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Incidence and Predictors of Mortality among Children on Anti-Retroviral Therapy in Public Health Facilities of Arba Minch Town, Gamo Gofa Zone, Southern Ethiopia; Retrospective Cohort Study

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Abstract

Background: Evidence shows that earlier access to Anti-retroviral Therapy helps to increase survival of children by delaying the progression to AIDS. However its long-term effect on mortality has remained unanswered in Ethiopia especially in the study area.

Objective: To assess incidence and predictors of mortality among Children on Anti-retroviral Therapy in Public Health Facilities of Arba-Minch Town, Gamo Gofa zone, Southern, Ethiopia.

Methods: Institution based retrospective cohort study was employed among 421 HIV-positive children enrolled on anti-retroviral therapy from January 1st 2009 to December 30th 2016. The data on relevant variables was collected from patients` medical cards and electronic database by trained data collectors. Data was entered and cleaned by Epi Info version 7 and analyzed by STATA version 11. Life table was used to estimate the cumulative survival of children and Kaplan Meier survival curve together with log rank test was used to compare survival between different categories of covariates. Cox proportional-hazard regression model was used to identify independent predictors of mortality.

Result: Overall, 15.4% of children (n=65) died over a follow-up period of 21,175 person-months of observation. The mortality rate of this cohort was 3.07 deaths per 1000 person-months. The cumulative probability of survival after 96th month of treatment was 73.9% (95% CI=63.2-81.9). During the multivariate analysis of baseline variables, we observed that the delayed and regressed developmental milestone (AHR=4.42, 95% CI=1.99-9.75), (AHR=6, 95% CI=2.68-13.45), opportunistic infection at baseline (AHR=1.93, 95% CI=1.03-3.64), tuberculosis co-infection at base line (AHR=2.28, 95% CI=1.23-4.22), low hemoglobin level (AHR=3.32, 95% CI=1.83-6.04), absolute CD4 below threshold (AHR=2.08, 95% CI=1.15-3.77), fair and poor adherence to ART were (AHR=2.17, 95% CI=1.12-4.79), (AHR=2.05, 95% CI=1.02-4.13), isoniazid preventive therapy (AHR=0.38, 95% CI=0.22-0.68) and Co-trimoxazole preventive therapy (AHR=0.26, 95% CI=0.15-0.46) were independent predictors of mortality.

Conclusions: Mortality was high especially during the first sixth months following anti-retroviral therapy initiation. Therefore, higher priority should be given to HIV-infected children with tuberculosis co-infection further intervention like isoniazid preventive therapy and co-trimoxazole preventive therapy as well close follow should be given to all children after start of anti-retroviral therapy.

Keywords: Incidence; Children; Anti-retroviral Therapy; Mortality; Cox proportional hazard; Ethiopia

Introduction

HIV/AIDS remains one of the world's most significant public health challenges, particularly in low- and middle-income countries [1]. Children are the most valuable group continues affect by HIV and a major contributing to childhood morbidity, mortality and the commonest reason for paediatric hospital admission [2].

The most common first line drug regimen combinations given for HIV-infected children usually consists 2NRTIs+1NNRTI [2]. The drugs do not kill or cure the virus, but decrease the amount of virus in your bloodstream. However, when taken in combination they can prevent the growth of the virus and stop the progression of HIV disease. Adherence to ARVs is very important for treatment to work. The viral load test is used to see if ARV drugs are working. Current New guidelines recommended that everyone who is infected with HIV should start ARV therapy [2,3].

According to seventh stocktaking report that among total 1.8 million children living with HIV an estimated 1,10,000 children died of AIDS-related illnesses and 290 children died of AIDS-related illnesses every day. Nearly 90% live in Sub-Saharan Africa in 2016 [4]. In Ethiopia it is estimated of 109133 children living with HIV, approximately 5760 AIDS related deaths each year in 2016 [5].

Evidence show that earlier access to ART shows that it help to increase survival of children by delaying the progression to AIDS [6,7]. It was estimated that earlier access to ART could have prevented 25% of HIV related death [8,9]. However, access to ART for children was only 12% among children under 15 years of age [1].

In Ethiopia, the HIV epidemic has remained a major public health problem, largely affecting children [10]. In Ethiopia, the fee based and universal free access antiretroviral (ARV) treatment was started in 2002/3 and 2004/5 respectively [10]. Ethiopia has been engaged in the scale-up of ART access to the level of health center starting since 2006 [11]. The number of sites providing the ART service had increased from 3 to over 1000 including both public and private facilities and people started on treatment increased from 24,000 to 308,000 from 2006 to 2016 [10].

Mortality under ART in Africa remains high ranging from 7.5% to 15% [12-15]. Ethiopia ranging from 4.3% to 10.4% during the first six months following ART initiation [16-18]. The high Mortality rates of HIV-infected children under treatment in Africa are likely to depend not only on the care delivered by ART programs, but more fundamentally related to low CD4 count, WHO clinical stage, opportunistic infection and anemia [7,19,20].

In addition, the durability of the treatment response and its long-term effect on mortality remained unanswered [16,21]. Consequently, in resource limited settings like Ethiopia, there is a pressing need for research to further refine HIV treatment strategies among the children in order to have better survival of children after initiation of ART and in order to develop appropriate interventions to achieve the desired outcome of ART program as well to avoid unclear conclusions on the cause of mortality associated with children after starting ART. Therefore, the aim of this study was assessing incidence and identify predictors that affect the mortality of HIV positive children after initiation of ART in Public Health Facilities of Arba-Minch Town, Gamo-Gofa zone, Southern Ethiopia.

