Assessment of the effect of malnutrition on survival of HIV infected children after initiation of antiretroviral treatment in Wolaita zone health facilities, SNNPR, Ethiopia.

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List of Acronyms

AIDS	Acquired Immune Deficiency Syndrome
AHR	Adjusted Hazard Rate.
ART	Anti-retroviral treatment
CMV	cytomegalo virus
CSA	Central Statistical Agency
DBS	Dried blood sample
EDHS	Ethiopia Demographic and Health Survey
EPTB	Extra Pulmonary Tuberculosis
HAART	Highly Active Antiretroviral Therapy
HAPCO	HIV/AIDS Prevention and Control Office
HIV	Human Immunodeficiency Virus
Hgb	Hemoglobin
HAZ	Height for Age Z score
MUAC	Mid-Upper Arm Circumference
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
OI	Opportunistic infection
PCP	Pneumocystis Carini Pneumonia
PGL	Persistent Generalized Lymphadenopathy
PML	Progressive multifocal leukoencephalopathy
SAM	Severe Acute Malnutrition
SNNPR	Southern Nations Nationalities and peoples region
TLC	Total Lymphocyte Count
UNAIDS	Joint United Nations Program on HIV/AIDS
UNICEF	United Nations Children's Fund
WAZ	weight for age Z score
W/A	Weight for age
W/H	Weight for Height
WHO	World Health Organization

ABSTRACT

BACKGROUND: Nutrition and HIV are closely interlinked creating a vicious cycle. Malnutrition is a common condition in HIV-infected children; however, its effect on survival of HIV infected children after initiation of antiretroviral therapy is not well understood.

OBJECTIVE: To assess the effect of malnutrition on survival of HIV infected children after initiation of antiretroviral treatment.

METHODS: A retrospective cohort study was conducted in HIV infected children starting antiretroviral treatment at Wolaita zone selected health facilities, Ethiopia. Demographic, nutritional, clinical and immunological data were extracted from the existing ART logbook and patient follow up records. Nutritional statuses of children were determined using the International Reference Population defined by the WHO. Height-for-age (HAZ), weight-for-height (WHZ), and weight-for-age (WAZ) Z-scores were calculated. Survival was defined as the time from nutritional and immunologic evaluation at the starting of ART to death. Data were analyzed by bivariate and multivariate analysis using Cox regression proportional hazard model. Survival were calculated and compared with the Kaplan Meier and log rank test.

RESULT: A total of 228 records of children were taken from ART registry from February, 2006 to March 2014 in 2 Hospitals and 3 Health centers in Wolaita zone. The mean survival time for this cohort using Kaplan Meier analysis was 89.34 months (95% CI 85.707-92.97). The cumulative proportion of survival was 98%, 97%, 94%, 92% and 84% at 6,12,24,60 and 96 months respectively. The incidence of mortality rate 21.02 per 1000 person years of observation (95% CI 12.8-34.3). Overall nutritional status, 62.5% were stunted, 43.0% were underweight and 44.7% were wasted at baseline. In our study residence living in rural AHR 4.30 (95% CI, 1.25-14.8), fair/poor of the first three month ART adherence AHR 8.95(95% CI 2.624-33.72) and Severe wasted children at baseline AHR 7.040 (95 % CI, 1.27-39.13) were predictors of reduce survival of children on ART. Age of children at starting ART also predictor for survival, children age as < 18 months than age 18 month-5 year, 5-14 years of age with AHR0.047 (95% CI, 0.006-0.368), 0.145(95% CI 0.032-0.663) respectively. Incidences of mortality rate for severe wasted children were 3.77 (95% CI 1.2-13.8).

CONCLUSION AND RECOMMENDATION: Our data analysis showed that Children on ART at initiation had high prevalence of malnutrition and malnutrition was found to be an important predictor of survival with residence, age of the children and first three month ART adherence.

1. Introduction

1.1 Background

Worldwide HIV /AIDS have created an enormous challenge on the survival of mankind. The number of people dying from AIDS-related causes began to decline in the mid-2000s because of scaled-up antiretroviral therapy and the steady decline in HIV incidence since the peak in 1997. Access to antiretroviral therapy (ART) has scaled up rapidly in resource-limited settings, with the goal of universal coverage for all those who are in need of it. From 1996 to 2012, antiretroviral therapy averted 6.3 million AIDS-related deaths worldwide, including 5.2 million deaths in low- and middle-income countries (1).

The goal of antiretroviral therapy (ART) is to restore immune function, to maintain maximal suppression of viral replication, to reduce HIV-related morbidity and mortality and improve quality of life and prolong survival (2).

Malnutrition is endemic in HIV/AIDs pandemic developing countries. Nutrition and HIV are closely interlinked creating a vicious cycle. HIV infection has a substantial impact on the nutritional status of infected people due to poor food intake as a result of poor appetite and difficulty eating, intestinal malabsorption because of chronic diarrhea and HIV caused intestinal cell damages, metabolic changes and increased nutrient requirements related to opportunistic infections (OIs). In turn malnutrition can further weak the immune system and worse the effects of the HIV-disease and related OIs (3).

All PLHIV require 10% more energy when asymptomatic and 20- 30% if symptomatic. Children who are symptomatic and experiencing weight loss need between 50- 100% more energy every day (3).

Ethiopia is among the countries most affected by the HIV pandemic and malnutrition endemic (4, 5). Both malnutrition and HIV immune suppressive for many people in Ethiopia (3).

1.2 Statement of the Problem

HIV develops very rapidly among infants and children. Pooled analysis from Africa showed that mortality in infected children was about nine-fold greater than that of uninfected children. They estimated that by 12 months of age, 35.2% of infected children would have died, compared with an

estimated 4·9% of uninfected children. At 2 years of age, an estimated 52·5% of` infected and 7·6% of uninfected children would have died (6).

Despite children on ART, study in South Africa showed mortality rate of 4.7 deaths per 100 child years on ART (7). Another study in Asia-pacific showed that during a median follow up of 3.1 years after ART, 6.6% deaths occurred, giving a crude mortality rate of 1.9 per 100 child-years (95% CI, 1.6-2.4) (8).

In Ethiopia also death rate was calculated to be 4.0 per 100 child-years of observation (9). In Addis Ababa also 8.8% died during a median study follow up of 12 months (10).

There are different risk factors for the death children after starting ART. Some of them are malnutrition status at initiation of ART, lower hemoglobin, age of children, CD4% at initiation of ART, chronic diarrhea, gender, not receiving cotrimoxazole preventive therapy at baseline and severe immunodeficiency (7-9, 11, 12).

Under nutrition and HIV are closely interlinked creating a vicious cycle. Malnutrition is a common condition in HIV-infected children and one of the predictors of mortality among HIV infected children after initiation of ART except study done in Bahir Dar which was malnutrition has no association with mortality (3, 7, 8, 10, 11). Study in AA, Ethiopia, showed that malnutrition has an impact on survival of HIV infected children after initiation of ART. This study also showed malnutrition prevalence is higher in HIV infected children but this study is done in Addis Abeba which has minimum prevalence of malnutrition in Ethiopia(10). So Ethiopia is one of the highest malnutrition and HIV prevalent areas in the world (4). Almost three fourth (64%) of the severely malnourished children were found in Oromia and SNNP Regions in 20012/2013.Wolaita zone is one of the malnutrition prevalent areas in SNNPR. This zone also have high HIV infection rate in children (13) .

To have better survival of children after initiation of ART, knowing effect of malnutrition is important. Therefore, aim of this study was assessing the effect of malnutrition in survival of HIV positive children after initiation of ART.

1.3 Rationale for the Study

The emergence of the HIV epidemic is one of the biggest public health challenges the world has ever seen in recent history. Ethiopia is among the countries most affected by the HIV epidemic. According to the report of the Ethiopia Demographic and Health Survey 2011, the overall prevalence of HIV was 1.5% all over the country with regional variation. Our ART coverage is in good progress. But the coverage is still low in children than adults (4, 5, 14).

Ethiopia is also one of the world's highest incidences of undernourished individuals. Ethiopia has high levels of food insecurity and is prone to acute food insecurity, primarily from draught, environmental degradation, and insufficient access to and availability of food. According to the report of the Ethiopia Demographic and Health Survey 2011, 44% of children under five experiences stunting which shows chronic malnutrition and 29% were underweight. Especially worse in SNNPR which is 48.6% of children experience stunting and 31.9% of them underweight (4, 5, 14).

