



ADDIS ABABA UNIVERSITY SCHOOL OF PUBLIC HEALTH

Survival and its predictors among children on ART in Hawassa Referral Hospital ,Adare Hospital and Bushulo Health centre ,South Ethiopia :Retrospective cohort study

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LIST OF ACRONYMS

AIDS; Acquired Immune Deficiency Syndrome

AHR; Adjusted Hazard Rate

ART; Antiretroviral Therapy

AZT; Zidovudine

CHR; Crude Hazard Rate

CI; Confidence interval

D4t; Stavudine

DCS; developed countries

EFV; Efavirenz

EPTB; Extra Pulmonary Tuberculosis

HAART; Highly Active Antiretroviral Therapy

HAPCO; HIV/AIDS Prevention and Control Office

HIV; Human Immunodeficiency Virus

MOH; Ministry Of Health

NNRTI; Non-Nucleoside Reverse Transcriptase Inhibitor

NRTI; Nucleoside Reverse Transcriptase Inhibitor

NVP; Nevirapine

PCP; Pneumocystis Carini Pneumonia

PI; Protease Inhibitor

PLWHA; People Living With HIV/AIDS

PTB; Pulmonary Tuberculosis

RLCS; resource limited countries

SNNPR; Southern Nations Nationalities Peoples Region

3TC; Lamivudine

TLC; Total Lymphocyte Count

UN; United Nation

WHO; World Health Organization

Abstract

Introduction: HIV develops very rapidly among infants and children, and, without treatment, a third of children with HIV will die of AIDS before their first birthday, with half dying before they are two. In 2009, there were 260,000 deaths attributed to HIV in under-15, most of which could have been prevented through early diagnosis and effective treatment. Highly Active Antiretroviral Therapy has improved the survival of HIV infected patients. Low baseline CD4, low weight for age, and high viral load levels were identified by studies as strong predictors of mortality.

Objective: To assess survival rate and predictors of survival among children on ART in Hawassa Referral Hospital , Adare Hospital and Bushulo Health Center, Hawassa .

Methodology: A retrospective cohort study was conducted among children on ART. A total of 222 patient's records enrolled between July 28, 2006 to September10, 2011 was reviewed. Kalpan Meir survival analysis was used to estimate mean survival time and Life table was used to estimate survival probability after introduction of ART and log rank test was be used to compare Hazard curves. Cox proportional-hazard regression was used to calculate the bivariate and adjusted hazard rate and then determine independent predictors of mortality.

Results: A total of 222 children started on ART were followed for a median of 20 months (IQR=9-35.25). Among the cohort 119 (53.6%) were male the median age was 7(IQR=4-10). The mean hemoglobin was 9.9 (SD, 4.22) and median CD4 count was 272.5 cells/ μ l (IQR=164.75-446.25). The mean survival time of the entire cohort was 53.2 months (95% CI 50.35-56.0). The independent determinants of mortality were WHO clinical stage IV AHR =9.64 (95%CI 1.92-48.41) and low haemoglobin value(Hgb<7.00gm/dl) AHR=4.28(95% CI 1.53-11.93), stunting AHR=3.992(95%CI1.24-12.77), wasting AHR=3.770 (95%CI1.28-11.12).

Conclusion: Despite apparent benefit of ART there is high early mortality. A careful monitoring of patients with low hemoglobin, advanced WHO staging, Stunting and wasting particularly during the first 6 months of HAART is necessary. Nutritional intervention may also benefit survival.

1. INTRODUCTION

1.1 Background

Globally paediatric HIV infection represents a major setback to child health. More than 1,000 children are newly infected with HIV every day, and of these more than half will die as a result of AIDS because of a lack of access to HIV treatment (1). In addition, millions more children every year are indirectly affected by the epidemic as a result of the death and suffering caused in their families and communities (1).

At the end of 2009, there were 2.5 million children living with HIV around the world. During 2009, an estimated 400,000 children became newly infected with HIV and 1.8 million people died of AIDS, of which one in seven was child (1). There are more than 16 million children under the age of 18 who have lost one or both parents to AIDS. Most children living with HIV/AIDS (almost 9 in 10) live in sub-Saharan Africa, the region of the world where AIDS has taken its greatest toll (2).

According to report of HIV/AIDS prevention and control office (HAPCO), the total number of People Living with HIV/AIDS (PLHIV) in year 2008 was estimated to be 1,037,267 of which 68,136 were children. Furthermore the number of deaths due to AIDS for the same period was estimated to be 58,290 and 9,284 of them were children (3).

1.2. Statement of the problem

HIV develops very rapidly among infants and children, and, without treatment, a third of children with HIV will die of AIDS before their first year of birthday, with half dying before they are two(4). In 2009, there were 260,000 deaths attributed to HIV in children of age below 15 years globally, most of which could have been prevented through early diagnosis and effective treatment (1). Though the number of children receiving antiretroviral therapy (ART) has increased significantly in recent years, at the end of 2009 only 29 percent of the 1.27 million children in need of ART in low- and middle-income countries were receiving it (2).

Ethiopia is currently decentralizing HIV care and treatment services to selected health centres. Decentralization increases access by taking services closer to more people, reducing transport and related costs for patients and families, resulting in improved adherence and enrolment in care and treatment services early in the course of the disease. Decentralization follows the health network model, ensuring linkages between services at hospital, health centre and community levels. Large scale in-service trainings in various programme areas have been carried out to build capacity of different cadres of health care providers. Efforts have been made to demystify HIV care and ART by developing standardized and simplified clinical tools, reference materials, and job aids. Building the capacity of clinical nurses to prescribe first-line ARVs for stable patients and provide primary chronic HIV care including ART was pioneered in 2006. Ethiopia is also piloting the use of trained non-health professional counsellors (5). In Ethiopia a total of 10, 952 children started ART up to year 2008 and 8,761 children were alive and on treatment (3). Currently there are 10, 4961 children on ART (6).

Highly Active Antiretroviral Therapy (HAART) has improved the survival of HIV infected patients. However, compared to patients in high-income countries, patients in resource-poor countries have higher mortality rates. A systematic review, which determined and compared baseline status and outcomes of children who were started HAART in resource limited countries (RLCS) and developed countries (DCS) reported that, mortality rates were dramatically lower with HAART than in studies before HAART and <10% in both settings (7). The post-HAART mortality rates for HAART-naive children were five to nine fold greater in RLCs than in DCs. Low baseline CD4, low weight for age, and high viral load levels were identified by individual studies as strong predictors of mortality in both RLCs and DCs (7).

A study in South Africa concluded that scaling up ART provision was associated with reduced early mortality (8). Early mortality rates in sub-Saharan Africa are very high; between 8 to 26 % of patients die in the first year of ART with most deaths occurring in the first few months (9).

A study conducted to assess antiretroviral treatment outcome in public hospitals, South Nations Nationalities and Peoples Region, Ethiopia reported that, there is an indication of improvement of survival in the patient population (10). A better knowledge of prognostic factors would allow closer follow up and more targeted interventions to improve survival.

1.3. Rationale

The Ethiopian Ministry of Health (MOH) introduced ART in 2003 on subsidized, fee-based scheme, and ART became freely available since 2005(11). Further, ART was decentralized to health centres in 2006, which marked the rapid scale-up phase in the history of the Ethiopian ART program (11). However, few studies have assessed predictors of survival inpatients on ART, especially in children. Therefore the aim of this study is to estimate survival rate and predictors of survival among children on ART in Hawassa. Furthermore it will provide empirical evidence for planning and implementing ART programmes and decision making at different levels.

2. Literature review

2.1. Burden of HIV/AIDS globally and ART in Ethiopia

In 2009, 33.3 million people around the world were living with HIV/AIDS (1). More than 60 million people have been infected with HIV since the pandemic began. AIDS is the leading cause of death in Sub-Saharan Africa, and the fourth leading cause of death globally. Approximately 97 percent of people living with HIV/AIDS live in low- and middle-income countries. Sub-Saharan Africa is the hardest-hit region and is home to 67 percent of all people living with HIV worldwide (1).

At the end of 2009, there were 2.5 million children living with HIV around the world. During 2009, an estimated 400,000 children became newly infected with HIV and 1.8 million people died of AIDS, of which one in seven were children (1). There are more than 16 million children under the age of 18 who have lost one or both parents to AIDS. Most children living with HIV/AIDS (almost 9 in 10) live in sub-Saharan Africa, the region of the world where AIDS has taken its greatest toll (2).