Methods

Study area and period

This study was conducted in Arba Minch town from March 20th-April 10th, 2017. Arba-Minch town was located about 505 km south west from Addis Ababa, about 275 km from Hawassa, the capital of the SNNPR region. Arba Minch town has one General hospital and one public health center, which provide ART service. Arba Minch hospital was among the first few public hospitals to start ART in Ethiopia in August 2003 and Arba Minch Health Center also start ART care by the end of 2007 [11]. According to Gamo Gofa zone health department report the Arba Minch hospital and Arba Minch health center provides HIV/AIDS interventions, including free diagnosis, treatment and monitoring. There are multidisciplinary professional's team that includes physicians, nurses, public health professionals, laboratory technologists, pharmacists, data clerks and volunteer adherence supporters. ART was being provided for children living with HIV regardless of CD4 count and World Health Organization clinical stage classification. Data from zonal health department also showed that A total of 664 children with HIV/AIDS ever enrolled on chronic care in both Hospital and health center since January 2009, but 460 ever start ART in Arba Minch General Hospital and 148 children ever start ART in Arba Minch Health Center (annual report 2016).

Study Design

An institutional-based retrospective cohort study was conducted to assess incidence and identify predictors of mortality among children on Anti-retroviral therapy in Public health facilities of Arbaminch town, Southern Ethiopia.

Source and study populations

All HIV infected children being on ART and registered for chronic care in public health facilities of Arba-Minch town providing ART service between 2009 to 2016 were the source populations. All children living with HIV/AIDS whose age ≤ 14 years being on ART and registered for chronic care at public health institution of Arba Minch town providing ART service from 1st January 2009 to 30th December 2016 were study populations.

Inclusion criteria and exclusion criterion

All children living with HIV/AIDS whose age ≤ 14 years being on ART and registered for chronic care at public health institution of Arba Minch town from 1st January 2009 to 30th December 2016 were included, but Children living with HIV/AIDS with incomplete intake form at least with baseline CD4, WHO staging and basic personal information were excluded.

Sample size determination

The sample size was calculated by applying two population proportion formula using Epi-Info Version 7. Co-trimoxazol preventive therapies, TB co-infection at baseline and anemia were considered. The most significant predictor of Mortality Anemia was used which was taken from the study conduct in Northwest Ethiopia [17] and the following assumption were considered, 95% CI, power 80%, ratio of unexposed to exposed 1:1 and parameters outcome in exposed (Hemoglobin <10 gm/dl)=14.56%,outcome in unexposed (Hemoglobin ≥ 10 gm/dl)=5.76% and HR=2.53. Accordingly, the calculated sample size was 412. Since we include all 421 samples in our analysis.

Sampling procedure and sampling techniques

In this study, secondary data from Public health facilities of Arba-Minch town was used to retrieve data from initial date of ART up to the end of the follow up. In this study, the sampling frames are those who had registered for chronic care during data retrieval period of eight consecutive years from January 2009 to December 2016 in Public health facilities of Arba-Minch town. Finally, All HIV-positive children on care and support follow up who had started ART at Public health facilities of Arba-Minch town and fulfill the inclusion criteria were selected (Figure 1).

Data Collection Procedure and Data Quality Control

The standard data extraction tools was prepared in English which is adapted from the revised 2014 federal ministry of health HIV care/ART follow up form which was used in the ART clinic [11]. Further by using different peer reviewed published literatures [7,17,18]. The data extraction format includes socio-demographic characteristics, clinical related information, immunological information, ART & chemoprophylaxis related information. The data was collected by nine diploma health professionals and supervise by

four health professionals who have Bachelor of Science as well who were trained on comprehensive HIV care to ensure the quality of data. The data was collected by reviewing the patient's medical cards (follow up and ART intake form) and ART electronic database, but no contact was made with any child so as to maintain privacy and confidentiality. Data on deaths of the HIV positive children while on ART was obtained from health professional report on the medical cards.

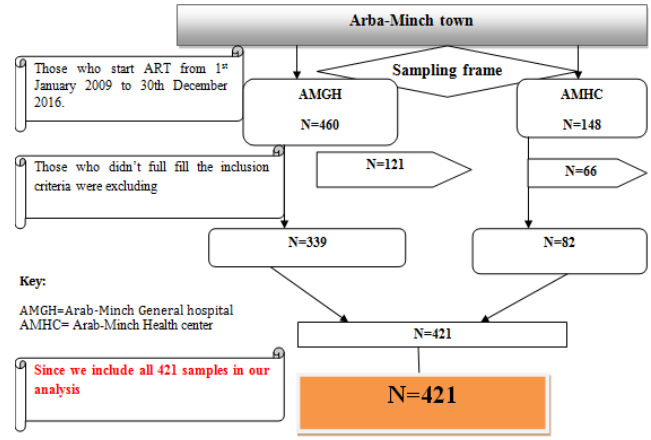

Figure 1: Schematic presentation of sampling procedure for cohort of children start ART between 1st January, 2009 up to 30th December, 2016 in public Health facilities of Arba-Minch town, Gamo Gofa Zone, Southern Ethiopia, March, 2017.

Besides, for those children who died at home, the drug adherence counselor communicated using the contact address and confirmed whether the children were alive or dead. The most recent laboratory results before ART initiation was use as a base line values. If there was no pre-treatment laboratory test, however, results obtained within one month of ART initiation was considered as baseline values. Data collectors and supervisor was trained for one days on objectives of the study, how to select study participants card, how to keep confidentiality of information, the contents of the questionnaire, how to filling on data collection format and data quality management by the principal investigator. The principal investigator and supervisor were conduct a day-to-day follows up during the whole period of data collection. Every day after data collection of the data each questionnaire was reviewed and checked for completeness by the supervisor and the principal investigator and the necessary feedback was given to the data collectors to the next day. The overall activity was supervised by the principal investigator of the study.

