ORIGINAL ARTICLE

PREDICTORS OF MORTALITY IN CHILDREN AND ADOLESCENTS LIVING WITH HIV ON ANTIRETROVIRAL THERAPY, ETHIOPIA: A RETROSPECTIVE COHORT STUDY

Negash Tagesse [1], Workeabeba Abebe[1]

ABSTRACT

Background : *Treatment of pediatric HIV infection has steadily improved since the introduction of highly active antiretroviral drugs. Knowledge of antiretroviral drugs results is limited and factors contributing to high mortality are poorly investigated in resource-poor settings. So, the aim of this study was to assess independent predictors of mortality in HIV infected children on antiretroviral treatment.*

Methods: *A retrospective institutional-based cohort study was conducted in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. Children who initiated treatment from 2011 to 2015 at the pediatrics antiretroviral treatment clinic are included. We reviewed the patients chart between June and July 2016. Mortality rates were analyzed using the Kaplan Meier method and Cox proportional hazard model used to identify independent predictors of mortality.*

Results: *Four hundred ten children included in this analysis, 22 died over a follow-up period of 1103 child-years with mortality rate of 19.9 deaths per 1000 child-years. Hemoglobin level < 9 gm/dl (hazard ratio (HR) = 3.23, 95% CI: 2.06-5.20), CD4 count < 100 cells (HR =2.25, 95% CI: 1.34-3.47), TB at baseline (HR=4.97, 95% CI: 2.06-11.99), advanced WHO stages (HR =2.32, 95% CI: 1.32-4.09), poor adherence for ART (HR=5.16, 95% CI: 2.97-8.97), and non-enrollment in youth support group (HR =2.53, 95% CI: 1.59-4.00) were the independent predictors of mortality.*

Conclusion: *Mortality observed in these children on antiretroviral treatment is of major concern. Important predictors of mortality are preventable and treatable conditions. The high early mortality rate would support the value of thorough evaluation at baseline and close follow up.*

Keywords**:** *HIV AIDS, antiretroviral therapy, mortality, pediatric, children*

INTRODUCTION

In 2019, an estimated 38 million people were living with HIV (including 1.8 million children) with a global HIV prevalence of 0.8% and 690,000 AIDS-related illnesses. In the same year, there were roughly 1.7 million new HIV infections, among which 150,000 were children (1). Most of these children live in sub-Saharan Africa and were infected via their HIV-positive mothers during pregnancy, childbirth or breastfeeding (1).

Access to ART for HIV-infected African children, has increased significantly in recent years. To mention few, prevention of mother-to-child transmission (PMTCT) strategies leading to decrement of new infection by 52%

[1] Department of Pediatrics & Child Health, College of Health Science, School of Medicine, Addis Ababa University, Addis Ababa, Ethiopia
Corresponding author: Workeabeba Abebe, workeabebasol@gmail.com

from that of 2010, virologic testing by using dried blood spot methodology for early infant HIV diagnosis and universal treatment of HIV infected children which have contributed to advancing pediatric HIV services in these countries (2). Mortality estimates in Africa showed that without treatment 35.2% of HIV-infected children die in their first year and 52.5% by age two (3)

HAART changed the outcome of HIV dramatically. In Africa and other low-income countries mortality of children living with HIV on HAART has decreased. However, despite the increased access of HAART mortality has been high in the first months of ART initiation (4-7). Factors contributing to this high mortality are poorly investigated in resource poor countries including Ethiopia. Therefore the aim of this study is to assess independent predictors of mortality in children living HIV on HAART including adolescents up to 18 years of age.

METHODS

Setting

The study was conducted at the Pediatric Infectious Disease Clinic (PIDC) at Tikur Anbesa Specialized hospital (TASH), the largest public teaching hospital in Ethiopia. Children and adolescents in the age range of 0-19years attend the clinic. During the time of the study, about 498 HIV infected children were attending the clinic, of which around 369 were above 10 years of age.