Nine out of the ten children with HIV were infected through their mother either during pregnancy, labour and delivery or breastfeeding (1). Without treatment, about 15-30 percent of babies born to HIV positive women will become infected with HIV during pregnancy and delivery and a further 5-20 percent will become infected through breastfeeding (12).

In Ethiopia 443,964 PLWHA were enrolled to ART until year 2008, 246,347 PLWHA started treatment and 179,183 are currently on ART (5). The total people on 1st line regimen are 166,444 of which 10,361 are children. The total number of persons on 2nd line regimen is 1000 of which 135 are children. Among children on the 1st line regimen 5,024 are on d4t-3TC-NVP, 1134 on d4t-3TC-EFV, 2724 are on AZT-3TC-NVP and 1479 AZT-3TC-EFV. The rest are on 2nd line regimen (6)

2.2 .Child survival and risk factors of mortality

A systematic review which compared major baseline characteristics and clinical end points after HAART between resource-limited and developed settings reported that, mean percentage of deaths per cohort and mean deaths per 100 child-years after HAART were significantly higher in RLCs than DCs (7.6 vs 1.6, $P < .001$, and 8.0 vs 0.9, $P < .001$, respectively) (6). Mean baseline CD4% was 12% in RLCs and 23% in DCs ($P = .01$). Mean baseline VLs were 5.5 vs 4.7 log₁₀ copies per mL in RLCs versus DCs ($P < .001$) (7).

A research conducted in the paediatric departments of four large Spanish paediatric referral hospitals indicated that HAART decreases VL, increases CD4⁺ T cell values, and increases survival (9). However, the toxicities associated with its long-term use may significantly outweigh the early initiation of treatment in clinically stable children with a relatively preserved immune status (13).

An observational study conducted to evaluate the effectiveness of treating HIV-1infected children with ART in Haiti between 2003 and 2006 reported that, 81%remained in care, 9%were died, and 10% were lost to follow-up (14). Independent baseline predictors of mortality were age <18 months, CD4⁺ T cell percentage $\leq 5\%$, and weight-for-age Z score (WAZ) less than -3 (14).

According to Research Institute for Health Sciences, Chiang Mai, hospitalization and mortality rates significantly decreased among HIV-infected children receiving HAART (11). Most hospitalizations and deaths occurred during the first 24 weeks of HAART. Identification of the causes of hospitalization and death is essential to decrease the high early mortality rate (15).

A study conducted in HIV infected children in Côte d'Ivoire (2004–2007) showed that, the overall mortality rate on ART was 14.4 per 100 child-years of follow-up and was significantly higher in the first 3 months of ART than during months 4–12, at 32.8 and 6.9 per 100 child-years of follow-up, respectively (12). Sixty-six percent of deaths during ART occurred within the first 3 months of therapy. During this period, the mortality rate was 43.7 per 100 child-years in children aged < 18 months and around 30 per 100 child-years in older children. Mortality rates decreased 4 to 6 times in all age groups after the third month on ART (16).

A study conducted between 2004 - 2006 in the ART clinic at Mzuzu Central Hospital, Mzuzu, Malawi indicated that the cumulative incidence of death in children less than 15 years at 3, 6, 12 and 24 months after ART was 8, 12, 13 and 15%, respectively (13). After multivariate analysis, being in World Health Organization clinical stage 4, having severe wasting and severe immunodeficiency were factors significantly associated with 3-month mortality and 6-month mortality, respectively (17).

According to a study conducted to identify predictors of mortality in patients initiating antiretroviral therapy (ART) in Durban, South Africa, from three hundred and nine patients, forty-nine (16%) had died by the end of the study (14). In univariate analysis, the strongest predictors of mortality were a CD4 cell count $<50/\mu\text{l}$ (hazard ratio (HR) 3.70, 95% confidence interval (CI) 1.96 – 7.14), a history of oral candidiasis (HR 3.17, 95% CI 1.70 – 5.87) and a history of cryptococcal meningitis (HR 2.76, 95% CI 1.80 – 19.2). A CD4 cell count $<50/\mu\text{l}$ (HR 3.08, 95% CI 1.54 – 5.88) and a history of oral candidiasis (HR 2.58, 95% CI 1.37 – 4.88) remained significant in multivariate analysis. A history of tuberculosis was not a significant predictor of mortality (18).

A 5-year prospective observational study among 149 HIV-1 infected children on antiretroviral therapy in Kenya showed that twenty children died at a median of 35 days post HAART initiation (IQR 13 - 99 days), of whom 18 (90%) died in the first 120 days (15). The mortality rate over the entire follow-up period was 8.4 deaths per 100 child-years (20 deaths over 238 child-years). Mortality in the first 4 months of follow-up was 46 deaths per 100 child-years (18 deaths over 39 child-years) but this dropped to 1.0 death per 100 child-years between 4 months and two years post-HAART (2 deaths over 199 child-years). The cumulative survival was 95% after one month of HAART, 89% after 3 months and 85% after 6 and 12 months respectively. The cumulative survival after 25 months was 84%, haemoglobin $< 9 \text{ g/dl}$ remained predictive of mortality (HR 2.95 [95% C.I. 1.04, 8.35], $p = 0.04$) (19).

According to Taye, et al, the average survival time for children on ART at Zewditu Hospital, Ethiopia was 27.9 months (16). Independent baseline predictors of mortality were severe wasting (Hazard ratio (HR) = 4.99, 95% CI 2.4-10.2, P < 0.00), absolute CD4 below the threshold for severe immunodeficiency (HR = 3.02, 95% CI 1.02-8.96, P = 0.04) and low hemoglobin value (HR = 2.92, 95% CI 1.3-6.7, P = 0.001 for those hemoglobin value < 7.0 gm/dl). The probability of surviving for wasted children declines sharply starting from 6th months and reach 76% in 12th months (20).

A study conducted among HIV positive children on ART in Northwest Ethiopia reported that, mortality was 4 deaths per100 child years and most deaths occurred in the first 6 and 12 months of ART(75.6% and 90.2%respectively) (21).

2.3. HIV treatment for children and its challenges

Children ideally need to be given drugs in the form of syrups or powders, due to difficulties in swallowing. However, drug treatments involving syrups for children are generally more expensive. As a result, carers are often forced to break adult tablets into smaller doses, running the risk that children are given too little or too much of a drug. Studies suggest that breaking down adult tablets into smaller doses can work effectively although this should only really be seen as a last resort (22).

One of the greatest challenges when it comes to treating children with HIV is loss to follow up. This is when a patient tests HIV positive but does not return to a health facility to receive treatment. Some of the reasons children are lost to follow up include "clinical organization and data flow of results, lack of caregiver contact information, stigma and counselling challenges, the burden on patients to return for results, and weak follow-up within clinics (23).

More drugs suitable for children are qualified by the WHO every year, but without access to cheap generic versions of them the majority of HIV infected children will not benefit. The latest WHO guidelines recommend children start treatment as early as possible after diagnosis and suggest that where necessary they receive a complex set of drugs including protease inhibitors to reduce the likelihood of drug resistance (24).

Opportunistic infections can be prevented using drugs such as cotrimoxazole: a cheap antibiotic that has been proven to significantly reduce the rate of illness and death among HIV-positive children. Countless lives could be saved if cotrimoxazole were made more widely available, but at the moment it is estimated that only 14 percent of children who could be benefiting from the drug are receiving it (24).

Despite previous attempts, many important questions related to the best use of ART especially in children are not fully answered, for example, when is the best time to start therapy, which are the best drug to use ,how long will the treatment keep people alive ,what factors predict survival. Thus the aim of this study is answer some of the above questions.