Data Processing and Analysis

The data collection form was checked for completeness and consistency by the principal investigator before data entry. Completed data abstraction form was coded by numbers and entered in computer software Epi-info version 7 and exported to STATA version 11 statistical packages for analysis. Exploratory data analysis was carried out to check the levels of missing values, presence of influential outliers, HIV status of care giver and viral load were highly missing and ART related side effect was highly collinear with ART regimen all were excluded. Descriptive statistics such as median, mean, standard deviation and proportions was used to describe the characteristics of cohort. Incidence of death with respect to person time at risk was calculated and reported as number of death per 1000 Person-months/ years of follow up by assessing the date of enrolment for ART and death or censoring. Life table was used to estimate the cumulative survival of children and kaplan meier survival curve together with log rank test was used to compare survival between different categories of independent variables. Bivariate and Multivariate Cox proportional hazards model were used to identify predictors. Multivariate Cox analysis was done and Hazard ratio, with 95% CI and P-value was used to assess the strength of association and statistical significance. Variables significant at P<0.20 level in the bivariate analysis [22] were included in the final multivariate Cox- regression analysis, to identify independent predictors of mortality.

Model was built by backward step wise procedure and compared by likely hood ratio test and harrell's concordance statistics test. Interactions and confounders were tested and cut-off point beta change greater than 20% used. Before fitting the covariate into the model all the Proportionality assumption was tested by global test based on scheonfeld residuals and by examining log minus log plots. The overall goodness of model fitness was checked by Nelson Aalen cumulative hazard function against Cox Snell residual. Multi- co linearity was checked using Pearson correlation, tolerance or variance inflation factor. In order to decide whether or not a variable is significantly associations with mortality were estimated with p-value less than 0.05 the final model. The crude and adjusted hazard ratios together with their corresponding 95% confidence intervals computed and interpreted accordingly. Nutritional status was defined by ENA for SMART software for generating Z score.

Ethical considerations

Ethical approval was obtained from ethical review committee of Arba Minch University, College of Medicine and Health Sciences with reference number CMHS/4268/09. Following the approval, Official letter of co-operation was written to concerned bodies by the department of Public Health of Arba Minch University. Permission was granted from the Hospital and Health center administrative as per the recommendation letter from the department. Personal identifiers were excluded during data extraction; rather code was used. Since it was secondary data obtaining informed consents from the participants was not possible, but the confidentiality of information was maintained by not recording their name from the chart and the recorded data will not be accessed by a third person except by the principal investigator.

Results

Socio-demographic characteristics of children

A total of 421 study participants (children ≤ 14 years) medical records of children living with HIV/AIDS and who started ART were reviewed for this study. Three hundred thirty nine (80.5%) and 82 (19.5%) children cards were recruited from Arba-Minch General Hospital and Arba-Minch Health center, respectively. The age of the children ranges from 3 month to 168 month with a median age of 72 month (IQR=33-108 Month) at the time of ART initiation and almost half (47.2%) children had started treatment prior to their fifth birthday. Of the total patients included in the study, More than half 241 (57.2%) were male and the remaining 180 (42.8) were female, regarding the presences of parental status, 84 (20%) lost their mother and father, 74 (17.6%) of the children have lost either of their parents (Table 1).

Co-variates	Categories	Survival status		
		Dead No (%)	Censored No (%)	Total No (%)
Health facility	Hospital	50 (14.75)	289 (85.25)	339 (80.5)
	Health center	15 (18.29)	67 (81.71)	82 (19.5)
Age category	<1 year	8 (26.67)	22 (73.33)	30 (7.1)
	1-5 years	16 (9.47)	153 (90.53)	169 (40.1)
	5-14 years	41 (18.47)	181 (81.53)	222 (52.7)
Sex	Male	30 (12.45)	211 (87.55)	241 (57.2)
	Female	35 (19.44)	145 (80.56)	180 (42.8)
Primary care giver	Parents	29 (44.62)	239 (67.1)	268 (63.66)
	Grand parents	13 (16.67)	65 (83.33)	78 (18.53)
	Orphanage centers	8 (23.53)	26 (76.47)	34 (8.08)
	Siblings	15 (36.59)	26 (63.41)	41 (9.73)
Marital status of care giver (n=387)	Married	24 (11.54)	184 (88.46)	208 (53.75)
	Single	13 (28.26)	33 (71.74)	46 (11.89)
	Divorced	9 (12.5)	63 (87.5)	72 (18.6)
	Widowed	11 (18.03)	50 (81.97)	61 (15.76)
Care giver HIV sero-status (n=387)	Positive	26 (9.52)	247 (90.48)	273 (70.54)
	Negative	9 (23.68)	29 (76.32)	38 (9.82)
	Unknown	22 (28.95)	54 (71.05)	76 (19.63)
Parental status	Both parents are alive	35 (13.46)	225 (86.54)	260 (61.76)
	Maternal orphan	9 (20)	36 (80)	45 (10.69)
	Paternal orphan	6 (19.35)	25 (80.65)	31 (7.36)
	Double orphan	15 (17.86)	69 (82.24)	84 (19.95)

Table 1: Baseline socio-demographic characteristics of children on ART at Public health facilities of Arba-Minch town, Gamo Gofa Zone, Southern Ethiopia, March, 2017.

Baseline clinical and immunological characteristic of children

Clinically 196 (47%) children initiated ART at an advanced stage of the disease i.e. WHO clinical stage III or IV. About 108 (25.7%) of children were at delayed developmental milestone status during ART initiation. One hundred ninety eight (47%) of them were malnourished among those 14.74% of children have several acute malnourished at initiation of ART. During the ART initiation 139 (33.02%) of children were affected by one or more opportunistic illness, of which 41 children found to be dead at the end of the study. Additionally 60 (14.25%) had history of Tuberculosis at the start of ART and 36 were died during the follow up time. At the initiation of ART, mean (SD) values for weight of children was 18.61 (± 9.65) kg and mean (SD) values for height of the cohort was 110.79 (± 32.19) cm. The base line median values for Hgb was 10.9 (IQR=8.8-12.3) g/dl. Similarly 181 (43.1%) of the children had absolute CD4 count below threshold for immune deficiency at initiation of ART (Table 2).