Malnutrition and HIV/AIDS fuels one another. Malnutrition contributes to immune impairment, making the body vulnerable to frequent illnesses and increasing demand for energy and nutrients, thereby accelerating disease progression. HIV/AIDs also contribute immune impairment which expose for frequent illness and it affect mostly productive age in families which aggravate food shortage. So the effect of malnutrition on survival of HIV infected children is not well known.

The study was to give evidence and information on the effect of under nutrition on survival of HIV/AIDs infected children after initiation of ART. This evidence and information will be used for governmental and non -governmental organizations which work in the area of HIV/AIDS specifically on ART and malnutrition at national, regional and district level. This study also used for further research.

2. Literature Review

2.1 Burden of HIV/AIDS Globally and ART in Ethiopia

Globally, an estimated 35.3 (32.2–38.8) million people were living with HIV in 2012. Around 9.7 million people in low- and middle-income countries received antiretroviral therapy, representing 61% of all who were eligible under the 2010 WHO HIV treatment guidelines (1).

About 3.4 million [3.1 million–3.9 million] children younger than 15 years were living with HIV. In 2011, 330 000 [280 000–390 000] children acquired new HIV infection. More than 90% of the children who acquired HIV infection in 2011 live in sub- Saharan Africa. There, the number of children newly infected fell by 24% from 2009 to 2011 (15).

Children living with HIV continue to experience persistent treatment gaps. In 2012, 647,000 children under 15 years of age were receiving antiretroviral treatment. HIV treatment overage globally for children (34% (31-39%)) remained half of coverage for adults (65% (61–70%)) in 2012. Although the number of children receiving antiretroviral therapy in 2012 increased by 14% in comparison to 2011, the pace of scale-up was substantially slower than for adults (a 21% increase). In priority countries, only three in 10 children receive HIV treatment (1, 15, 16).

In 2011, 1.7 million [1.5 million–1.9 million] people died from AIDS-related causes worldwide. The number of people dying from AIDS-related causes in sub-Saharan Africa declined by 32% from 2005 to 2011, although the region still accounted for 70% of all the people dying from AIDS in 2011(15).The number of children younger than 15 years receiving ART in low- and middle-income countries increased from 566,000 in 2011 to 630,000 in 2012, but the increase was substantially less than for adults (16).

In Ethiopia, DHS 2011 data show an overall prevalence of 1.5% among the general population. This is lowest prevalence from East African countries prevalence. Estimates show 789,900 people currently living with HIV/AIDS (607,700 adults and 182,200 children aged 0-14 years); and 952,700 AIDS orphans. In Ethiopia, around 53,831 deaths among adults and around 13,749 deaths among children less than 14 years are occurred in 2011due to HIV/AIDS with regional variation (4, 5, 14).

According to the Ethiopian Demographic and Health Surveys (EDHS) HIV prevalence ranges from 0.9% in SNNPR and 1.0% in Oromia region to 5.2% in Addis Ababa and 6.5% in Gambella region. The Government of Ethiopia launched fee-based antiretroviral treatment in 2003 and frees ART in

2005. During 2011, a total of 333,434 people had ever started ART. There were 249,174 adults (86% of eligible) for a CD4 cutoff less than 200 and 16,000 children currently on treatment (20% of eligible) by the end of 2011. Overall, with the increase and fast expansion of facilities providing ART, coverage has increased over the years (4, 5).

2.2. Magnitude and Factors Affecting Mortality of Children from HIV

Magnitude of Mortality of children after initiation of ART

Even though children on ART, they have still high rate of mortality when compare with HIV free children. Retrospective cohort study was done in 2006 by Medicines Sans Frontie`res HIV/AIDS programs in 14 countries, the overall probability of survival (death plus loss to follow up) at 6, 12, and 24 months was 0.92 (95% CI, 0.90–0.94), 0.89 (95% CI, 0.86–0.92), and 0.82 (95% CI, 0.78–0.86), respectively. Seventy six percent of deaths occurred within 6 months of commencement of ART (median, 1.4 months; IQR, 0.6–5.6 months) (11). In Uganda study also mortality rate was six times higher in ART-naive HIV infected children than in HIV-exposed but uninfected children (HR = 6.4, 95% CI = 2.4–16.6) (17).

In Ethiopia, retrospective cohort study done at Bahir Dar referral hospital revealed at 22 months median follow up 7.5% were dead which mortality was 4.0 deaths per 100 child-years of follow-up period. The mean survival time was 56.5 months (95% CI: 54.62, 58.38 months). The cumulative probabilities of survival at 3, 6, 12, 24 and 60 months of ART initiation were 0.96, 0.94, 0.93, 0.92 and 0.83 respectively in the real case assumption while it was 0.93, 0.92, 0.90, 0.88 and 0.71 respectively while assuming the worst case scenario (9).

Another retrospective cohort study at Addis Abeba zewditu memorial hospital shows there is 8.8% of death after 12 month of ART initiation. The mean survival time for the entire cohort was 27.9 months (10).

Baseline socieodemographic factors

The pooled analysis result on Africa, mortality was significantly associated with low maternal CD4+ cell count or maternal death. Mortality did not differ significantly between ever-breastfed and never-breastfed children. children whose mothers had evidence of advanced HIV disease (either because they had died or on the basis of their CD4+ cell count) were at substantially increased risk of death in the univariate and multivariate analyses (6).

From South Africa study most of the deaths occurred early; 64% occurred within 3 months, and 83% within 6 months of ART initiation. This study also showed that age of <3 years (p = 0.003) and female gender (p = 0.03) are predictors of mortality (7).

Another study done in ten pediatric treatment programs in four countries in Southern Africa 4.8% of them died in the first year of ART initiation. From this study age (AHR 0.37; 95% CI 0.25 0.54 comparing ≥120 months with <18 months) were risk factor for death (12). Study done in Malawi also Children <18 months old were 2.15 times more likely to die as children aged at least 18 months (95% CI 1.00–4.61) (18). Among HIV-infected ART-naive children, mortality was highest in those <2 years of age, with a crude rate of 12／100 person-years (17).

Age is the only socio demographic predictor of mortality study done in Bahir Dar. The estimated HR for 1.5 to 5years against the referent age group which is age less than 1.5 was 0.285(CI 0.0144-0.564) and HR for age group 5-15was 0.184 (CI 0.093-0.365). The children in the age group 1.5-5 years was 71.5% less likely to die, children 5-15 years was 81.6% less likely to die compared to children age less than 1.5 year (19). However, age and sex was not predictors of mortality in another study from Ethiopia (9, 10).

Clinical and laboratory factors

Study from South Africa the mortality of children after initiation of ART were significantly associated with chronic diarrhea (p = 0.0002), lower hemoglobin (p = 0.002) and CD4% <10% (p = 0.005) (7). Same from another South Africa study included CD4 cell percent (HR 0.56; 95% CI 0.39–0.78 comparing ≥ 20% with <10%), and clinical stage (HR 0.12; 95% CI 0.03–0.45 comparing WHO stage I with III/IV) were important predictors of mortality at the individual level (12).

Study from Asia, the risk of death showed a significant decreasing trend as CD4 percentage increased. The hazard ratio dropped from 33.85 (95%CI: 14.96-76.59) in children with a CD4 <5% to 4.02 (95% CI: 1.53-10.57) in children with a CD4 of 15-19%, when compared with the reference category (CD4 ≥20%). Mortality risk was significantly higher for those with WHO clinical stage 4 at baseline (HR 4.78, 95% CI, 1.84-12.41) (8).

Another study done in South Africa which is randomized control trial on infant's shows disease progression occurred in infants in the early-therapy groups (6.3%), as compared with infants in the deferred-therapy group (25.6%) (HZ, 0.25; 95% CI, 0.15 to 0.41; P<0.001) *P. jiroveci* pneumonia, CMV disease, and esophageal candidiasis occurred only in the deferred- therapy group. Failure to

thrive was the most common event in both the deferred-therapy group and the early-therapy groups (20).