2.4. Conceptual frame work for the project

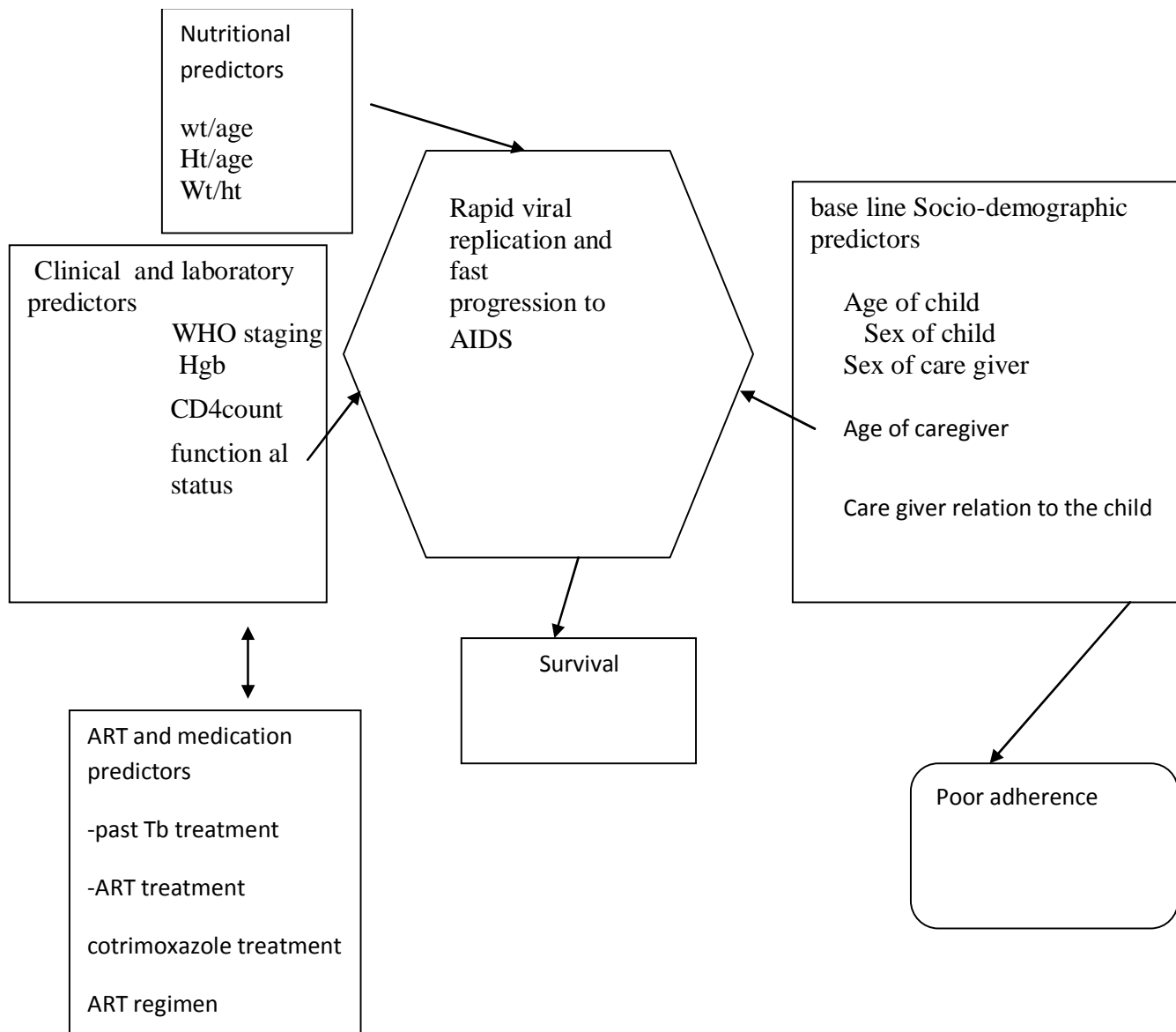


Fig1: Conceptual frame work to asses predictors of survival among children on ART in Hawassa ,January 2012

3. Objectives

3.1. General objective

To assess survival and its predictors among children aged less than 15 years on ART in Hawassa Referral Hospital, Adare hospital and Bushulo Health Center, Hawassa

3.2 .Specific objectives

- To estimate mean survival time among children below the age of 15 years who are on ART
- To assess factors associated with survival among children below the age of 15 years who are on ART

4. METHODOLOGY

4.1. Study Design

A retrospective cohort study was conducted in HIV infected children started ART in Hawassa Referral Hospital, Adare Hospital and Bushulo Health Center for period of 5 years (2006-2011).

4.2. Study setting and period

The study was conducted in Hawassa Referral Hospital, Adare Hospital and Bushulo Health Center, Hawassa from December, 2011 to January, 2012.

Hawassa Town is found 270kms south of Addis Ababa, the capital city Ethiopia. The town is divided into 8 sub cities and 32 kebeles. Its population estimated to be 291,277. It has two government hospitals, five health centres and three Private hospitals, 47 private clinics.

4.3. Study population

All HIV infected children aged less than 15 years who were on ART in Hawassa town from July 28, 2008 to September 10, 2011.

4.4 Sample size determination

The sample size was calculated based on the single mean formula

$$N_o = \frac{(Z_{\alpha/2})^2 \sigma^2}{d^2}$$

Where $Z_{\alpha/2}$ = critical value for α level

σ^2 = variability of estimated survival

d = precision level

N_o = sample size required

Based on previous study estimate of mean survival=27.9 months with $\sigma = 6.67(16)$

α – error of 5% and precision of 5% (1.4 months)

The calculated sample size n=121

But, all 222 HIV infected children aged less than 15 years on ART in Hawassa Town from July 28, 2006 to September 10, 2011 were involved in the study

4.5. Sampling technique

The study subjects were taken from two hospitals and one health center. 186 from Hawassa referral hospital, 19 from Adare hospital and 17 from Bushulo health center. Profiles of all children on ART between July 28, 2006 to September 10, 2011, were assessed.

4.6. Data collection

4.6.1. Variables

1. Dependent variable

- The main outcome measure is death from the initiation of ART to September 2011

2. Independent variable

A. Socio demographic characteristics (age, sex)

B. Nutritional history

- nutritional status (weight for age, height for age, weight for height)

C. Baseline clinical, laboratory and ART information (WHO clinical staging, Functional status ART treatment, chemoprophylaxis, drug allergies, Hgb count, CD4count, side effects)

4.6.2. Data collection tools

A data collection form was developed from ART entry and follow up form being used in the ART clinic(Annex II).

4.6.3. Data collection procedure

The data was collected by reviewing pre-ART register, lab request, monthly cohort form, and follow up form, ART intake form, patients' card and death certificate complemented by registration by home visitors. The most recent laboratory results before starting ART was used as a baseline value. A total of 3 days training was given for data collectors. Three advanced ART nurses, who were trained on Comprehensive HIV care, collected the data. The overall activity was controlled by the principal investigator of the study.

4.7. Data quality control

Data quality was controlled by designing the proper data collection materials and pretesting, through continues supervision. All completed data collection form was examined for completeness and consistency during data management, storage, cleaning and analysis. The data was entered and cleaned by principal investigator before analysis.

4.8. Operational Definition

Above threshold ; CD4 count greater than WHO criteria for severe immune deficiency in infant and children

Below threshold; CD4 count less than WHO criteria for severe immune deficiency in infant and children

Censored; remain alive up to the end of the study

Event; occurrence of death or lost to follow up

4.9. Data processing and analysis

Data was entered to Epi-Info 5.0 for windows and analyzed using SPSS version 16.0 for windows. The data was cleaned and edited before analysis. Data exploration was undertaken to see if there were odd codes or items that were not logical and then subsequent editing was made. We described the patient cohort characteristics in terms of mean/median value for continuous data and percentage for categorical data. Deaths were confirmed by reviewing the death certificates, medical registration in the hospital, or registration by ART adherence supporter through calling using the registered phone number. Finally, the outcome of each subject was dichotomized into censored or death. Cox proportional hazard model used to assess relative risk of death. Relative hazard with 95%CI from model was used to assess which variable is associated with mortality.

Multivariable adjusted model was fitted with factors that are statistically significant. Kaplan Meir survival analysis was used to estimate mean survival time. Life table was used to estimate cumulative probability of survival after introduction of ART.

4.10. Ethical Considerations

Ethical clearance was obtained from Institutional Review Board (IRB) of Addis Ababa University, College of health of Health science, School of public health. Following the approval by IRB, Official letter of co-operation was written to concerned bodies by the School of Public Health AAU. As the study was conducted through review of medical records, the individual patients were not subjected to any harm as far as the confidentiality is kept. To preserve the confidentiality, nurses working in the ART clinic of Hawassa Referral hospital, Adare Hospital, and Bushulo Health Center extracted the data from the medical records. Moreover, no personal identifiers were used on data collection form. The recorded data was not accessed by a third person except the principal investigator, and kept confidentially.