Study design and period

A retrospective institutional based cohort study for the time period January 1, 2011 through December 31, 2015 was conducted on 410 records of children on ART.

Sampling

All HIV- positive children on follow-up at the pediatric infectious diseases clinic during the specified time were included. Patients with incomplete records were excluded for the study. The data abstraction forms were used to extract the necessary information from the ART recording format. Socio demographic characteristics, baseline clinical, laboratory measurement information and treatment outcome were abstracted from cards of the patient.

Data collection and quality control

The standard checklist was used for recording information extracted from patient cards. The laboratory results of CD4 count recorded before starting ART were used as a baseline values; if there is no pre-treatment laboratory test, results obtained within one month of ART initiation were considered as baseline value. Primary investigator supervised the data were collection to avoid incompleteness, inconsistency and inaccuracy on the measurements. SPSS version 20 statistical package for windows used for data entry and analysis.

Statistical analysis

Descriptive statistics like mean, median and proportions were used to describe the general

characteristics of the cohort. Person years of follow up were calculated by assessing the date of enrollment for ART and death or censoring. The role of the variables on patient survival was analyzed using Kaplan-Meier survival analysis method. Hazard ratios (HR) with a 95% confidence interval were used as effect measures. Multivariable Cox proportion hazards regression was used to assess the effect of baseline predictors on the survival of children on ART. Variables with P < 0.05 in bivariate analysis were taken to multivariable analysis to estimate hazard ratios of 95% confidence interval for the mortality rate among children on ART (8).

Ethical clearance

Ethical clearance was obtained from Addis Ababa University, College of Health Sciences Department of Pediatrics and Child health research publication committee. All information collected from patients cards were kept strictly confidential and names of children or their parents were not included in the abstracted data.

RESULTS

Baseline characteristics of the cohort

Four hundred ten children and adolescents living with HIV on HARRT were included, majority 395 (96.3%) were from Addis Ababa. The cohort comprised 220(53.7%) males and with 190(46.3%) females. Nearly two third 56.1% the cohort started ART at 5-12 years of age. First line ART was started by CD4 criteria 109(26.6%), by clinical criteria 105(25.6%), by both clinical and CD4 167 (40.7%), DNA PCR 12(2.9%), and age under 15 year 17(4.1%). While ART initiated 48 (11.7%) had tuberculosis out of these 8 were died. One-third 142(34.6%) had their initial drug regimen changed and out of this 29 (20%) were due to first line treatment failure. Majority 400 (97.6%) had good (>95%) adherence for ART. Additionally 228 (55.6%) knew their HIV status and almost all 226 (99.1) enrolled in hospital youth support group **(Table 1).**

Table 1 Socio demographic and clinical characteristics of children on HAART, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Baseline Characteristics	**Dead N=22**		**Total N=41**	
	N	%	N	%
Gender				
Male	10	45.5	220	53.7
Female	12	54.5	190	46.3
Age at ART initiation				
>120 months	10	45.5	68	16.6
60- 120 months	8	36.4	230	56.1
36 -59 months	1	4.5	63	15.4
18- 35 months	1	4.5	32	7.8
<18 months	2	9	17	4.1
TB at baseline				
Yes	8	36.4	48	11.7
No	14	3.4	362	88.3
CD4 count				
<100/ml	7	31.8	44	10.7
≥100/ml	15	68.2	366	89.3
Hgb level				
<9 gm/dl	7	31.8	18	4.4
≥9 gm/dl	15	68.2	392	95.6
Adherence for ART				
Good	17	77.3	400	97.6
Fair	0	0	2	0.4
Poor	5	22.7	8	2
Disclosure status				
Yes	1	4.5	228	55.6
No	21	95.5	182	44.4

Survival pattern of the cohort

A total of 410 cohorts of children were followed for a median of 36 months with interquartile range (IQR) from 18 months to 44 months after initiation of ART. The cohort contributed to a total of 1103 person-years of follow up. Twenty-two (5.4%) death observed and 20(4.9%) lost to follow up with a mortality rate of 19.9 deaths per 1000 child-years. Out of 22 deaths, 14 died within the first 12 months of ART initiation (Figure 1).