Study done in Malawi shows also Children presenting with stage IV illness were 2.0 times more likely to die as those with stage I–III illness (95% CI 1.07–3.76) and weight loss also significant predictor of mortality (18).

Mortality of children on ART also determined by the adherence to the ART. Non-adherence to ART was significantly associated with mortality. Non-adherent participants had a mortality of 42.5 deaths per 100 person-years and, after adjusting for age, sex and education level, were two times as likely to die as adherent participants (21).

In Ethiopia, one study done retrospective cohort at Bahir Dar referral hospital showed that not receiving cotrimoxazole preventive therapy at baseline AHR 4.74 (95% CI: 2.17, 10.34) and delayed or regressing developmental history 6.31(95 CI%: 2.52, 15.83) were predictors of mortality to their counterparts. Similarly, low haemoglobin level AHR = 2.44, 95 CI%: 1.26, 4.73) and absolute CD4 count below the threshold for severe immunodeficiency 2.24 (95% CI: 1.07, 4.69) were significantly and independently associated with mortality of HIV-positive children after initiation of ART. However in contrary to another study presence of OI, baseline nutritional status and WHO clinical stage were not significant predictors of mortality (9).

Another retrospective cohort study done in Addis Abeba shows 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 immune- deficiency (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) (10).

2.3. Malnutrition and HIV/AIDS in Children

Child malnutrition, encompassing both under nutrition and overweight are global problems. According to UN estimates, globally in 2011 the prevalence of underweight, wasting and sever wasting were 16%, 8% and 3% respectively. More than 70% of the world's children with wasting live in Asia, most in south-central Asia, where an estimated 15% (28 million) are affected. Globally Under nutrition, including fetal growth restriction, suboptimum breastfeeding, stunting, wasting, and deficiencies of vitamin A and zinc, cause 45% of child deaths, resulting in 3·1 million deaths annually (22).

According to EDHS prevalence of underweight, wasting, stunting and sever wasting were 29%, 10%, 44% and 3% respectively in the under five children. In SNNPR region prevalence of underweight, wasting and stunting was 31.9%, 9.9% and 48.6% respectively (4).

Malnutrition is a common condition in HIV-infected children and is a major contributor to mortality both HIV-uninfected and HIV-infected children. Malnutrition independent of HIV infection has a high morbidity and mortality, and this effect may be exaggerated in HIV-positive individuals (3, 22). Study in Niger shows around 9% of children hospitalized for severe malnutrition were HIV infected, and during re-nutrition or treatment given, 20% and 14% HIV positive and HIV negative children were died, respectively ($p = 0.81$). During re-nutrition also was longer in HIV positive than HIV negative children (mean: 22 vs. 15 days; $p = 0.003$) (23).

Effects of nutritional status on HIV are malnutrition decrease in CD4 cells, suppression of delayed hypersensitivity and abnormal B-cell response. This leads to reduced body defense and rapid disease progression. Wasting has been associated with reduced length of survival. Micronutrient deficiencies lead to increased oxidative stress and further damage to the immune system, viral replication and decrease in CD4 (3).

HIV has an impact on survival of malnutrition children and vice versa (10, 24).Prospective Study from Malawi shows clearly that mortality among children with SAM was markedly increased in those with HIV. Overall mortality was 14.8% and HIV prevalence was 17.4% on all SAM. HIV-infected children were significantly more likely to die than uninfected children [35.4% vs.10.4% $P < 0.001$], relative risk (RR) = 3.41, 95% CI 2.24—5.20] in all SAM (24).

Studies in South Africa show lower weight-for-age Z-score ($p<0.0001$) is the predictor of mortality among children on ART (12).Same as in Asia risk of death decreased by 10% for each unit increase in weight-for-age z score (95% CI 0.81-0.98) (8).

Study in Tanzania shows ART-treated HIV-positive children had higher rates of under nutrition than their HIV-negative counterparts. Among the ART-treated HIV-positive children, 36.6% were stunted, 22.1% were underweight, and 13.6% were wasted (25).

WHO stage 3 or 4 was associated with 3.19 higher odds of being underweight (WAZ <−2) at baseline [OR 3.19, 95% CI 1.68, 6.05; $P <0.01$]. Children 3–5 years were 74% less likely to be wasted (WHZ <−2) at baseline than those 6–10 years (OR 0.26, 95% CI 0.09, 0.77; $P = 0.02$) (26).

Nutritional regaining after ART initiation is also important. Study done in Kenya on HIV infected children shows children below 3years were two to three-fold more likely to attain population age-

norms (Z-score = 0) than 6–10 years (WAZ: P = 0.055; WHZ: P = 0.005) at 12 months post-HAART. After adjustment, children below 3 years had higher increases in WAZ and WHZ following HAART than 6–10 years (WAZ: P = 0.006; WHZ: P = 0.005). Nutritional regaining also associated with Children at WHO stage at least 3 at baseline experienced more rapid WHZ reconstitution (P = 0.002). Food supplementation while on HAART was associated with increased monthly gains in weight indices (WAZ: P = 0.001; WHZ: P = 0.005), and multivitamins were associated with greater increases in height (P < 0.01) (26).

From study done on ART children in Ethiopia, malnutrition at base line is higher than other children. From Study 61.1% of children, 55.6% of children, 27.3% of children at base line were underweight, stunting and wasting respectively. In addition children were also assessed severity of malnutrition as severe stunting; severe wasting and severe underweight were 34.1%, 7.4% and 40.8% respectively. Most affected age group was less than1.5years. From this study univariate analysis of severe malnutrition as sever wasting, severe stunting and underweight, the risk of death increased by 2 fold for sever wasting HR=6.28(2.8-14.4),and sever underweight HR=3.66(1.85-7.2), But sever stunting shows less pronounced with HR=1.92(1.01-3.60). The probability of surviving for wasted children declines sharply starting from 6th months and reach 76% in 12th months (10).

HIV positive children are generally at significantly higher risk of death compared to HIV negative children if they arrive with severe malnutrition (10, 18, 24).

Assessing the effect of malnutrition on HIV infected children after initiation ART is very crucial. This study was aimed to assessing the effect of malnutrition in survival of HIV infected children after initiation of ART.