5. RESULT

5.1. Cohort Basic Characteristics

5.1.1. Demographic Characteristics

A total of 222 HIV infected children started anti retroviral treatment from July 2008 to September 2011 were included in the study. Among the cohort 119 (53.6%) were males, the median age was 7 years (IQR=4-10), 12 (5.4%) were aged less than 18 months, 70(31.5%) 18 -48 months, and 140 (63.1%) were 5-14 years (Table 1).

Table 1: Demographic characteristics of children started anti retroviral treatment at Hawassa Referral Hospital ,Adare Hospital and Bushulo Health center ,Hawassa, January 2012.

Variable	Frequency (n=222)	Percent
Sex of the child		
Male	119	53.6
Female	103	46.4
Age group		
<18 months	12	5.4
18-48months	70	31.5
5-14 years	140	63.1

5.1.2. Clinical and Laboratory characteristics Characteristic

Majority 120(54.1%) of the cohort were WHO clinical stage III followed by WHO clinical stage II 57(25.7%) and WHO clinical stage IV 25(11.3%). The mean hemoglobin was 9.9(SD, 4.22), 34(15.7%) had low hemoglobin (<7.00gm/dl), 38(17.1%), had hemoglobin between 7.00 and 8.50 gm/dl. The median CD4count was 272.5 cells/ μ l (IQR=164.75-446.25); one hundred seventy (76.6%) of children were severely immune deficient. Among the cohort 186 (83.7) were given cotrimoxazole at the time of initiation of ART and 63(28.4 %) were positive for TB screening test. The most widely used regimen in this cohort was d4t-3TC-NVp 128 (57.7%) followed by AZT-3TC-NVP 40 (18%) and d4t-3TC-EFV 39 (17.6%). Two hundred eight (93.7%) of the cohort had good adherence. Children change the first line regimen due to new TB were 6(2.7%), new drug available 3(1.4%), adverse drug event 2(0.9%). The clinical and laboratory characteristics of the cohort are shown in table 2

Table 2: Clinical and Laboratory characteristics of children started anti retroviral treatment at Hawassa Referral Hospital, Adare Hospital and Bushulo Health center, Hawassa, January 2012

Variable	Frequency	Percent
WHO clinical staging		
I	20	9.0
II	57	25.7
III	120	54.0
IV	25	11.3
Hemoglobin(gm/dl)		
<7.00	34	15.3
7.00-8.50	38	17.1
8.51-10.00	55	24.8
>10.00	9	42.8
Absolute CD4count		
Below threshold	70	76.6
Above threshold	152	23.4
TB test		
No		
Positive	153	68.9
Negative	63	28.4
	6	2.7

TB treatment		
Yes	58	73.9
N0	164	26.1
Regimen given at start		
d4t_3TC_NVP	128	57.7
d4t_3TC_EFV	39	17.6
AZT-3TC-NVP	40	18.0
AZT-3TC-EFV	8	3.6
Others	7	3.3
ARV adherence		
Good	208	93.7
Fair	10	4.5
Poor	4	1.8
Out come of the patient		
Active	196	88.3
Dead	26	11.7

5.1.3. Nutritional Characteristics

The nutritional status of the study participant at baseline showed that, 112(50.5%) were under weight, 95(42.7%) stunted and 70(31.5%) wasted. In addition children were also classified sever malnutrition as sever stunting 50(22.5%), sever wasting 38 (17.1%) and sever under weight 49(22%) with the most affected age group by sever malnutrition were age group<18 months (Table3).

Table 3: Baseline nutritional status children started anti retroviral treatment at Hawassa Referral Hospital , Adare Hospital and Bushulo Health centre , Hawassa, January 2012

Nutritional parameter	Age group			
	<18 months	18-59 months	5-14years	Total
Stunted (HAZ<-2)	4(33.3%)	34(48.6%)	57(40.7%)	95(42.7%)
Sever stunting(HAZ<-3)	3(25%)	16(22.8%)	31(22.1%)	50(22.5%)
Under weight (WAZ<-2)	7(58.3%)	29(41.4%)	76(54.2%)	112(50.5)
Sever under weight(WAZ<-3)	4(33.3%)	15(21.4%)	30(21.4%)	49(22%)
Wasted(WHZ<-2)	5(41.7%)	15(21.4%)	50(35.7%)	70(31.5%)
Sever wasting(WHZ<-3)	4(33.3%)	10(14.3%)	34(24.3%)	38(17.1%)

5.2. Survival Analysis

A total of 222 children started ART have been monitored from 0 to 60 months. The median follow up was 20 months, the minimum and maximum follow up was 1 and 60 months respectively. The treatment outcomes of children ever started ART were 196 (88.3%) alive and on ART, 26 (11.7%) died of whom 13(50 %) were died within the first 6 months. The cumulative proportion of survival was 94%, 92%, 90%, 87% and 83% at 6, 12, 18, 24 and 60 months , respectively (Table4).

The mean survival time of the entire cohort using Kaplan Meier analysis was 53.2 months (95% CI 50.35-56.0). Further analysis comparing the mean survival time according to nutritional status (WHZ) stratified by sex showed that there is significant difference in mean survival time (log rank test $\chi^2 = 22.23$, $df = 1$ $p < 0.001$). The mean survival of female children with wasting was 40.7 months (95% CI 29.86-51.626), while it was 47.5 months (95% CI 40.65-54.44) for male children with the same condition. Similarly analysis of survival for stunting (HAZ) with sex strata showed lower likelihood of survival for female children (log rank test, $\chi^2 = 15.42$, $df = 1$, $p < 0.001$) which was 36 months (95% CI 28.74-43.38) compared to 49.7 months (43.39-56.0) for male (Table 5).

Table 4: Actuarial Table estimates of the cumulative progression to death for 222 cohort starting ART b/n July 2006 up to September 2011.

Interval Start Time	Number Entering Interval	Number of Terminal Events	Cumulative Proportion Surviving at End of Interval	Hazard Rate
0	222	13	.94	.01
6	188	3	.92	.00
12	149	3	.90	.00
18	125	4	.87	.01
24	83	3	.83	.01
30	67	0	.83	.00
36	55	0	.83	.00
42	37	0	.83	.00
48	26	0	.83	.00
54	11	0	.83	.00
60	5	0	.83	.00

Table 5; Mean survival time according to nutritional status stratified by sex for 222 cohort starting ART b/n July 2006 up to September 2011 in Hawassa.

Nutritional status	Mean survival time		
	Male	Female	Over all
Wasting			
No	55.97	55.09	56.30
Yes	47.55	40.74	45.22
Stunting			
No	56.55	55.09	56.59
Yes	49.67	40.74	47.25
Over all	53.85	51.63	53.20

