, 4.8% of children with severe anemia²⁰ in 2016 Uganda, Anemia was 11.8% among 12–14 years respectively³⁷. This difference could be explained by the differences in the outcome measurement, ethnicity, sample size, study design, and follow up period. Moreover, the heterogeneity of the data inherent in a multinational cohort, the type's health care service and study setting.

Children who were WHO clinical staging III and IV increased a risk of anemia by 4.2 times as compared with WHO clinical staging I and II. The median duration of free from anemia was significantly shorter in persons with WHO clinical staging III and IV in follow-up period. The finding is in line with a study from Mozambique, west Africa, and Kenya ^{7,20,23}. This might be due to having advanced WHO clinical staging might compromise immunity, and can lead to severe illness due to viral replication, depletion of CD4 count, and the added burden of disease. Moreover, children who had CD4 count below the threshold level were increased a risk of anemia by 1.9 times as compared with CD4 count above the threshold level. Besides, the median survival time of free from anemia was significantly longer time in persons with CD4 count above the threshold level. This finding was also supported by several studies conducted in Asia, Malawi, and Nigeria ^{3,9,32}. Moreover, the finding was also similar in a study conducted in Black Lion and Zewudtu referral hospital in Ethiopia < 350 cells/ μ l ^{21,22}. This could be explained by low CD4 count elicited dysfunction of the immune system and increased vulnerability of the host to infection, immunological deficiency that enhances the severity of the disease, and delayed recovery time and increase viral load across time.

Children who were CPT non-users increased the risk 2.2 times higher than those who had those CPT users. A study conducted in Ethiopia revealed that CPT non-users anemia as an independent predictor of anemia³⁸. Moreover, the median survival time of free from anemia was significantly shorter in persons with CPT non-users. Indeed, CPT can prevent or reduce the occurrence of opportunistic infection and further complication, therefore, it is important to increase the immune status of the children to decrease viral replication which increases their survival rate by preventing and treating OI infection of which is supported, by a study conducted northwest Ethiopia²⁴. CPT prophylaxis has been recommended for the benefit of HIV/AIDS-infected individuals to prevent opportunistic infection since it is a simple and effective intervention to reduce morbidity, and to improve the quality ³⁹. Besides, children presenting with poor level of adherence was increased a risk of anemia by 2.4 times as compared with good level of adherence. Furthermore, the median of survival time to develop anemia was significantly longer time in persons with good level of adherence. This could be explained poor level of adherence has been shown to influence the natural history of HIV disease by accelerating the rate of disease progression, opportunistic infection, and mortality. Moreover, counseling about the importance of adherence has been provided in ART service to prevent opportunistic infection since it is a simple and effective intervention.

This study has some limitations. First, data were collected from routine medical care records and there were limited data on possible predictors of anemia, such as viral load level and psychological support. Second, age, educational, and occupation status of the care givers, as the presence of these variables might be causal for the occurrence of anemia during the initiation of ART.

Conclusion

The incidence rate of anemia was found to be high. Monitor hemoglobin levels routinely with concurrently CD4 cell count levels, WHO clinical stage, and level of adherence. Hence, preventing and correcting of those predictors in a systematic manner in ongoing basis is crucial. Moreover, strategies need to be strengthened cotrimoxazole preventive therapy supplementation

Declarations

Ethics approval and consent to participate:

Ethical clearance was obtained from Debre Tabor University ethical review Committee and permission letter was also obtained from each hospital administrators. Besides, Verbal informed consent was obtained from all the child's

caregiver before data collection and the principles expressed in the Declaration of Helsinki and the Good Clinical Practices.

Consent for publication: Not applicable

Availability of data and materials: Data will be had upon request from the corresponding author

Competing interests: The authors have no competing interests to declare

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Authors' contributions: All authors have read and approved the final article. ESC contributed to conception, study design, data acquisition, data interpretation, and writing original article. GL contributed to conception and design, data acquisition, critically revising article. GA contributed to data acquisition, critically revised this article. BB contributed to conception and design, data acquisition, statistical analysis, ATD contributed to data acquisition, critically revised this article. SAA contributed to data acquisition, critically revised this article. WAB contributed to data acquisition, critically revised this article. BB contributed to data acquisition, critically revising article, and data interpretation.

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Figures

Figure 1

Diagrammatic presentation of sampling procedure among children received Antiretroviral Therapy at Debre Tabor Referral Hospital and University of Gonder Compressive Specialized Hospital, Northwest, Ethiopia 2020 (n=357) Key: DTRH=Debre Tabor Referral Hospital, UOGCSH= University of Gonder Compressive Specialized Hospital

Figure 2

Kaplan-Meier failure estimate of anemia among children received Antiretroviral Therapy at Debre Tabor Referral Hospital and University of Gonder Compressive Specialized Hospital, Northwest, Ethiopia 2020 (n=357)

Figure 3

Kaplan-Meier failure estimate of anemia of the main predictor variable among children received Antiretroviral Therapy at Debre Tabor Referral Hospital and University of Gonder Compressive Specialized Hospital, Northwest, Ethiopia 2020 (n=357) (continued): Kaplan-Meier failure estimate of anemia of the main predictor variable among children received Antiretroviral Therapy at Debre Tabor Referral Hospital and University of Gonder Compressive Specialized Hospital, Northwest, Ethiopia 2020 (n=357)

Figure 4

Cox-Snell residual Nelson- Alen cumulative hazard graph for the goodness of model fitness which shows the hazard function follows the 45o closeness among children received Antiretroviral Therapy at Debre Tabor Referral Hospital and University of Gonder Compressive Specialized Hospital, Northwest, Ethiopia 2020 (n=357).