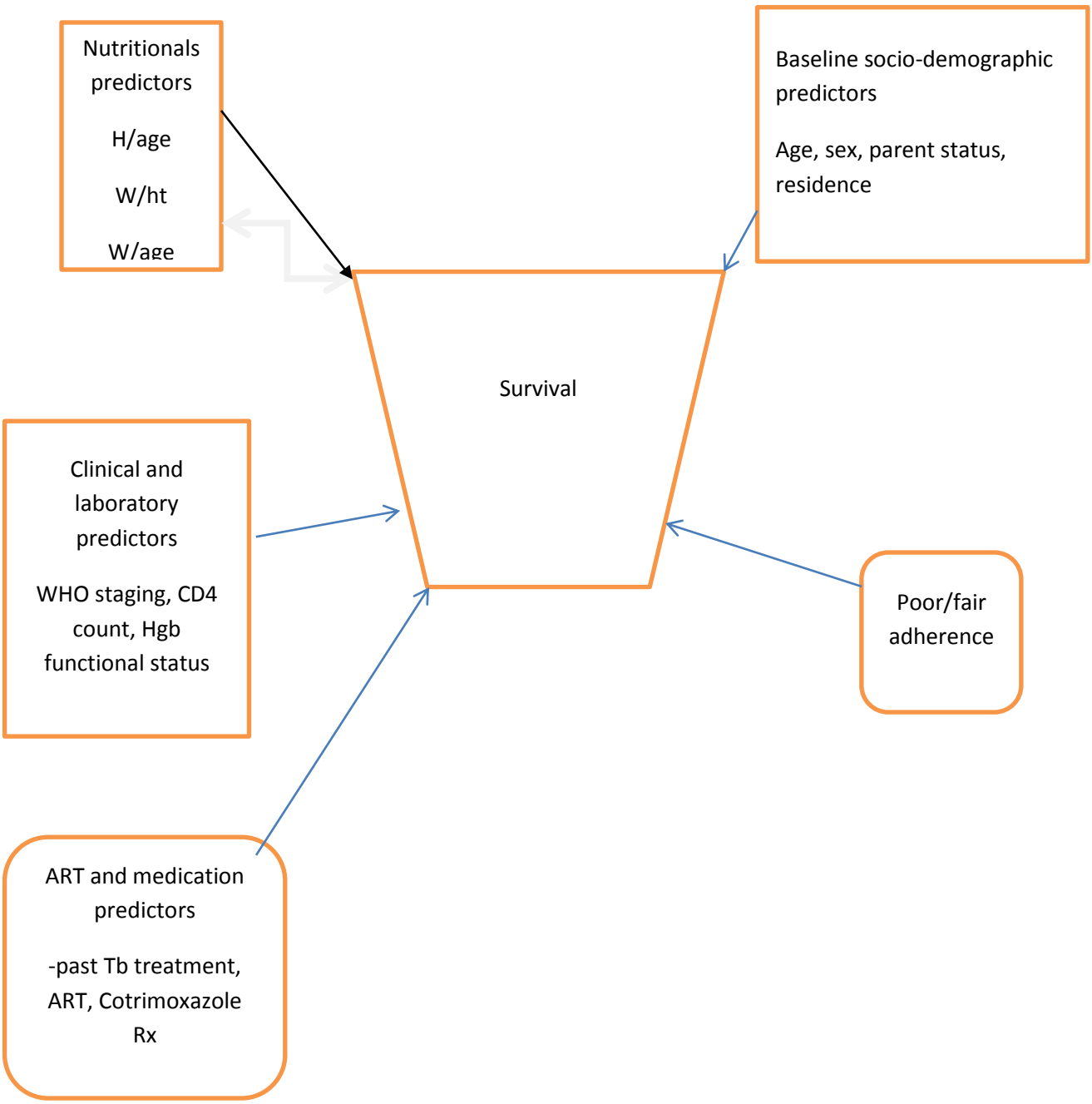

Figure 1: Conceptual frame work for assessment of the effect of malnutrition on survival of HIV infected children after initiation of ART developed from literature.

3. Objectives

3.1 General Objective

To assess the effect of malnutrition in survival of HIV infected children after initiation of antiretroviral treatment (ART) in Wolaita zone selected health facilities, 2013.

3.2 Specific Objectives

- To estimate the magnitude of malnutrition on HIV infected children at initiation of ART.
- To estimate time to death of HIV infected children who are on ART
- To determine factors affecting survival of HIV infected children after initiation of ART
- To assess the effect of malnutrition on survival of HIV infected children after initiation of ART

4. Methodology

4.1 Study Area and Period

The study was conducted in Wolaita zone from February 28, 2014 to March 14, 2014.Wolaita zone is one of the 13 zones of SNNPR and it has 12 Woredas and three town administrations. Wolaita Sodo town, 330 km is far away from south of Addis Ababa. It is an administrative center for Wolaita zone. In this zone there are three hospitals, one government, one private hospital and one NGO hospital, 68 health centers and two non-governmental health centers that render preventive, curative and rehabilitative service for the catchment area population. Among all there are 12 health centers and all hospitals give ART service in Wolaita zone.

4.2 Study Design

Retrospective cohort study was conducted among HIV infected children who had started ART between February, 2006 to March, 2014 among patients who have socieodemographic, immunological and anthropometric data.

4.3 Source and Study Population

4.3.1 Source population

Children with HIV/AIDS, aged<15years and started ART treatment in Wolaita zone health facilities.

4.3.2 Study population

All Children with HIV/AIDS, aged<15years and started ART treatment in Wolaita zone selected health facilities.

Those patients fulfilling the following criteria

Inclusion criteria

- HIV positive children aged <15yrs, who were on ART at least one full month from February, 2006 to March, 2014.

Exclusion criteria

- HIV positive children aged <15yrs, who have not started ART.
- HIV patients with incomplete intake form at least with nutritional data, registers and follow up form

4.4. Sample Size Determinations and Sampling Technique

4.4.1 Sample size

Severe wasting, severe underweight and severe stunting were considered in order to calculate the required sample size. To calculate sample size all the above exposure variables were considered and severe underweight was chosen as an independent variable since it gave maximum sample size as compared to other exposure variables.

The sample size was determined using a formula for two population proportions and calculated by OpenEpi version 2.3 statistical software package by considering that

P_1 is percent of exposed (sever underweight) with outcome 17.68%

P_2 is percent among the non-exposed with outcome 4.83% is estimated from other study (10).

$Z_{\alpha/2}$ is taking CL 95%, Z_{β} 80% power and

r is ratio of non-exposed to exposed 1:1

$$n1 = \frac{\left[\left(\frac{Z\sigma}{2}\sqrt{\left(1+\frac{1}{r}\right)p(1-p)} + z\beta\sqrt{p1(1-p1) + \frac{p2(1-p2)}{r}}\right)\right]^2}{(p1-p2)^2}$$

After calculating sample size was 109 for each total 218. Accordingly, after adding 10% for contingency a total sample size was 240.

4.4.2 Sampling procedure

Health facilities were selected based on their number of pediatrics ART user. From all 12 health centers which have given this service we choose 3 which have maximum user which were Bodity, Soddo and Areka health center. From 3 hospitals which give ART service we choose Wolaita sodo referral hospital and Dubo sent marry hospital based on their amount of ART user. At the beginning Profiles of all children on ART who have been managed between February, 2006 and March, 2014 in selected health facilities were evaluated. Finally, all samples were selected starting from February, 2006 to March, 2014.

4.5. Variables

4.5.1. Dependent variables

The dependent variable is survival status from the initiation of ART to March 2014 and the main outcome measure is time to survival from the initiation of ART.

Event = Survival of children from initiation of ART.

Time origin = Initiation of ART

Time scale = Months from initiation of treatment

T= Time from initiation of treatment (ART) to survival of children.

4.5.2 Independent variable

The independent variables are

- Socio demographic characteristics(age, sex, ethnicity ,marital status of mother or care giver , employment for mother or care giver)
- Base line clinical, laboratory and ART information(opportunistic illness, WHO clinical staging, TB test and treatment, ART treatment, chemoprophylaxis, drug allergies, Hgb, T-cell lymphocyte count,CD4count, side effects)
- Anthropometric data (weight, height/length, MUAC) accordingly, nutritional status will be defined with stunting (height for age Z score < -2), Wasting (weight for height Z score -2) and underweight (weight for age Z score < -2) by WHO.
- ART treatment

4.6 Data Collection Instrument

The questionnaire consists of the following data

- ✓ Socio demographic data
- ✓ clinical, laboratory and Anthropometric data
- ✓ ART treatment related data
- ✓ Follow up data

4.7. Data Collection and Quality Control

A data collection form was developed from ART entry and follow up form used in the ART clinic. The data was collected by reviewing pre-ART register, laboratory request, monthly cohort form, and follow up form, ART intake form, patients' card. The most recent laboratory a result prior to

initiation of ART was used as a base line value. In case, there is no pre-treatment laboratory test, results obtained within one month of ART initiation was used. If two results are obtained within a month time the mean was used.

Data was collected by trained ART health officers and nurses at the Hospital and health center. Two days long training was given for 1supervisor and 5 data collectors. The overall activity was controlled by the principal investigator of the study. Data quality was assured through designing a proper data collection material and through continuous supervision. All completed data collection form was examined for completeness and consistency during data management, storage and analysis. Data was entered and cleaned by trained data clerk and principal investigator respectively before analysis.