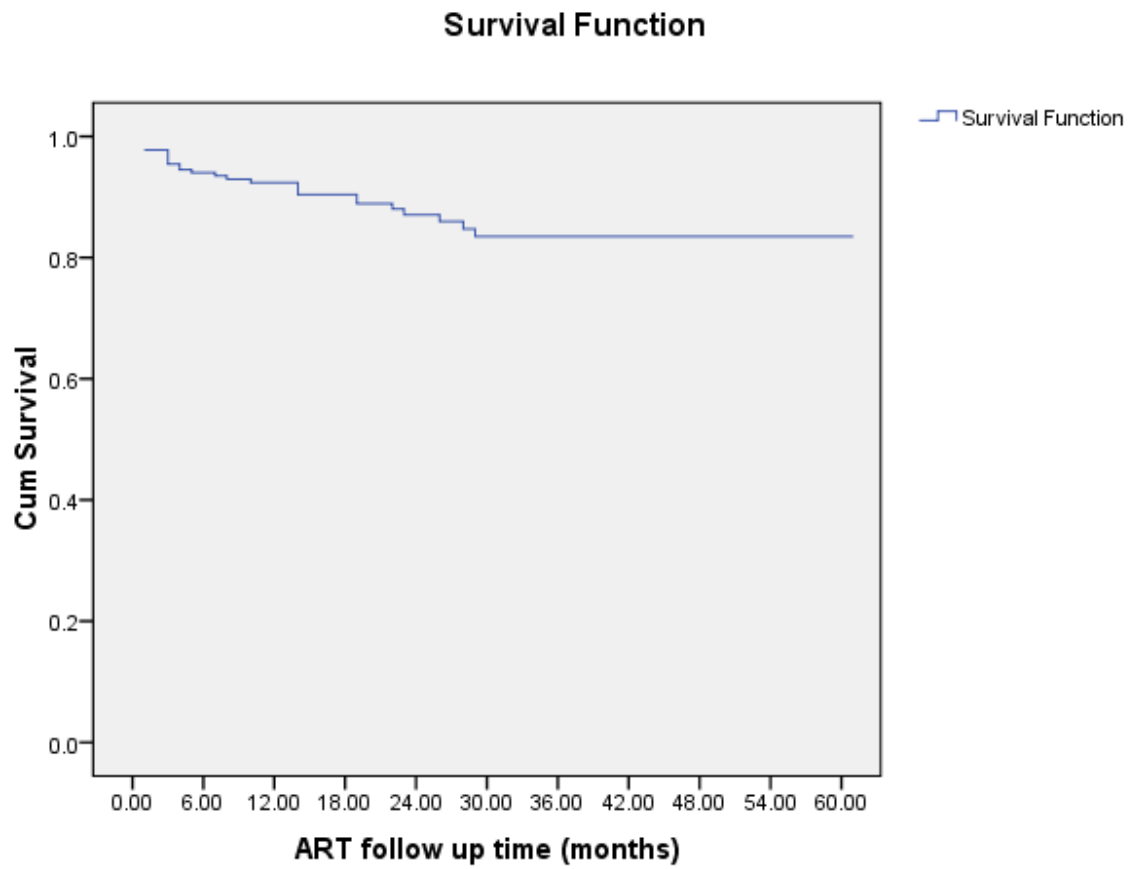


Figure 2: Cumulative survival function of children started anti retroviral treatment at Hawassa Referral Hospital ,Adare Hospital and Bushulo Health center from July 2006-September 2011

5.3. Death as an outcome

The cumulative mortality rate was 6.29 per 100 person year observations (26 deaths /413 person year observation 95%CI 4.27-9.22). The estimated mortality was 6%, 8%, 10%, 13% and 17% at 6, 12, 18, 24 and 60 months, respectively (Table 4).

The mortality patterns of ART patients were different at the various WHO stage classifications (Figure3). The hazard of death was higher in advanced WHO stages (log rank test $\chi^2=18.89$, $df=2$, $p < 0.001$). The hazard of death is also different according to nutritional status (Figure4 and 5). The risk of death was higher among wasted children than non wasted (log rank test $\chi^2=20.01$, $df=1$, $p < 0.001$) and stunted children had higher risk of death than non stunted (log rank test $\chi^2=14.22$, $df=1$, $p < 0.001$).

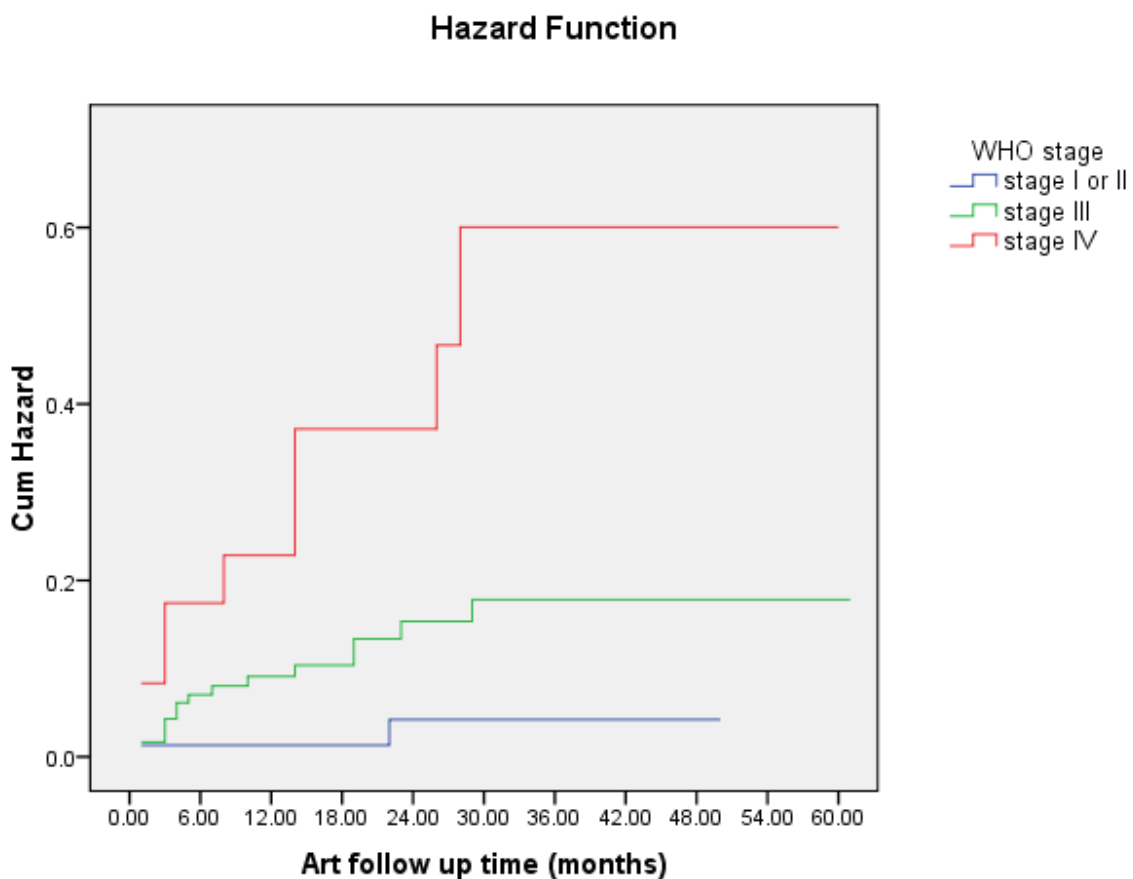


Figure 3: Hazard graph by WHO stage at start of ART among children started anti retroviral treatment at Hawassa Referral Hospital ,Adare Hospital and Bushulo Health center from July 2006-September 2011