Baseline ART and chemoprophylaxis status of children on ART

Among the reviewed participants 407 (96.67%) were on first line ART regiment while the rest started on second line. Concerning the type of ART regimens around 59.6% of children were taking D4T based drug regimens while they start treatment. The majority, (56.1%) children had regimen substitution their initial regimen during the follow up period mainly to a combination of AZT+3TC+NVP (4c) 122 (29%) and 27 (11.44%) patients were switched to second line ART. Among the study participant 152 (36.1%) of children are develop ART related side effect 335 (79.6%) children had good adherence for ART,

314 (74.6%) were taking CPT and 302 (71.7%) were taking INH prophylaxis therapy at ART initiation (Table 3).

Co-variates	Categories	Survival status		
		DEAD No (%)	Censored No (%)	Total No (%)
Developmental milestone	Appropriate	16 (5.99)	251 (94.01)	267 (63.4)
	Delayed	22 (20.37)	86 (79.63)	108 (25.7)
	Regressed	27 (58.70)	19 (41.30)	46 (10.9)
Baseline WHO clinical staging	Stage I	9 (9.89)	82 (90.11)	91 (21.62)
	Stage II	12 (8.96)	122 (91.04)	134 (31.83)
	Stage III	20 (13.51)	128 (86.49)	148 (35.15)
	Stage IV	24 (50)	24 (50)	48 (11.40)
Baseline Nutritional status	Normal	28 (12.39)	195 (87.61)	223 (52.97)
	Mild	8 (15.09)	45 (84.91)	53 (12.59)
	MAM	11 (13.25)	72 (86.75)	83 (19.7)
	SAM	18 (29.03)	44 (70.97)	62 (14.74)
Opportunistic Infections at baseline	Yes	41 (29.50)	98 (70.50)	139 (33.02)
	No	24 (8.52)	258 (91.48)	282 (66.98)
TB co-infection at baseline	Yes	36 (60)	24 (40)	60 (14.25)
	No	29 (8.03)	332 (91.07)	361 (85.75)
Baseline Viral Load	Undetectable	20 (12.99)	134 (87.01)	154 (36.6)
	Detectable	23 (21.10)	86 (78.89)	109 (25.9)
	Not done	22 (13.92)	136 (86.08)	158 (37.5)
Hemoglobin	<10 gm/dl	35 (44.87)	43 (55.13)	78 (18.5)
	≥ 10 gm/dl	30 (8.75)	313 (91.25)	343 (81.5)
Absolute CD4	CD4 above threshold	27 (11.25)	213 (88.75)	240 (57)
	CD4 below threshold	38 (20.98)	143 (79.02)	181 (43)

Table 2: Baseline clinical and immunological status of children on ART in Public health facilities of Arba-Minch town, Gamo Gofa Zone, Southern Ethiopia, March, 2017.

Incidence of mortality after initiation of ART

Out of the 421 cohort of children on ART, 261 (62%) children were alive, 43 (10.2%) were lost to follow-up, 52 (12.4%) were transferred out to other facilities and 65 (15.4%) were reported dead. Out of the 65 mortality 14 (21.5%) died within the first 6 month, 10 (15.4%) in the 36 month and 11 (16.9%) in the 60 month. After initiation of ART, children were followed for different periods; a minimum of 1 month and a maximum of 95 month with median follow up period of 50 months with IQR of 24 to 80 months and the cohort contributed to a total of 21,175 person-months (1764.58 person-years) of follow up. The overall mortality rate of the cohort was found to be 3.07 (95% CI=2.37-3.91) per 1000 person-months of observation or 36.8 per 1000 person-year of observation.

Co-variates	Categories	Survival status		
		DEAD No (%)	Censored No (%)	Total No (%)
ART Regimens at baseline	D4T-based regimen	33 (13.14)	218 (86.86)	251 (59.62)
	AZT-based regimen	16 (14.81)	92 (85.19)	108 (25.65)
	TDF-based regimen	10 (20.83)	38 (79.17)	48 (11.40)
	2nd line	6 (42.86)	8 (57.14)	14 (3.33)
ART Adherence on follow up	Good	29 (8.66)	306 (91.34)	335 (79.6)
	Fair	15 (45.45)	18 (54.55)	33 (7.8)
	Poor	21 (39.62)	32 (60.38)	53 (12.6)
Regimen Substitution	Yes	21 (8.90)	215 (91.10)	236 (56.1)
	No	44 (23.78)	141 (76.22)	185 (43.9)
ART drug side effect	Yes	41 (26.97)	111 (73.03)	152 (36.1)
	No	24 (8.92)	245 (91.08)	269 (63.9)
Cotrimoxazol prophylaxis	Yes	24 (7.64)	290 (92.36)	314 (74.6)
	No	41 (38.32)	66 (61.68)	107 (25.4)
INH prophylaxis	Yes	28 (9.27)	274 (90.73)	302 (71.7)
	No	37 (31.09)	82 (68.91)	119 (28.3)

Table 3: Baseline ART and chemoprophylaxis related factors among children on ART in Public health facilities of Arba-Minch town, Gamo Gofa Zone, Southern Ethiopia, March, 2017.

Out of the 65 mortality cases, highest incidence rate of death was observed within 6 months of the ART initiation 14 (7.93 per 1000 child year of observation) but, 19 (0.89 per 1000 Person-months) died within 12 months of ART initiation while 46 (2.17 per 1000 Person-months) died after 12 months. The overall mean estimated survival time of the children under the study was 82.32 month with 95% confidence interval that as high as 85.14 month and as small as 79.48 month after ART initiation. The cumulative probability of survival at the end of 6^{th}, 12^{th}, 24^{th}, 60^{th} and 96^{th} month was 96.6%, 95.9%, 93.4%, 82.9% and 73.9% respectively. The cumulative survival after 96^{th} months was 73.9 % (Table 4 and Figure 2).