4.7 Operational Definitions

- CD4 percentage or count; a way of measuring immune-competency by counting the lymphocyte that carry the CD4 molecules.
- Drop out; if a patient discontinued ART for at least three month as recorded by ART physician
- Fair Adherence; if the percentage of missed dose is between 85-94 %(3-5 doses of 30 doses or 3-9 dose of 60 dose) as documented by ART physician
- Good Adherence; if the percentage of missed dose is between >95 %(< 2 doses of 30 doses or <3 dose of 60 dose) as documented by ART physician.
- HAART; The name given to treatment regimens recommended by leading HIV experts to aggressively suppress viral replication and progress of HIV disease.
- Immunodeficiency; break down in immune-competence to resist or fight off infections.
- Lost; if a patient discontinued ART for at one to three month as recorded by ART physician
- Malnutrition; if the child has either of one H/age< -2, or W/age<-2 or MUAC<12.5 cm or W/H <-2 standard deviation according to WHO 2006 curve.
- Opportunistic infections; illness caused by various organisms, some of which usually do not cause disease in persons with healthy immune systems.
- Poor Adherence; if the percentage of missed dose is between <85 %(> 6 doses of 30 doses or >9 dose of 60 dose) as documented by ART physician
- Survival; lack of experience of death

4.8 Data Entry, Analysis and Processing

Data were entered in Epi-Info 3.5.3 for windows and analyzed using SPSS version 21 for windows to see the frequency and predictors. Nutritional status will be defined by ENA for SMART software for generating Z score of stunting (height for age Z score < -2), Wasting (weight for height Z score -2) and underweight (weight for age Z score < -2) by WHO. Data were cleaned and edited before analysis. Data exploration was undertaken to see if there are odd codes or items that were not logical and then subsequent editing was made. Cox proportional hazard assumption was checked using STATA 11 by schoenfeld residuals test which P>0.1 assumes fulfill the criteria

Patient's cohort characteristics were described in terms of central tendency and dispersion value for continuous data and frequency distribution for categorical data. Death was confirmed by reviewing death certificates, medical registration in the hospital, or registration by ART adherence supporter through calling using the registered phone number. Individuals alive on ART, lost follow up and transfer out at the end of the study period was censored. Finally, the outcome of each subject was dichotomized into censored or death.

Univariate analysis was used to describe patient's baseline characteristics. Actuarial table was used to estimate survival after initiation of ART, and log rank test was used to compare survival curves. Cox proportional-hazard regression was used to calculate the bivariate and adjusted hazard ratio and then determine independent predictors of time to death.

Missing value was analyzed using simple imputation method for median. In multivariate cox regression analysis, only those variables that were significantly associated with survival on a crude analysis were entered to the final model.

4.9 Ethical Consideration

The proposal was submitted to the Research and Ethics Committee (REC) of the School of Public Health, College of Health Sciences of Addis Ababa University for approval. Following the approval by REC, an official letter of co-operation was written to the concerned bodies by the School of Public Health AAU. As the study was conducted through review of medical records, the individual patients was not subjected to any harm as far as the confidentiality is kept. No personal identifiers were used on data collection form. The recorded data will not be accessed by a third person except by the principal investigator, and were kept confidentially.

4.10 Dissemination of Results

Findings of the study will be communicated to school of public health, Wolaita Sodo referral hospital where the study will be conducted, to the NGOs who support the ART at pediatrics through soft and hard copy after presentation. The findings will be attempted to be published in journal for wider dissemination of the information.

5. Result

5.1 Cohort baseline characteristics

5.1.1 Demographic characteristics

A total of 260 HIV infected children started anti-retroviral treatment from February, 2006 to March, 2014 in 2 Hospitals and 3 Health centers in Wolaita zone. Among all of them 228 HIV infected children who were on ART were fulfilling the inclusion criteria and included in this study. Among the cohort 121(53.1%) were males, the rest 107 (46.9%) were females. The median age 6 years (IQR= 3-9), the mean age was 6.29 years, 16(7%) were aged less than 18 months, 89 (39%) were aged between 18-59 months, the rest 123 (53.9%) were aged between 5-14 years. From the cohort 158 (69.3 %) were urban in residence. The children parent status were 104 (45.6%) both alive, 45(19.7%) were both dead at baseline. Among the cohort 21(9.2 %) children were cared by NGO centers the rest were cared by their families or relatives. Educational status of the care giver showed 78 (37.68%) achieved primary level, 50 (24.15%) were not educated. Major ethnicity of the children from this cohort was Wolaita 149(65.4%) followed by Amhara 38(16.7%) (Table1).

Table 1.Socieodemographic characteristics of children on ART follow up in Wolaita Sodo selected health facilities, March 2014.

Variables		Frequency n=228	Percent
Sex	Male	121	53.1
	Female	107	46.9
Age group	<18 months	16	7.0
	18-59 months	89	39.1
	5-14 years	123	53.9
Residence	Urban	158	69.3
	Rural	70	30.7
Parent status for the children	Both alive	104	45.6
	mother alive but father dead	43	18.9
	Mother dead but father alive	36	15.8
	Both dead	45	19.7
Caregiver for children	Parents	165	72.4
	Other relative	42	18.4
	NGO	21	9.2
Educational status of care giver	Primary	78	37.7
	Secondary	53	25.6
	Tertiary	26	12.5
	Not educated	50	24.2
Ethnicity of the children	Wolaita	149	65.4
	Amhara	38	16.7
	Gamo	15	6.6
	Kembata	7	3.1
	Others	19	8.2

5.1.1 Clinical and laboratory baseline characteristics

Majority (91.2%) of the children who were HIV positive had at least one history of past opportunistic illness at the time of initiation of ART. Pneumonia 62(29.8%), unexplained persistent diarrhea (>=14 day) 59(28.3%), unexplained persistent fever (>=30days) 51(24.52%), oral thrush 46 (22.11%) EPTB 24(11.54%) and PCP 16(7.7%) were the commonest type of opportunistic illnesses in HIV infected children in Wolaita Zone selected health facilities. The HIV infected children functional status at baseline were 202(88.6%) were working or ambulatory the rest were bed ridden. Above half of the children developmental status were appropriate for their age 163(71.5%), 60(26.3%) were delayed for their age and the rest were regressive at the starting of ART. At baseline majority 90(39.5%) were WHO classified as clinical stage III followed by stage II 79(34.6%), stage IV 36(15.8%), least were WHO clinical stage I 23(10.1%) at base line. Fifty nine percent (135) of children CD4 count or percentage were below normal threshold at baseline. Majority 151 (66.2%) had hemoglobin level of >10 gm/dl at baseline the rest were ≤ 10 gm/dl at baseline after missing value analysis.

One hundred fifty (65.8%) were screened for pulmonary TB at initiation of ART. Among them 44(29.33%) were positive for TB screening. Forty five (30%) of them were took TB treatment. Among those who took TB treatment 19(42.22%) were took 2SRHZ/4EH regimen and the rest were took different regimen. Almost all (80.7 %) were taken past medication including prophylaxis. Eighty percent were took Cotrimoxazole prophylaxis before initiation of ART and 31(13.6%) were taken INH prophylaxis.

Children ART eligibility criteria were 90(39.5%) based on CD4 count or percentage cutoff points, 88(38.6%), based on WHO clinical stage II or III and TLC <1200, 43(18.9%) based on WHO clinical stage III or IV and the rest were started based on different criteria's.

Based on ART physician registered for this cohort first Three month ART adherence were 196(86.0%) were good, 16(7%) were fair and the rest were poor 13(5.7%). Twelve percent of children experience at least minor type of drug side effect. From these side effects 59.25% were nausea, 25.92% were diarrhea, 55.5 % were rash and the rest 8% were others like night mare, vomiting and others.

Twenty four percent of children were change their regimen during follow up due to new TB 16(29.09%), drug out stock 16(29.09%), drug side effect or toxicity 12(21.8 %), new drug available

4(7.27%), weight change and age change 4(7.27%) and the rest 3 (5.45%)were different reasons such as clinical failure, and others (table 2).

Table 2: Clinical, laboratory characteristic of children on ART at Wolaita Sodo zone selected health facilities in March 2014.

Variable		Frequency N=228	Percent
History of Past opportunistic illness	Yes	208	91.2
	No	20	8.8
Functional status at base line	Working/Ambulatory	202	88.6
	Bed ridden	26	11.4
Developmental History at base line	Appropriate	163	71.5
	Delayed	60	26.3
	Regressive	5	2.2
WHO clinical staging of HIV at baseline	Stage I	23	10.1
	Stage II	79	34.6
	Stage III	90	39.5
	Stage IV	36	15.8
CD4 count or percentage	Below normal threshold	137	60.1
	Above normal threshold	91	39.9
Hemoglobin level	≤10 gm/dl	77	33.8
	>10 gm/dl	151	66.2
past TB test before ART	Yes	150	65.8
	No	78	34.2
past TB test result n=150	Positive	44	29.3
	Negative	106	70.6
past TB treatment n=45	2SRHZ/4EH	19	42.2
	2HRZES/1HRZE	2	4.4
	2HRZE/4EH	24	53.3
Past history of Cotrimoxazole	Given	183	80.3
	Not given	45	19.7
INH history of taking	Yes	31	13.6

	No	197	86.4
ART eligibility criteria	CD4<350 or 500	90	39.5
	WHO stage III and IV	43	18.9
	WHO stage II or III and TLC<1200	88	38.6
	DBS positive	5	2.2
	Others	2	.9
First three month ART adherence	Good	196	86.0
	Fair	16	7.0
	Poor	13	5.7
Regimen change during follow up	No	168	73.7
	Yes	55	24.1
Recent adherence	Good	182	79.2
	Fair	21	9.2
	Poor	20	8.8

The commonest regimen in this historical cohort 4a= d4t-3TC-NVP which is 135(59.2%) followed by 4c= AZT-3TC-NVP 31(13.6%) from the total (figure 2).