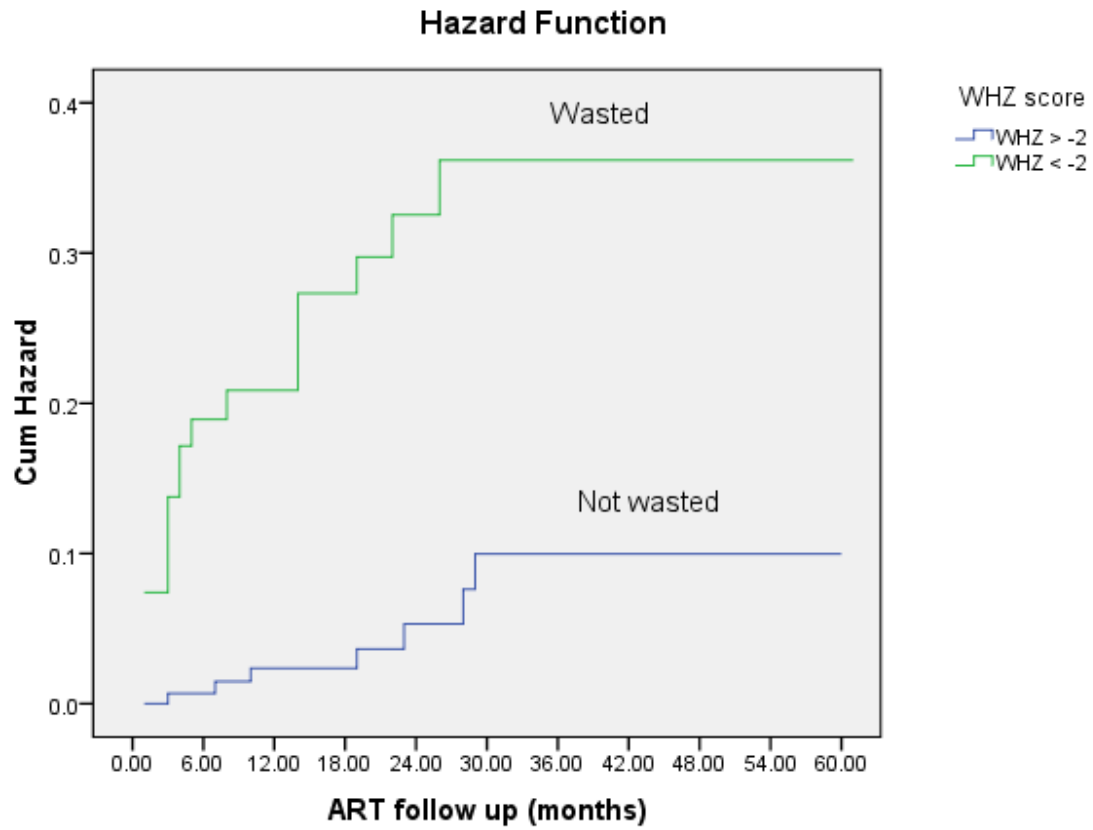


Figure 4: **Hazard graph by nutritional status (WHZ score) at start of** of ART among children started anti retroviral treatment at Hawassa Referral Hospital ,Adare Hospital and Bushulo Health center from July 2008-September 2011

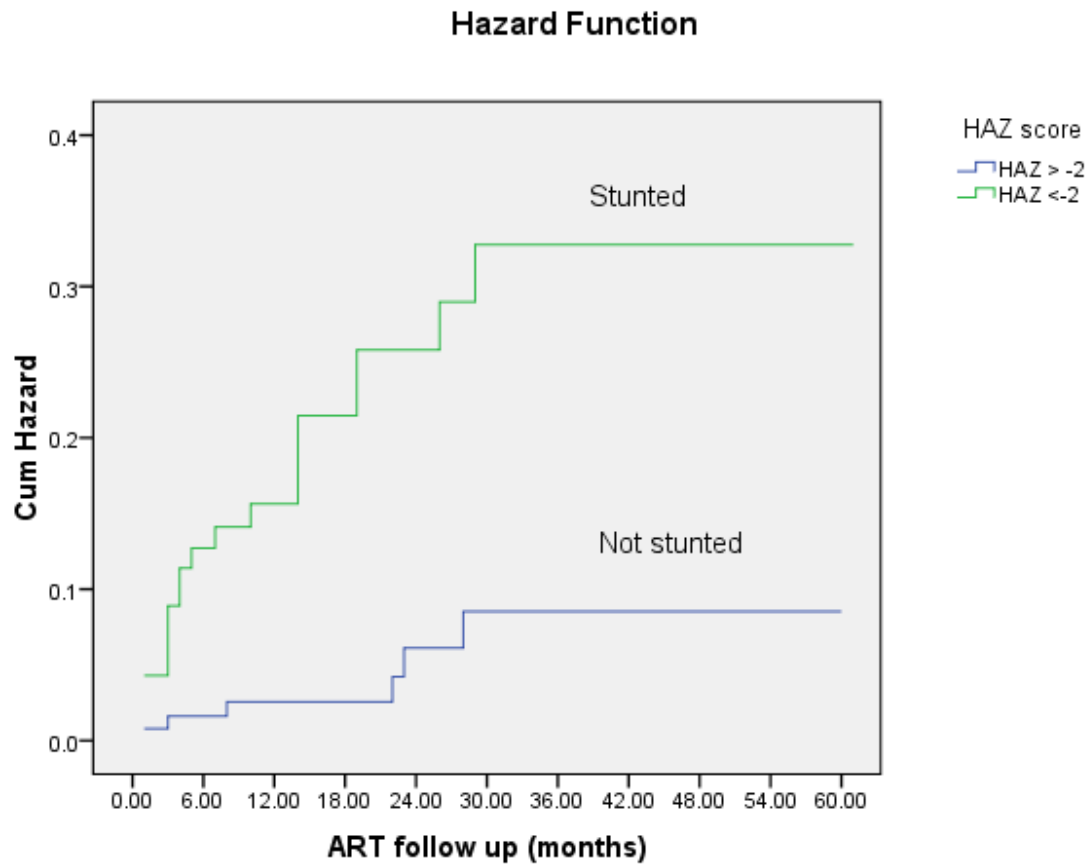


Figure 4: **Hazard graph by nutritional status (HAZ score) at start of** of ART among children started anti retroviral treatment at Hawassa Referral Hospital ,Adare Hospital and Bushulo Health center from July 2006-September 2011

5.4. Predictors of survival

The relationship between main variable and the risk of death was analyzed using bi variate cox proportional model. The result has shown that there is no significant difference in mortality between male and female HR=0.81 (95% CI 0.37-1.75). Children aged <18 months had 81% lower risk of death compared older children (5-14 years) but it was not statistically significant (Table 6). In bivariate analysis, functional status, OI prophylaxis, TB treatment; absolute CD4 count, ARV adherence and ART regimen were not significantly associated with survival. However, WHO clinical staging and low haemoglobin value(Hgb<7.00gm/dl) were associated with survival (Table 7).

Compared to the reference in the variable, the result of bi variate analysis showed that the risk of not surviving was 14 times higher among study subjects with base line WHO clinical stage IV (95% CI 2.99-64.31) and it was nearly 4 times higher among children with baseline WHO stage III (95% CI 1.08-19.32). In the study the risk of death was 8 times higher among children with low haemoglobin value (Hgb<7.00gm/dl) compared to children with haemoglobin value >10gm/dl (95% CI 3.11-20.21).

The result also showed that patients who were Stunted HR=4.86 (95% CI 1.19-12.11), under weight HR= 2.85 (95% CI 1.18-6.72), wasted HR=5.61 (95% CI 2.35-13.36) and severely wasted HR= 3.52 (95% CI 1.61-7.67) by nutritional status were significantly at increased risk of mortality. Variables such as sever stunting and sever under weight were not significantly associated with mortality (Table 8).

Table 6: Demographic predictors of death(N=222) among children started anti retroviral treatment at Hawassa Referral Hospital ,Adare Hospital and Bushulo Health center ,Hawassa, January 2012

Covariates	Number at risk	Number of Death	Hazard Ratio(HR)	(95% CI)	p-value
Gender					
Male	119	13	0.81	0.37-1.75	0.602
Female	103	13	1.0		
Age group					
<18months	12	1.0	0.81	0.11-6.13	0.840
18-48months	70	9	0.71	0.56-2.90	0.556
5-14 years	140	16	1		

Table 7: Clinical and Laboratory predictors death (N=222) among children started anti retroviral treatment at Hawassa Referral Hospital ,Adare Hospital and Bushulo Health center ,Hawassa, January 2012

Covariates	Number at risk	Number of Death	Hazard Ratio(HR)	(95% CI)	p-value
Clinical staging					
I or II	77	2	1.0		
III	120	15	4.41	1.08-19.32	0.049
IV	25	9	13.88	2.99-64.31	0.001
Hgb value					
<7.00	34	13	7.931	3.11-20.21	0.000
7.01-8.50	38	3	1.235	0.319-4.78	0.76
8.51-10	55	3	0.739	0.191-2.86	0.662
>10	95	7	1.0		
Prophylaxis given					
Cotrimoxazole	186	24	0.488	0.115-2.069	0.330
Others	36	2	1.0		

TB treatment						
Yes	58	9	0.68	0.30-1.53	0.354	
No	164	17	1.0			
AbsoluteCD4 count						
Below threshold	170	18	0.62	0.27-1.43	0.268	
Above threshold	52	8	1.0			
Regimen given						
d4t_3TC_NVP	128	15	0.24	0.07-1.55	0.270	
d4t_3TC_EFV	39	4	0.28	0.06-1.27	0.100	
AZT-3TC-NVP	40	4	0.26	0.06-1.16	0.078	
AZT-3TC-EFV	7	0	-	-	-	
Others	8	3	1.0			
ARV adherence						
Good	207	25	0.66	0.09-4.92	0.691	
Fair	9	0	-	-	-	
Poor	6	1	1.0			

Table 8: Nutritional predictors of death(N=222) among children started anti retroviral treatment at Hawassa Referral Hospital ,Adare Hospital and Bushulo Health center ,Hawassa, January 2012