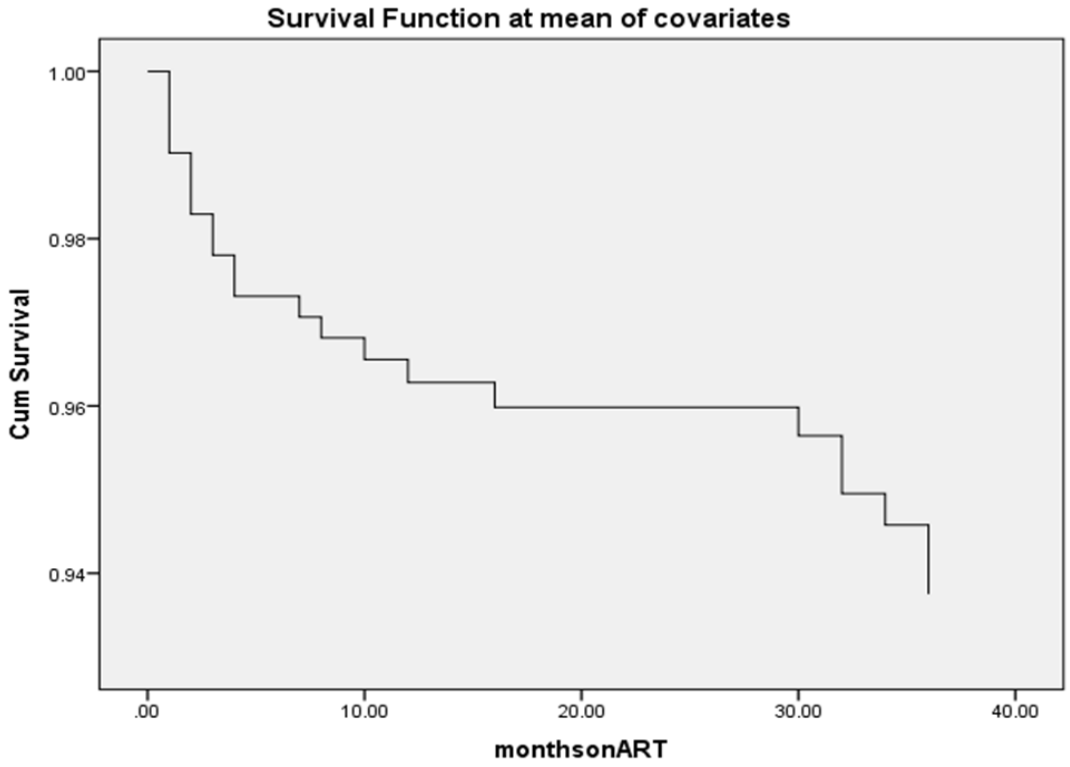

Figure 1 Overall Kaplan - Meier probability of survival functions at mean of covariates of children on ART, Tikur Anbessa Specialized Hospital, Ethiopia

Predicators of mortality

Those patients who have Hgb level < 9 g/dl at ART initiation three times more likely to die than Hgb level>= 9g/dl at ART initiation (hazard ratio (HR) = 3.23, 95% CI: 2.06-5.20). Patients who have tuberculosis during treatment initiation were five times more likely to die compared with those who have not (HR=4.97, 95% CI: 2.06-11.99). Those patients whose CD4 count was below 100 cells were two times more likely to die than those patients CD4 >=100 cells at baseline (HR =2.25, 95% CI: 1.34-3.47). Those patients with WHO stage (III and IV) were two times more likely to die than patients on stage I and II (HR =2.32, 95% CI: 1.32-4.09). Those patients whose adherence for ART poor were five times more likely to die than those with good adherence (HR=5.16, 95% CI: 2.97-8.97). Those not disclosed HIV status were thirty times more likely to die than those disclosed of their status (HR =29.86, 95% CI: 3.99-223.54). Those adolescent who were not enrolled in the hospital youth support group were more than two times more likely to die than those enrolled (HR =2.53, 95% CI: 1.59-4.00). In summary, seven characteristics, Hgb level < 9 g/dl, CD4 < 100 cells, Tuberculosis at ART initiation, advanced WHO stages, poor adherence for ART, undisclosed status, and not enrolled in hospital youth support group were found to be independent predictors of mortality (Table 2).