Comparison of survival probability among categories of covariates

Kaplan Meier survival curve together with log rank test was used to check for the existence of any significant differences in survival probability between the various categories of variables considered in this study. Accordingly, Children that initiated ART at advanced stage of the disease (WHO stage III & IV) progression had significantly lower survival probability compared to those who start early in the disease progression (log rank, P<0.05). The survival probability for children with low hemoglobin level (<10 gm/dl) were significantly lesser survival probability compared to those with higher hemoglobin level (log rank, P<0.05).

Time in Month	No of children at start	Number of deaths	Survival function	(95% CI)	
6	421	14	0.966	0.943	0.979
12	391	5	0.959	0.934	0.974
24	342	4	0.934	0.904	0.954
36	287	4	0.905	0.87	0.931
48	237	5	0.854	0.811	0.888
60	204	4	0.829	0.782	0.867
72	172	2	0.825	0.755	0.847
84	117	0	0.782	0.726	0.827
96	36	1	0.739	0.632	0.819

Table 4: Actuarial life table cumulative survival of children after start of ART at a specific time, Public Health facilities of Arba-Minch town, Gamo Gofa Zone, Southern Ethiopia, March, 2017.

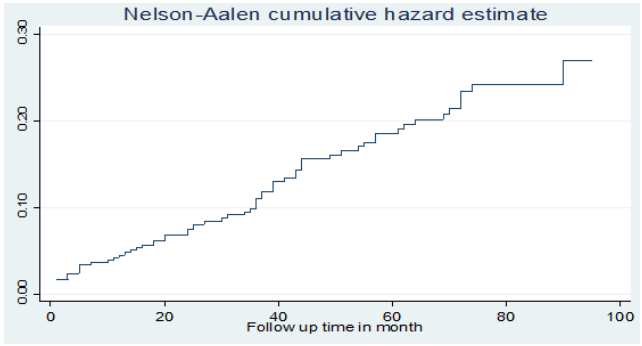

Figure 2: Nelson-Alen cumulative hazard of children on ART at Public Health facilities of Arba-Minch town, Gamo Gofa Zone, Southern Ethiopia, March, 2017.

Children on ART that had evidence of TB co-infection at initiation of ART as well as after they start ART had lesser survival probability compared to those with no evidence of TB (log rank, P<0.05). Children on ART that had OI at baseline had lesser survival probability compared to those with no OI at baseline (log rank, P<0.05). Children on ART who had taken CPT and INH prophylaxis have significantly higher survival probability compared to those who did not taken those prophylaxis (log rank, P<0.05). However, the p-values of the log-rank test don't showed that the mean survival experience of patients among those categories of sex, type of health institution and Absolute CD4 count (The log rank test result is shown in Figures 3 and 4).

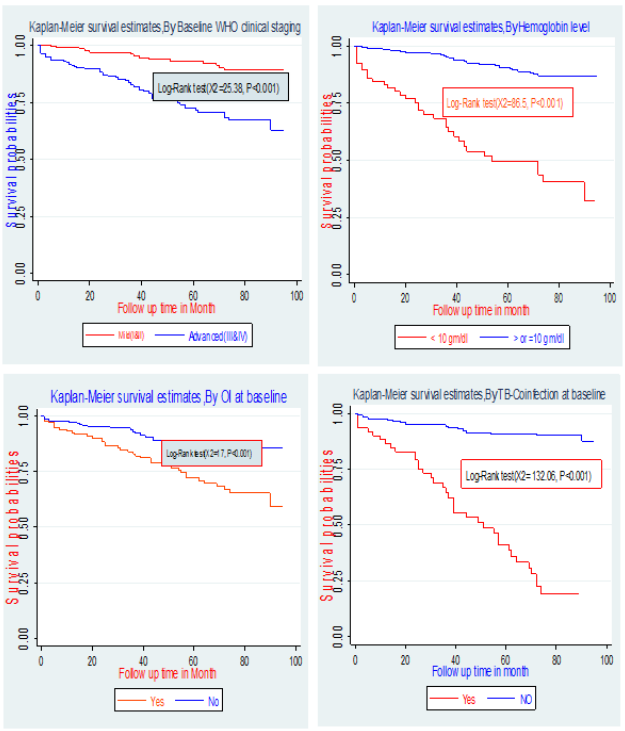

Figure 3: Survival curves for children on ART according to their WHO clinical stage, OI at baseline, TB-Co-infection Hemoglobin level at public health facilities of Arba-Minch town, Gamo Gofa Zone, Southern Ethiopia, March, 2017.

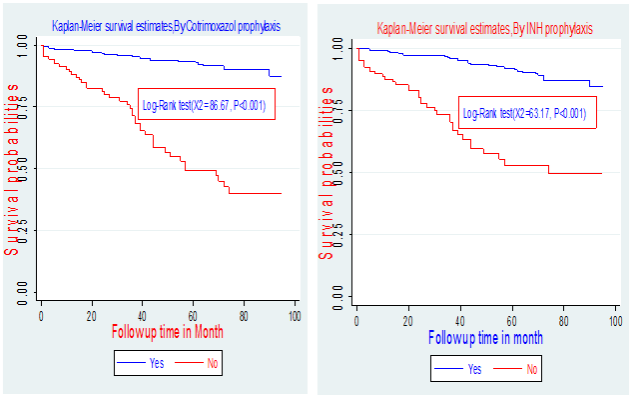

Figure 4: Survival curves for children on ART according to their CPT prophylaxis and INH prophylaxis at public health facilities of Arba-Minch town, Gamo Gofa Zone, Southern Ethiopia, March, 2017.