Covariates	Number at risk	Number of Death	Hazard Ratio(HR)	(95% CI)
Stunted				
No	127	6	1.0	1.19-12.12
Yes	95	20	4.86	
Severely stunted				
No	152	7	1.59	0.68-3.71
Yes	70	19	1.0	
Under weight				
No	110	7	1.0	1.19-6.72
Yes	112	19	2.85	
Severely under weight				
No	173	20	1.0	0.41-2.55
Yes	49	6	1.01	
Wasted				
No	152	7	1.0	
Yes	70	19	5.61	2.35-13.36
Severely Wasted				
No	164	15	1.0	1.61-7.67
Yes	38	11	3.52	

In multivariate Cox regression analysis, only those variables significantly associated with survival were entered in to the final model. Each variable was checked to fit the model using Cox regression analysis. After adjustment, the independent significant predictors of not surviving in children living with HIV/AIDS after initiation of ART remain WHO clinical stage IV AHR=9.643(95% CI 1.92-48.41, p=0.006), low haemoglobin value (Hgb <7.00 gm/dl) AHR =4.28(95% CI 1.53-11.93, p=0.005), Stunting AHR=3.992(95% CI 1.24-12.77, p=0.020), wasting AHR=3.770 (95% CI 1.28-11.12, p=0.016) (Table 9).

Table 9: multivariate predictors Survival(N=222) among children started anti retroviral treatment at Hawassa Referral Hospital ,Adare Hospital and Bushulo Health center ,Hawassa, January 2012

Covariates	Number at risk	Number of Death	Hazard Ratio(HR)	(95% CI)
Clinical staging				
I Or II	77	2	1.0	
III	120	15	3.49	0.77-15.78
IV	25	9	9.64	1.92-48.41
Hgb value				
<7.00	34	13	4.28	1.53-11.93
7.01-8.50	38	3	1.54	0.38-6.28
8.51-10	55	3	0.80	0.20-3.19
>10	95	7	1.0	
Under weight				
No	110	7	0.66	0.22-1.96
Yes	112	19	1.0	
Stunted				
No	127	6	1.0	
Yes	95	20	3.992	1.24-12.775
Wasted				
No	152	7	1.0	1.28-11.12
Yes	70	19	3.770	
Severely Wasted				
No	164	15	1.0	
Yes	38	11	0.99	0.38-2.52

6. Discussion

In this historical cohort study, we found high early mortality rate during the first 6 months of follow up. The independent significant predictors of not surviving in this children living with HIV/AIDS after initiation of ART were WHO stage IV, low haemoglobin value (Hgb<7.0gm/dl), stunting and wasting.

The result of the present study has also shown that the mortality rate of 11.7% is in agreement with cohort study among HIV infected children in central Malawi (11%) (17). Moreover the high early mortality is consistent with study in Côte d'Ivoire, Malawi, Addis Ababa and Northwest Ethiopia (16, 17, 20 and 17). The high mortality rate during the first months of HAART among patients in developing countries had also been documented in a study comparing post HAART outcome between low-income and high-income countries (7).

Specific reasons for early mortality could be: late diagnosis of HIV; late presentation of patients who thus come to health facilities with advanced HIV disease; life-threatening complications such as bacteraemia and immune reconstitution diseases.

The result of this study showed that the mean survival time for children in the cohort was 53.2 months. Similar study in HIV infected children at Zeweditu Hospital, Addis Ababa reported the average survival time 27.9 months (20). This difference could be due to short duration of follow up (0 to 30 months) in previous study. We found that wasting had reduced survival by 6 to 12 months for males and females, respectively. This was in agreement with previous study (20) which reported reduced survival by 2 to 7 months for wasted males and female's children respectively. Studies conducted in Haiti and Malawi (14, 17) also reported that malnutrition in form of under weight and wasting was responsible for reduced survival.

A study conducted among children on ART in Thailand reported that the probability of survival was 92.3% at 6 months, 91.0% at 12 months, and 88.1% at 18 and 24 months (15). The current study also found almost the same pattern of survival with 94%, 92%, 90% and 87% at 6, 12, 18 and 24 months, respectively. An observational study among HIV-1 infected children on antiretroviral therapy in Kenya (19) showed that the cumulative survival after 25 months was

84%, which is in agreement with our finding in which cumulative survival was 83% after 24 months.

Advanced clinical stage was a strong predictor of mortality in our study. Patients with WHO stage IV had nearly 10 times higher risk of dying during ART compared to those with WHO stage I or II. The association observed between advanced WHO staging and mortality in this study is similar with finding from previous studies (17, 18, 21).

Patients with severe anaemia had nearly 4 times higher risk of dying compared to those with a normal haemoglobin level. The relation between low haemoglobin value and mortality among HIV infected children on ART was also shown in similar studies in Durban, South Africa and Addis Ababa, Ethiopia (18, 20). One retrospective cohort study in rural Tanzania (26) also reported anaemia was a strong predictor of mortality in patients on ART.

A retrospective cohort study in Singapore to see the impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy reported that Malnutrition at the time of starting ART was significantly associated with decreased survival, but the effect appeared not to be mediated by impaired immune reconstitution (27). The current study also found that malnourished children had lower survival, in which the hazards of death in wasted children was nearly four times higher than non wasted children and stunted children had 3.8 times higher risk of death than non stunted children. The association between Malnutrition and child death is also documented in similar studies before (14, 17, and 20).

The mechanism by which malnutrition reduces survival is not well known; but one of proposed explanations is the effects of malnutrition on immunity which are quite diverse (28). Other mechanisms for explaining the adverse effect of malnutrition include potential adverse effects on drug absorption, a lower threshold for drug toxicity, and the decreased physical function that may accompany malnutrition (27).

According to a study conducted to identify predictors of mortality in patients initiating antiretroviral therapy (ART) in Durban, South Africa (18) a history of oral candidacies (AHR 2.58, 95% CI 1.37 – 4.88) remained significant in multivariate analysis but history of tuberculosis was not a significant predictor of mortality. We also found non significant

association between history of tuberculosis and child mortality .The relation ship between other opportunistic infections and child death is not addressed in this study since they were found incompletely recorded.

According to Taye etal , absolute CD4 below the threshold for severe immune deficiency was significantly associated with child mortality(20). One retrospective cohort study in Malawi (17) also documented similar finding. Similar study in Durban, South Africa reported significant association between CD4 cell count $<50/\mu\text{l}$ and child mortality. In contrary the result of our finding indicated non significant association between CD4 cell count at baseline and child death. This may be explained by generalized use of HAART which results in clinical benefit, with a parallel decrease in viral load and an increase in CD4⁺ cell percentage (13), leading to a decrease in opportunistic infections and tumor (29). Another possible explanation could be opportunistic infections which may lead to death in immuno deficient patients were prevented by the use of cotrimoxazole.

7. Strength and Limitation

Strength: The main strength of this study was involvement of rural health centre which might decrease selection bias towards patients with more severe disease in a hospital setting. Second, the study may give an insight for researchers especially in carrying out prospective cohort.

Limitation: The main limitation of this study was incomplete data on some of predictors of child survival. Second competing causes of death may overestimate mortality due to HIV/AIDS. Generalizability is questionable as information on incomplete variables was not considered.

8. Conclusion and Recommendation

High early mortality was observed in this cohort of children receiving ART in the first 6 months. Advanced WHO stage (IV), low baseline haemoglobin, Stunting and wasting were independent predictors of not surviving.

Based on this study finding, the following recommendations can be forwarded.

1. To improve outcomes of HIV-positive children, they must be identified and treated early.
2. Early recognition and managements of risk factors or clinical markers of survival.
3. Giving in-service training for the health care giver on HIV/AIDS care and support.
4. Additional studies are required in order to identify how malnutrition reduces survival in .children receiving ART.
5. Nutritional intervention may benefit survival.

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10. ANNEXES

ANNEX I

This patient information collection sheet is intended to assess survival of and risk factors of mortality in children after the advent of Highly Active Antiretroviral Therapy in the ART unit Of-----Hospital, Hawassa, Ethiopia. The study will be conducted through reviewing secondary data and visiting the home/calling if the status of the patient is not recorded or found

in the ART follow up form. The study is aimed to fill the information gap and provide empirical evidence for program planner, decision makers and ART program implementer at the different level by enabling them to access a base line data on survival and risk factors of mortality. If you have question you can contact principal investigator.