Table 2 Multivariate Cox regression analyses of predictors of mortality among HIV infected cohort of children on HAART in TASH, Addis Ababa, Ethiopia.

Variables	**P value**	**HR**	**(95%CI)**	
TB at base line				
No				
Yes	.000	4.970	2.060	11.990
Disclosure status				
Yes	.001			
No		29.863	3.989	223.54
Hgb at baseline				
>9gm/dl				
<9gm/dl	.000	3.272	2.058	5.200
CD4 count				
>100/ml				
<100/ml	.002	2.252	1.335	3.469
Adherence for ART				
Good				
Fair				
Poor	0.000	5.164	2.974	8.966
Enrolled in Youth club				
Yes				
No	0.000	2.525	1.591	4.006
WHO stages of HIV				
I and II				
III and IV	0.003	2.324	1.322	4.085

DISCUSSION

There were 22 deaths in 1103.41 person-years of retrospective follow up, providing an incidence density of 19.94 deaths and 18.1 lost to follow-up per 1000 child-years. Out of 22 deaths, 14 died within the first 12 months of ART initiation. The overall mortality rate was lower when compared with other studies in Ethiopia and other African countries (9-12). Early mortality (death less than 12 months) after ART initiation was higher than late mortality (>12 months) after ART initiation in this study. This finding was also consistent with the study done in the USA, 10 European countries South Africa, Tanzania, and Ethiopia (13-18). The comparable low mortality showed that improvement in the care and treatment of HIV in children however the relatively high early mortality still showed that there is a need to have a close follow up.

Children with poor adherence (< 85%) were four times more likely to die than those with good adherence (> 95%). This is similar to a study done in Harar, Ethiopia in which children with adherence < 85% were four times more likely to die than those with good adherence (> 95%) for ART (14). Children with TB at baseline were five times more likely to die than those without TB. This finding was consistent with a study done in Ethiopia and Nigeria (14, 19)

Children with low Hgb, CD4 count < 100 cells, and advanced stage (III and IV) were at the highest risk of mortality following HAART initiation. This is also comparable with clinical cohort studies in Kenya, Zambia, South Africa, Coted'Ivoire, Malawi, and Ethiopia (20-23).

Performing analysis including the composite endpoint of death and Lost to follow-up (LTFU) gave 10.3 % (38 per 1000 child-years), which almost doubled the mortality rate. Ignoring LTFU led to substantial underestimation of mortality, which was shown, from ten treatment programs across sub-Saharan Africa (24).

The main limitation of this study was the composition of the study participants with more than half of the children being 5 years or more. As the mortality of HIV infected children was higher in lower age groups, this may underestimate the estimates because many younger patients with poor prognosis were probably not included.

Conclusion and Recommendation

In conclusion, it was advisable to give due emphasis on children with TB-HIV co-infection, poor adherence, advanced HIV, and undisclosed HIV status. Strengthening comprehensive early HIV treatment, care, and support to improve the survival of children on HAART. In addition important predictors of mortality must be addressed to improve the outcome of these patients.

Consent for publication: Not applicable

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions

Both authors conceived and designed the study. NT involved in the data collection and drafted the manuscript. WA and NT were actively involved in the data interpretation, critically reviewed and approved the final manuscript.

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