Predictors of Mortality after Initiation of ART

Before fitting the covariate into the model all the proportional hazard assumptions were checked by Schoenfeld residual and by examining log minus log plots no variable were violate the assumption. To identify independent predictors of mortality, a multivariate Cox-Proportional hazard adjusted model was fitted by forward stepwise procedures with the variables having a P-value less than 0.20 in the bivariate analysis. Multi-colinearity was checked using Pearson correlation, tolerance or variance inflation factor and we found that baseline ART regimen and ART side effect was highly correlated (r=0.728), so that further analysis in the final model were not done.

The risk of mortality was increased among children with baseline opportunistic infections (AHR=1.93, 95% CI=1.03 to 3.64, P=0.041), TB co infected at ART initiation (AHR=2.28, 95% CI=1.23 to 4.22, P=0.009), CD4 count below threshold for immunodeficiency (AHR=2.08, 95% CI=1.15 to 3.77, P=0.016), Low hemoglobin level (<10 gm/dl) (AHR=3.32, 95% CI=1.83 to 6.04, P=0.001) compared with their counter parts. Similarly Children with delayed developmental milestone at initiation of ART (AHR=4.42, 95% CI=1.99 to 9.75, P=0.001), as well as children who were regressing developmental milestone at initiation of ART (AHR=6.0 95% CI=2.68 to 13.45, P=0.001) more likely to die early as compared to clients with appropriate developmental milestone.

Another important predictor of mortality in this was adherence status of children. The risk of mortality among children who were on poor adherence was nearly two times higher than that of good adherence (AHR=2.05, 95% CI=1.02 to 4.13, P=0.044). Similarly the risk of mortality among children who were on fair adherence was 2.17 times higher than that of good adherence (AHR=2.17, 95% CI=1.12 to 4.79, P=0.025). Regarding to prophylaxis preventive therapy the estimated AHR for children on INH prophylaxis and CPT prophylaxis was 0.38 (AHR=0.38, 95% CI=0.22 to 0.68, P=0.001) and 0.26 (AHR=0.26 95% CI=0.15 to 0.46, P=0.001). This means the death hazard in the among children who take INH prophylaxis were 62 % and those on CPT prophylaxis were 74% reducing the risk than their counterpart at any given time respectively (Table 5).

Co-variates	Survival status		CHR (95% CI)	AHR (95% CI)	p-value
	Dead	Censored			
Sex					
Male	30	211	1		
Female	35	145	1.62 (0.99, 2.63)	0.79 (0.42, 1.52)	0.486
Age category					
<1 year	8	22	1.59 (0.74, 3.39)	2.31 (0.87, 6.13)	0.092
1-5 years	16	153	0.51 (0.29, 0.90)*	0.91 (0.44, 1.88)	0.789
5-14 years	41	181	1		
Baseline Developmental Milestone					
Appropriate	16	251	1		
Delayed	22	86	4.21 (2.21, 8.04)*	4.42 (1.99, 9.75)	0.001**
Regressed	27	19	16.51 (8.84, 30.85)*	6.00 (2.68, 13.45)	0.001**
Baseline Nutritional status					
Normal	28	195	1		
Mild	8	45	0.77 (0.29, 2.00)	1.74 (0.59, 5.08)	0.312
MAM	11	72	1.1 (0.60, 2.42)*	1.76 (0.77, 4.03)	0.181
SAM	18	44	2.48 (1.41, 4.38)*	1.27 (0.61, 2.65)	0.53
Baseline WHO clinical staging					
Mild (I&II)	21	204	1		
Advanced (III&IV)	44	152	3.49 (2.21, 7.01)*	1.38 (0.68, 2.77)	0.372
OIs at baseline					
Yes	41	98	2.70 (1.65, 4.42)*	1.93 (1.03, 3.64)	0.041**
No	24	258	1	1	

TB co-infection at baseline					
Yes	36	24	10.56 (6.41, 17.42)*	2.28 (1.23, 4.22)	0.009*
No	29	332	1	1	
Hemoglobin at baseline					
<10 gm/dl	35	43	7.29 (4.47, 11.92)*	3.32 (1.83, 6.04)	0.001**
≥ 10 gm/dl	30	313	1	1	
Absolute CD4					
CD4 above threshold	27	213	1	1	
CD4 below threshold	38	143	1.67 (1.02, 2.74)*	2.08 (1.15, 3.77)	0.016**
ART Adherence on follow up					
Good	29	306	1	1	
Fair	15	18	6.23 (3.35, 11.70)*	2.17 (1.12, 4.79)	0.025**
Poor	21	32	5.94 (3.38, 10.44)*	2.05 (1.02, 4.13)	0.044**
CPT prophylaxis					
Yes	24	290	0.12 (0.07, 0.20)*	0.26 (0.15, 0.46)	0.001**
No	41	66	1	1	
INH prophylaxis					
Yes	28	274	0.17 (0.10, 0.27)*	0.38 (0.22, 0.68)	0.001**
No	37	82	1	1	

Note: CPT, cotrimoxazole; ART, antiretroviral therapy; INH, isoniazid; TB, tuberculosis; OI, opportunistic infections *p<0.2 which are candidate for Multivariate Cox regression model, **p-value ≤ 0.05 statistically significant. 1:- Reference category

Table 5: Bivariate and multivariate cox proportional hazard analysis for predictors of mortality among children on ART at public health facilities of Arba-Minch town, Gamo Gofa Zone, Southern Ethiopia, March, 2017.

Discussion

This study assessed incidence and predictors of mortality among children on ART in public health facilities of Arba-Minch town. A total of 421 children were followed for 21175 person-month of observation. During the follow up period 65 (15.4%) died making overall incidence density rate of 3.07 (95% CI=2.37-3.91) per 1000 person-months of observation. Survival probabilities at the end of 6th, 12th, 24th, 60th and 96th month was 96.6%, 95.9%, 93.4%, 82.9% and 73.9% respectively and overall mean survival time was 82.32 month. (95% CI: 79.48-85.14). Delayed/regressed developmental milestone, OI at baseline, TB co infection at baseline, low hemoglobin level, absolute CD4 below threshold, poor/fair adherence to ART were factors increased occurrence mortality. However, the preventive factors were taking INH prophylaxis and cotrimoxazole prophylaxis.