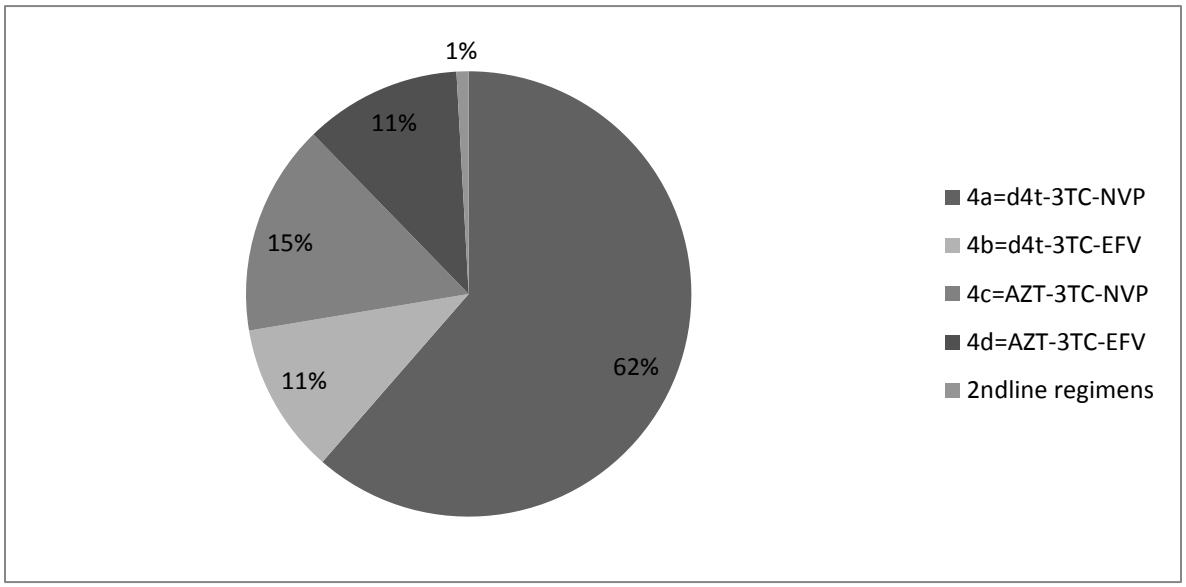

Figure 2: ART regimen given for children started ART at Wolaita zone selected health facilities. March 2014.

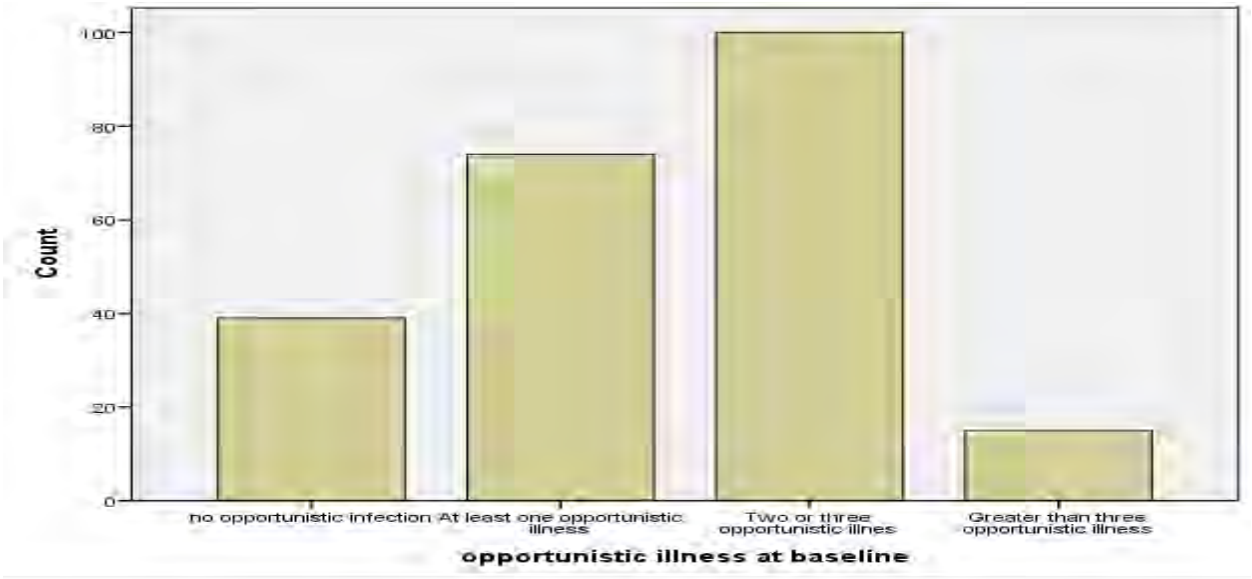

Figure 3: Frequency of opportunistic illness for children at initiation of ART at Wolaita zone selected health facilities. March 2014.

5.1.2 Nutritional characteristics

Based on weight for height Z score, the nutritional status of this historical cohort at base line showed that 83(41.9 %, 35.3 - 48.9 95 C.I.) had global malnutrition of these 50.5% were males and 31.9% were females respectively. The prevalence of moderate malnutrition based on weight for height Z score was 13.1% (95% CI 9.1-18.5), with sex distribution of 18.7% (95% CI 12.4-27.1%), and 6.6% (95% CI 3.1-13.6%) for males and females respectively. The prevalence of severe malnutrition was 36 % with the prevalence 43 % in males, 28 % in females. Overall nutritional status, 143(62.5%) were stunted, 98(43.0%) were underweight and 102(44.7%) were wasted at baseline (table 3).

Table 3: Baseline nutritional status of children started ART at Wolaita zone selected health facilities. March 2014.

Nutritional parameter	Age category			
	<18months (n=16)	18-59 months (n=89)	5-14 years (n=123)	Total (n=228)
Stunted (HAZ<-2)	10(62.5%)	51(57.3%)	82(66.7%)	143(62.5%)
Severe stunting(HAZ<-3)	6(37.5%)	36(40.4%)	46(37.4%)	88(38.6%)
Underweight (WAZ<-2)	5(31.3%)	45(50.6%)	48(39.0%)	98(43.0%)
Severe underweight (WAZ<-3)	3(18.8%)	35(39.3%)	40(32.5%)	78(34.2%)
Wasted (WHZ<-2)	5(31.3%)	39(43.8%)	58(47.2%)	102 (44.7%)
Severe wasting (WHZ<-3)	4(25%)	34(38.2%)	44(35.8%)	82(36%)

5.2 Survival analysis

A total of 228 children started ART have been followed from 0 to 96 months. The mean follow up duration was 40.05 months, the minimum and the maximum follow up time was 1 and 97 months respectively. The cumulative proportion of survival was 98%, 97%, 94%, 92% and 84% at 6,12,24,60 and 96 months respectively (Table 4).

The mean survival time for this cohort using Kaplan Meier analysis was 89.3 months (95% CI 85.7-92.9). No median was found (figure 4). Further analysis of mean survival time was done using socio demographic, nutritional and clinical and laboratory characteristics. The mean survival time had significant difference between urban and rural with log rank test X^2 =9.07 df =1 p<0.003.The mean survival time had difference across the age of the children. Mean survival time did not show a difference across sex of the children with log rank test X^2 =1.083 df =1 p=0.298. The mean survival time has also difference across severe wasted children stratified by age of the children. Mean survival time among severe wasted HIV infected aged <18 months children on ART was 16 (95% CI, 1-39) compared to non-severe wasted children with mean 80(95% CI 70-89.3 months).