(Solomon Ashagre)mobile 0922121548, Email solomonashgre77@gmail.com

ANNEX II: QUESTIONNAIRE

Date of review -----day-----month-----year

Name and signature of reviewer-----

Time Started_____ Time ended_____

Name and signature of the supervisor.....

Date.....

Total no of records reviewed-----

Reviewed Patient's card No from _____ to_____

Result:

a) Completed ----- b) Incomplete -----c) excluded-----

Action taken for the incomplete data_____ (please use additional blank paper if the space is not enough)

Part-I SOCIO DEMOGRAPHIC CHARACTERISTICS				
101. Age of patient (-----) years				
102. Sex of patient 1.Male 2.Female				
103. Main caregiver's relation to child.....				
104. Age of main caregiver.....				
105. Sex of main caregiver 1. Male 2. Female				
106. Religion of main caregiver				
1. Protestant 2. Catholic 3. Orthodox 4. Muslim 99. Others specify----- ----				
107.Ethnicity of main caregiver				
1. Sidama 2.Wolaita 3. Amhara 4. Gurage 99. Others specify-----				
Part-II Base line clinical, laboratory and ART information				
201. past opportunistic illness				
1. No 2. CMV 3. PCP 4. PGL 5. PML 6.EPTB 7. Candidiasis 8. Diarrhoea 9. Pneumonia 10. Herpes simplex 11. Kaposi sarcoma 12. Toxoplasmosis 13. Encephalopathy 14. Wasting syndrome 15.Herpes zoster 99. Other specify-----				
202. Weight at base line (-----) kg				
203. Height at base line (-----) cm				
204. Functional status at base line				
1. Working 2. Ambulatory 3. Bed ridden				
205. WHO clinical staging of HIV at base line				
1. Stage I 2. Stage II 3. Stage III 4. Stage IV				
206. Past TB test				
1. No 2. Not determined 3. Positive 4. Negative				
207. TB treatment at start				
1. No 2. Yes				
208. OI prophylaxis given at base line				
1. No 2. Cotrimoxazole 3. INH 99. Other specify-----				
209. CD4 count at base line (-----) date-----/-----/----				

210. Hgb count at base line -----
211. TLC count at base line
Part-III ART treatment
301. ART eligibility criteria -----
303. Regimens given at Start 1. 4a =d4t-3TC-NVP 2. 4b=d4t-3TC-EFV 3. 4c=AZT-3TC-NVP 4. 4d=AZT-3TC-EFV 5. 2 nd line regimens 99. Others specify-----
Part-IV patient follow up information (filled from ART follow up form) recent results
401. Date confirmed HIV positive (-----/-----/-----)
402. Eligible date (-----/-----/-----)
403. Last follow up date (-----/-----/-----)
404. Duration since initiation of ART (----- month)
405. OI prophylaxis given 1. Not given 2. Cotrimoxazole 3. INH 4. Fluconazole 99. Others specify-----
406. Recent functional status 1. Working 2. Ambulatory 3. Bedridden
407. Recent WHO staging 1. Stage I 2. Stage II 3. Stage III 4. Stage IV
408. TB prophylaxis 1. No 2. Yes
409. TB screened 1. No 2. Negative 3. Positive 4.unknown
410. TB treatment 1. No 2. Yes
411. Opportunistic infections 1. No 2. Zoster 3. Pneumonia 4. Pulmonary TB 5. EPT 6. Oral trush 7. genital/oral ulcer 8.Diarrhoea 9. Cryptococcal meningitis 10. CNS toxoplasmosis 11. PCP 12.Others specify-----
412. Cotrimoxazole Given 1. No 2. Yes
413. Recent ARV adherence 1. Good 2. Fair 3. Poor

414. Reason for fair/poor adherence				
1. Toxicity/SE	2. Share with others	3. Forgot	4. Felt better	
5. Too ill	6. Stigma	7. Drug stoke out	8. Travelling problem	
9.Alcohol	10. Depression	99.. Others specify-----		
415. Drug side effect				
1. No	2. Nausea	3. Diarrhea	4. Fatigue	5. Headache
6.Numbness	7. Rash	8. Anemia	9. Fat change	10. Night mare
11.Dizziness	99. Others specify-----			
416. Reason for regimen change				
1. Not change	2. Toxicity/SE	3. Pregnancy	4. Risk of pregnancy	
5. New drug available	6. Drug out of stoke	7. Clinical failure		
8.NewTB	9 9. Other specify-----			
417. Reason for stopping regimen				
1. Not stopped	2. Pregnancy	3. toxicity/SE	4. Treatment failure	
5. Poor adherence	6. Drug out of stock	7. Other patient decision	9. Planned treatment interruption	
99. Other specify-----				
418. Recent CD4 count (-----date-----/-----/-----)				
419. Recent TLC count (-----)				
420. Recent Hgb count (-----)				
421. Out come of the patient				
1.Active 2.Dead 3.lost to follow up				

ANNEX III. Informed consent form and questionnaire (be used in home visiting or calling) research as partial fulfillment for the requirement of Masters in Public Health at Addis Ababa University.

This study is intended to assess survival children after the advent of Highly Active Antiretroviral Therapy in the ART unit of -----hospital in Hawassa, Ethiopia. The study is aimed to fill the information gap and provide empirical evidence for program planner, decision makers and ART program implementer at the different level. The information will be collected through reviewing secondary data in the ART clinic . We would like to assure you that the privacy and confidentiality will strictly be secured throughout the study.

If a report of results is published, only information about the total group will appear.

The interview is voluntary. Your participation/ non-participation, or refusal to answer questions will no effect now or in the future on services that you or any member of your family may receive from health service providers.

Are you willing to participate in this study?

Yes No (end the interview)

Q.1.what is the current status of the patients?

a) Dead b) alive c) Lost to follow up

ANNEXIV Consent form (Amharic version)

ለጥናቱ ተሳታፊዎች የፈቃደኝነት መጠየቂያ ቅጽ

ስሜ _____ ይባላል፡፡ እኔ በህብረተሰብ ጠፍ አጠባበቅ የሁለተኛ ደግሪ የመሥሪታዎች ምርምር እየሰራ ካለው ሰለሞን አሻግራ ጋር እየሰራሁ እገኛለሁ ፡፡ የምርምሩ አላማ ህፃናት የኤች አይቪ ኤድስ መድሀኒት ከጀመሩ በኋላ ለምን ያህል ጊዜ እንደሚቆዩ ለሞት የሚያበቃቸውን ምክንያቶች ለማጥናት ነው፡፡ ምርምሩ በሀዋሳ ባሉ ሆስፒታሎች የሚከናወን ሲሆን የመረጃ እጥረትን ለመቅረፍ እንዲሁም ለመንግስት አካላት መረጃ ለመስጠት ያገለግላል፡፡

ምርምሩ የሚከሄደው የህክምና ካርዶችን በማጽዳት፣ ወደ ታካሚው ቤት በመደወል፣ እንዲሁም የታካሚውን ቤት በመጎብኘት ይሆናል፡፡ ለአረጋግጥሎት የምፈልገው ነገር ቢኖር የታካሚውን ማስገባት እና ገመና በጥብቅ የሚጠበቅ መሆኑን እና ስሜን ለመሰጠት ሳይሆን የማስገባት ቁጥር ብቻ ለምርምሩ አገልግሎት እንደሚውል ነው፡፡ በተጨማሪም ከእርሶ የምናገኘው መረጃ ለሌላ ምንም አገልግሎት የማይወልድና የእርሶ መሳተፍ/አለመሳተፍ በማይገኙት አገልግሎት ላይ ምንም አይነት ተፅእኖ አለመኖሩን ነው፡፡ በምርምሩ ለመሳተፍ ፍቃደኛ ነዎት ?

- 1. አዎ
- 2. አይደለሁም /ምልልሱ ያበቃል

ተቁ 1 ታካሚውንም አይነት ሁኔታ ላይ ይገኛሉ ?

- 1. ሞቲል
- 2. በህይወት አለ
- 3. ክትትሉን አቋርጧል

የጠያቂው ስም ፊርማ