The findings of this study showed that, the overall incidence of mortality rate of 3.07 (95% CI=2.37-3.91) per 1000 person-months of observation. This finding was comparable from study conducted of eastern Ethiopia (3.8 per 1000 person-months of observation), south west Ethiopia (2.5 per 1000 person-months of observation) and study conduct in Cameron (2.43 per 1000 person-months of observation) [16,21,23]. But lower than finding of Kenya (7 per 1000 person-months of observation) and south Africa (3.95 per 1000 person-months of observation) [12,23,24]. However, this finding was higher than the finding of study conduct Northern Ethiopia (1.40 per 1000 person-months of observation) and Nigeria (0.97 per 1000 person-months of observation) [15,18]. These variations might be explained in three ways. Firstly, the difference could be longer follow-up period than study conducted previously. Secondly it might be related to expansion ART program was significantly reducing deaths among AIDS children proves that the ART program is functioning well. Thirdly it might be associated with effect of INH which prevents the occurrence of OIs like TB and life-threatening bacterial infections.

The finding of this study revealed that mean survival time of cohort under the study was 82.32 month (95% CI=79.48-85.14). This finding was in line with a study conduct in Southwest Ethiopia 83 months (95% CI=79-87) [21]. However, this finding was higher when compared with study from conduct in Northwest Ethiopia 56.5 months, Felege-Hiwot Referral Hospital 22.4 months and study conduct in Zewditu memorial hospital Ethiopia 27.9 months [18,20,25]. This discrepancy might be associated with high proportion (74.3%) of children in our study taken CPT prophylaxis as compared to the other finding conduct in Ethiopia (52.3%-70.4%) another it may associated with increased access of ART services.

The cumulative probability of survival children on ART in this study was 82.9% after 5 years (95% CI: 78.2%-86.7%). This finding was comparable from study conducted in Felege hiwot referral hospital Bahir Dar, Ethiopia 83% and finding conducted in Northwest Ethiopia 83% [18,20]. However this finding was much lower than findings from Adama referral hospital and medical college, Ethiopia (91.6%) and study conducted in wolaita zone health facilities (92%) [7,19]. These variations might be this study include health center and general hospital, but previously study were conduct in referral hospital, so health centers have most of simple cases as severe cases were refer to hospital secondly it might be related to type of care provided vary from institution to institution.

In multivariate Cox proportional hazard model revealed that CPT prophylaxis, INH prophylaxis, low baseline hemoglobin, absolute CD4 count below the threshold, OIs at baseline, TB co infection at baseline, delayed or regressing baseline developmental milestones and adherence to ART were predictors of mortality.

The finding of this study revealed that higher risk of mortality was found among children who had regressing developmental milestone at initiation of ART. The HR for death among children who had regressing developmental milestone at initiation of ART were 6 times (CI: 2.68, 13.45) more likely to die early as compared to appropriate developmental milestone. As well as the risk of earlier death was 4.42 times (AHR=4.42, 95% CI=1.99 to 9.75, P=0.001) higher for children who have delayed developmental milestone than children who have appropriate developmental milestone. This finding was support by study conduct in North West Ethiopia and study conduct in Kenya [12,17]. This is might explained in three form be due to first developmental milestone was related to cognitive development of children and high HIV virus was high cognitive effects on children. Secondly it might related to children with HIV are subject to the potential impact of the virus which reduced stimulation. Thirdly it might associated with burdens of HIV and AIDS in families, such as stigma, orphan-hood or severe parental illness, caretaker changes, separation and poverty.

In this study we found that having CD4 cell count below the threshold level was significantly associated with an increased incidence of mortality. Therefore, children with absolute CD4 count below the threshold level for immunodeficiency at initiation of ART was 2.08 times (AHR=2.08, 95% CI=1.15 to 3.77, P=0.016) more likely to be become died at any time than whose baseline CD4 count above threshold. The finding was supported by different study done in Ethiopia [17-19]. This similarity might be related to children with absolute CD4 count below the threshold level were more prone to opportunistic infections, like tuberculosis. Another explanation might be due to starting ART in advanced stage (III & IV) will reduce immunity may lead to immune compromised.

The risk of death in children who have low hemoglobin level (<10 gm/dl) was all most 3.32 times (AHR=3.32, 95% CI=1.83 to 6.04, P=0.001) higher than those who have normal hemoglobin level. This finding is in line with finding of study conduct in Adama referral hospital, Felege hiwot referral hospital, Kenya and rural hospital of Tanzania [12,13,19,20].

This discrepancy could be explained in three ways. The first it might relate to side effect associated with AZT based ART regimen. Secondly it might associate with presence of severe immunodeficiency which was indicator of late presentation for health care, resulting in late HIV diagnosis and treatment which could lead to poorer outcomes. Lastly it might be associated with malnutrition. Majority of our study participant (47%) were affect by malnutrition. In our study, though severe malnutrition was not an independent predictor of mortality in the multivariate Cox regression modeling; it was associated with mortality in the bivariate modeling. This finding contrasts the finding of study in Kenya [6,12,26].