Table 4: Actuarial Table estimates of the cumulative progression to death for 228 study subjects Starting ART b/n February 2005 up to March 2014.

Interval Start Time	Number Entering Interval	Number Withdrawing during Interval	Number Exposed to Risk	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval
0	228	13	221.500	5	.02	.98	.98
6	210	17	201.500	1	.00	1.00	.97
12	192	23	180.500	2	.01	.99	.96
18	167	14	160.000	1	.01	.99	.96
24	152	9	147.500	2	.01	.99	.94
30	141	15	133.500	0	.00	1.00	.94
36	126	14	119.000	1	.01	.99	.93
42	111	20	101.000	2	.02	.98	.92
48	89	16	81.000	0	.00	1.00	.92
54	73	20	63.000	0	.00	1.00	.92
60	53	11	47.500	0	.00	1.00	.92
66	42	8	38.000	1	.03	.97	.89
72	33	13	26.500	0	.00	1.00	.89
78	20	7	16.500	1	.06	.94	.84
84	12	6	9.000	0	.00	1.00	.84
90	6	3	4.500	0	.00	1.00	.84
96	3	3	1.500	0	.00	1.00	.84

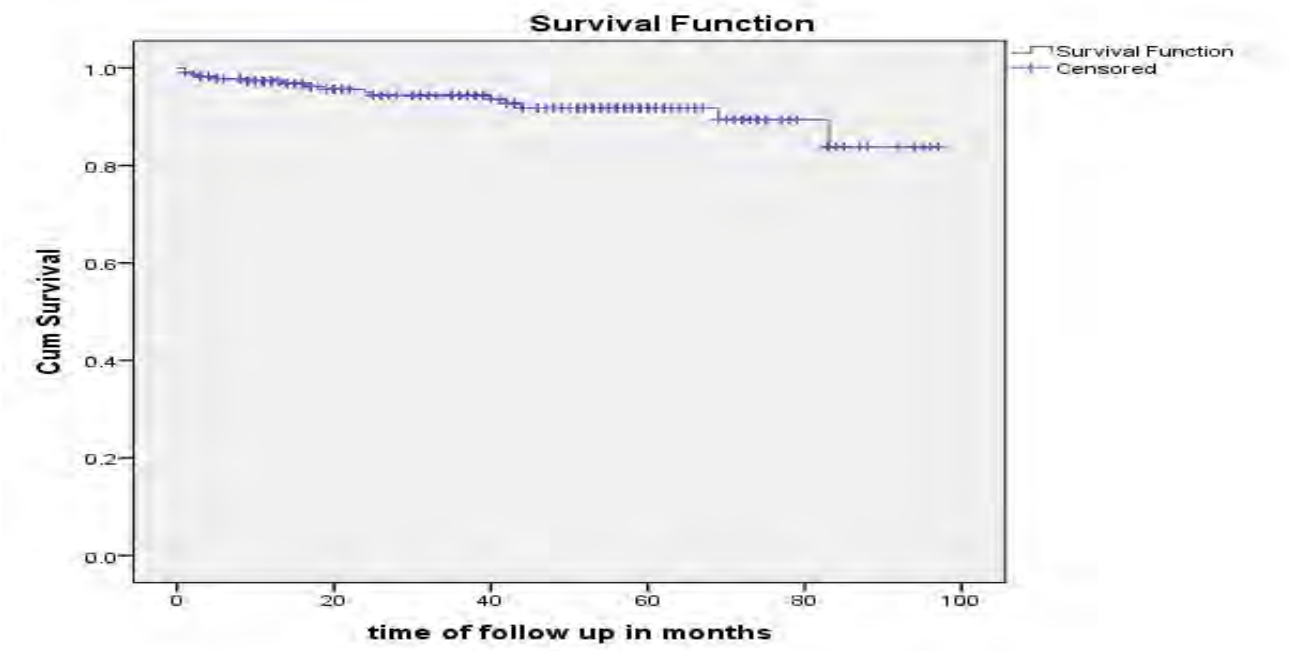

Figure 4: Survival curve for children on ART at Wolaita Zone selected health facilities, March 2014.

5.1.2 Death as an outcome

The cohort showed that current status of the children was 191(83.8%) alive, 16(7%) dead, 13(5.7%) transferred to other facility and the rest 8(3.5%) lost to follow up during the follow up time. The cumulative incidence of mortality rate 21.02 per 1000 person years of observation (95% CI 12.8-34.3 per 1000 person years of observation). The estimated mortality was 2%, 3%, 6%, 8% and 16% at 6,12,24,60 and 96 months of follow up respectively (Table 4).

The mortality pattern of ART patients was different at various socieodemographic, clinical and nutritional characteristics. The hazard of death was lower in age category 18 to 59 months and 5-14 years compared with age group of less than 18 months with hazard rate 0.083(95% CI, 0.015-0.453) and 0.274 (95% CI 0.086-0.873) respectively. The hazard of death was also different in residence being higher in rural than in urban setting with hazard rate of 4.214 (95% CI, 1.531-11.60) p value 0.005. Our analysis did not show difference in hazard rate across sex of the child and current status of the parents (Table 5).

Table 5: Bivariate cox regression for socio demographic variables for children on ART in Wolaita zone selected health facilities March 2014.

Covariates		Number at risk	Number of death	Crude Hazard ratio (HR)	95% CI
Age of the child	<18 months	16	4	1	
	18months -59months	89	2	0.083	(0.015-0.453)
	5-14 years	123	10	0.274	0.086-0.873
Sex of the child	Male	121	6	1	
	Female	107	10	1.703	0.617-4.696
Residence of child	Urban	158	7	1	
	Rural	70	9	4.214	1.531-11.600
Current parent status	Both alive	104	7	1	
	Only Mother alive	43	5	1.623	0.513-5.137
	Only Father alive	36	3	1.080	0.277-4.209
	Both dead	45	1	0.266	0.033-2.178

Mortality pattern of children on ART was different when analyzed by various clinical and laboratory baseline characteristics. The hazard rate of death at baseline bed ridden children on ART was nine times higher than working/ambulatory children with HR 9.121(95% CI 3.430-24.73) times higher than working/ambulatory children. Hazard of death for children developmental status has significant difference between delayed/regression and appropriate developmental status with HR 4.26 (95% CI 1.55-11.72). Hazard rate of death for WHO clinical stage IV at baseline was 7.016 times higher than WHO clinical stage I and II with 95% CI 1.805-27.277, but WHO clinical stage III has no difference with stage I &II. The hazard rate of death for Fair/poor ART adherence at first three month was 13 times higher than good adherence HR 13.0 (95% CI HR 4.6-35.9). The Hazard rate of death for hemoglobin less than or equal to 10 gm/dl was 5.35 (95% CI, 1.862-15.88) times higher than who have greater than 10gm/dl.

Our finding shows that hazard rate of death for children on ART was not different across children who have history of Past opportunistic illness, type of regimens given at follow up time, history of Cotrimoxazole intake and CD4 count or percentage at baseline (Table 6).

Table 6: Bivariate cox regression for Clinical, laboratory characteristic of children on ART at Wolaita Sodo zone selected health facilities, March 2014.