The another co-variates that have a significant effect on incidence of mortality was adherence to ART when adherence to ART assed by counting number of table those children miss within the first three month after staring of ART. The HR for poor adherence was 2.05 times and HR for fair adherence was 2.17 times more likely to die early than when we compare to children good adherence (AHR=2.05, 95% CI=1.02 to 4.13, P=0.044) and (AHR=2.17, 95% CI=1.12 to 4.79, P=0.025) respectively. This finding was supported by studies conducted in north west Ethiopia, Wolaita zone health facilities and Eastern Ethiopia [7,16,27]. The possible reason for higher risk of mortality might be explained in three reason, The first may be due to staff as well as adherence supporters is not provided regular counseling and caregiver/patient education that are critical for the supportive care of HIV-infected children. Secondly might be those children with fair/poor adherence are much more to development of ART related side effect in our study ART related side effect is also significantly associated with early mortality among those children. Thirdly might be those children lack of appreciation that drugs can help persons who are asymptomatic, thus may increase to the development of drug-resistant.

The finding of this study revealed that those children who have opportunistic infections at a baseline is 1.93 times (AHR=1.93, 95% CI=1.03 to 3.64, P=0.041) more likely to die early than those without opportunistic infections. Similarly, those children with a history of TB co-infection at base line were 2.28 times (AHR=2.28, 95% CI=1.23 to 4.22, P=0.009) at higher risk of death than those without it during the follow-up period. This finding was support by the finding of study conducted in South Africa, Tanzania, Nigeria and Ethiopia [13,15,21,24].

The effect of CPT and INH at the time of starting of ART among cohort suggested a lower risk of mortality. Being put the children on cotrimoxazole prophylaxis were 0.26 (AHR=0.26 95% CI=0.15 to 0.46, P=0.001). This means risk of death in patients with CPT prophylaxis were 74% reduced the hazard of early death than their counterpart throughout the follow-up time. This finding was supported by studies conducted in Felege hiwot referral hospital Ethiopia and Zambian [17,28].

The hazards of death for children on INH prophylaxis was 0.38 (AHR=0.38, 95% CI=0.22 to 0.68, P=0.001). This means at those children who take INH prophylaxis were 62% reduced the hazard of early death than their counterpart throughout the follow-up time. This finding is agreed with the finding of the study conducted in Mizan-Aman general hospital, Ethiopia and South Africa [21,24]. The possible reason may be INH prophylactic therapy was prevent the occurrence opportunistic infections like TB.

The finding of this study in multivariate Cox modeling shows that nutritional status of children was not predictor of mortality. Even though this cohort reveals a high proportion child had either moderate or severe acute-malnutrition and malnutrition was a major contributor to deaths. Malnutrition impair immune reconstitution and there by prolong the period at which patient remain at increased risk of opportunistic infection. This is might be due to in this study

nutritional status of children was assessed according to the guide line by considering weight and height as result malnutrition may represent over diagnosis related to recoding weight and height. This highlights the pressing need for improved diagnostics for malnutrition, it is better to use weight for age way of diagnosis.

Another covariate which was not predict mortality was advanced WHO clinical stage III and VI. As most studies, mortality was higher among children with advanced WHO clinical stage III and VI [15,16,19], but in this study advanced WHO clinical stage III and VI was not predictor of mortality. This contrast might be associated with diagnostic procedure as well as skill of professional. Secondly it may associated with the type of care provide for children.

Strength and Limitation of the Study

Strengths of this study are the use of standard measurements which is enabled to make the comparison of findings with other national and international literatures to be valid. In addition, considering long duration of follow up period of children on ART which use of analytical study (retrospective cohort); the availability of data on important predictors of mortality (CPT, INH and Nutritional status). Since the outcome was death it was easy to establish temporal relationship with predictor variables which were documented at time of starting ART. Predictor variables were not biased by knowledge of the subjects' outcomes. It helps increase the quality of care given for children in ART clinic. It gives a clue how effective care and treatment of children on ART in resource limited settings like Ethiopia. It can serve as baseline information for further study, especially on the impact of INH and CPT prophylaxis of children on ART.

As limitation of this study mortality might be underestimated as the considerable number of children lost to follow up may include children who died. In addition, it is retrospective study and based on records availability of data for all variables were difficult and those with incomplete information were excluded from analysis, while missing data couldn't be ascertained and potential bias, we suspect that the impact should be minimal given that no more than 10% of values were missing for any given predictor (except in the case of viral load and HIV status of care giver) therefore, we excluded from analysis.

The sensitivity analysis was performed in order to determine the impact of lost to follow up by composite end point of LTFUP and death. According this study there was no significant difference, but mortality rate nearly double which is 5.52 per 1000 person month of observation. In bivarate analysis CD4 below threshold was not longer sig (p=0.542), but other variable remain significant and in multivariate analysis OI at baseline was not longer significant (p=0.237), but other variable remain significantly associated with death.

Conclusions

In this study a total of 65 deaths were reported in the follow-up period which gives an overall of 21175 person month of observation. The overall incidence rate mortality of cohort was 3.07 per 1000 person-months of observation and high mortality was observed in the first 6 months after initiation of treatment. The cumulative probability of survival at the end of 6^{th}, 12^{th}, 24^{th}, 60^{th} and 96^{th} month was 96.6%, 95.9%, 93.4%, 82.9% and 73.9% respectively. The probability of survival of children on ART was 73.9% after 96 months and overall means survival time was 82.32 month. (95% CI: 79.48-85.14). The main predictors of mortality among children after starting ART in our study area were Delayed/Regressed developmental milestone, Low Hemoglobin level, Poor/Fair adherence to ART, OI at baseline, TB co infection at baseline, Absolute CD4 below threshold, Absence INH prophylaxis and cotrimoxazole prophylaxis. However, sex of children, Age of children, Advanced WHO clinical stage and nutritional status of children at baseline were not independent predictors of death.

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Authors' Contributions

NB has made substantial intellectual contributions to conception, design, and acquisition of data, analysis and interpretation of data to this study. He also has been involved in drafting the manuscript and revising it critically for important intellectual contents. MK, BO and DM has made substantial contributions to conception, design, analysis and interpretation of data and participated in the critical review and editing of all the manuscript drafts for scientific merit and depth. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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