Covariates		Number at risk	Number of death	Crude Hazard ration (HR)	95% CI
History of Past opportunistic illness	No	20	2	1	
	Yes	208	14	2.031	0.453-9.110
Functional status at base line	Working/Ambulatory	202	8	1	
	Bed ridden	26	8	9.121	3.430-24.73
WHO clinical staging of HIV at baseline	Stage I or II	101	3	1	
	Stage III	90	6	2.217	0.553-8.878
	Stage IV	36	7	7.016	1.805-27.277
CD4 count or percentage	Above normal	91	5	1	
	Below normal	137	11	1.533	0.532-4.48
Past history of Cotrimoxazole	Given	183	15	1	
	Not given	45	1	3.798	.501- 28.768
DevelopmentaHistory at base line	Appropriate	163	6	1	
	Delayed/ Regression	65	10	4.257	1.546-11.718
Regimens given at follow up time	4a=d4t-3TC-NVP	135	8	1	
	4b=d4t-3TC-EFV	22	2	1.986	0.421-9.374
	4c=AZT-3TC-NVP	31	1	0.537	0.067-4.295
	4d=AZT-3TC-EFV	26	3	2.177	0.574-8.253
	2nd line regimens and others	14	2	2.717	0.571-12.930
First three month ART adherence	Good	198	6	1	
	Fair/poor	30	10	13.000	4.699- 35.964
Hemoglobin level	>10 gm/dl	151	5	1	
	=<10 gm/dl	77	11	5.349	1.862-15.882

Mortality pattern also had difference across baseline nutritional characteristic of the children on ART. Hazard rate of death for children on ART who were sever underweight 2.98 times higher than others with 95% CI 1.081-8.22. Sever wasted children at baseline were 3.79 with (95% CI, 1.34-10.9) times hazard rate of death than not sever wasted. The incidences of mortality rate for sever wasted children 3.79 (95% CI 1.3-10.9) times higher than non-sever wasted children. Wasted children have lower survival than non-wasted children by HR= 3.37 (95% CI 1.08-10.5). The other nutritional characteristics underweight, sever stunting and stunted has no effect on the hazard rate of children on ART (Table 6)

Table 6: Nutritional characteristic of children on ART at Wolaita Sodo zone in selected health facilities, March 2014.

Covariates		Number at risk	Number of death	Hazard ratio (HR)	95% CI
Sever underweight	No	150	6	1	
	Yes	78	10	2.982	1.081-8.22
Underweight	No	130	6	1	
	Yes	98	10	0.494	0.179-1.363
Sever stunting	No	140	13	1	
	Yes	88	3	0.337	0.096-1.186
Stunted	No	143	8	1	
	Yes	85	8	0.570	0.213-01.520
Wasting	No	126	4	1	
	Yes	102	12	3.379	1.087-10.506
Sever wasting	No	171	5	1	
	Yes	71	11	3.79	1.34-10.99

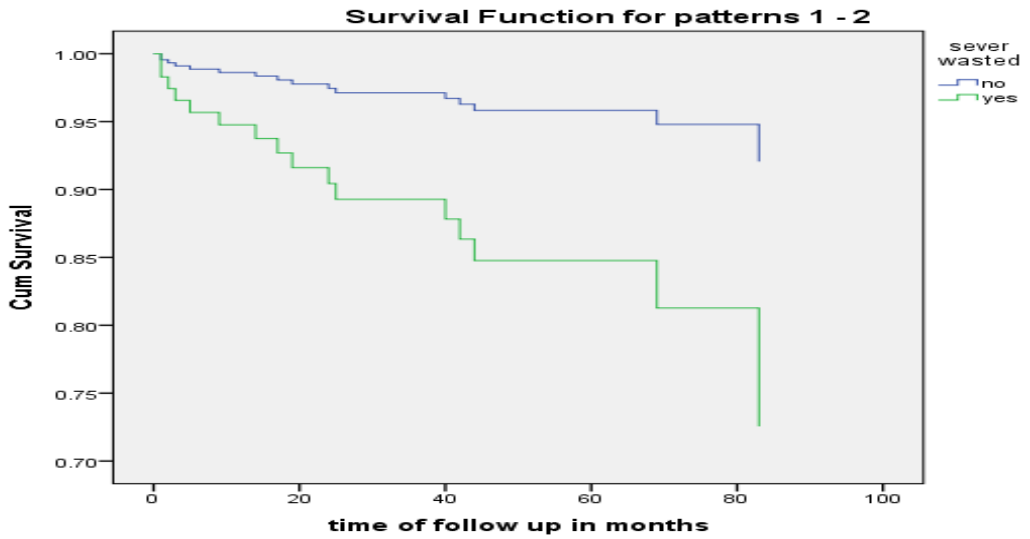

Figure 5: Survival graph by nutritional status (WHZ score) at start of ART among children who have started ART in Wolaita zone selected health Facilities, March 2014.

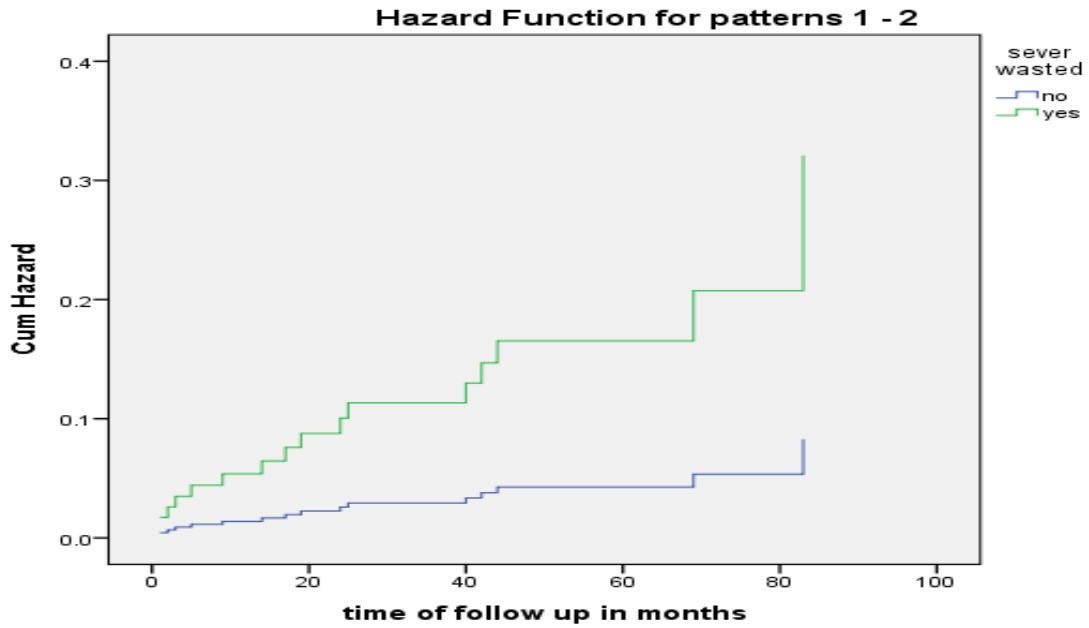

Figure 6: Hazard graph by nutritional status (WHZ score) at start of ART among children started ART at Wolaita zone selected health facilities, March 2014.

5.1.3 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 children age, place of residence, WHO clinical stage III & IV, functional status at baseline, developmental status at base line, first three month ART adherence, hemoglobin value (<=10gm/dl), sever underweight, wasted and sever wasted children has significant association on Hazard rate of death (HZ). The rest has no significant association with survival status of the children.

In multivariate cox regression analysis, only those variables significantly associated with survival on bi variate were entered to the final model. After adjusted, the independent significant predictor of reduced surviving in children living with HIV/AIDS after initiation of ART remain residence of children, age of the children, first three month ART adherence and sever wasting. Residence of children is one of the predictor of reducing survival of children on ART living in rural AHR 4.302 (95% CI, 1.25-14.8) than urban children. Children aged < 18 months were less likely to survive than aged 18 month-59 month, 5-14 years of age with AHR 0.047(95% CI, 0.006-0.368), 0.145(95% CI 0.032-0.663) respectively. Fair/poor of the first three month ART adherence of children were not surviving as good adherence with AHR 8.95(95% CI 2.624-33.72). Sever wasting at baseline was the important predictor in reducing survival of HIV/AIDS infected children after initiation of ART with AHR 7.040 (95 % CI, 1.267-39.13) (Table 7).

Table 7: Multivariate predictors of survival among children started ART at Wolaita Zone health facilities March 2014

Covariates		Number at risk	Number of death	Adjusted Hazard ration (AHR)	95% CI
Age of the child	<18 months	16	4	1	
	18months -59months	89	2	0.047	0.006-0.368
	5-14 years	123	10	0.145	0.032-0.663
Residence of child	Urban	158	7	1	
	Rural	70	9	4.302	1.25-14.8
Functional status at base line	Working/Ambulatory	202	8	1	
	Bed ridden	26	8	1.801	0.281-11.54
WHO clinical staging of HIV at baseline	Stage I or II	101	3	1	
	Stage III	90	6	1.042	.213-5.09
	Stage IV	36	7	3.121	.400-24.35
Developmental History at base line	Appropriate	163	6	1	
	Delayed/ Regressive	65	10	0.982	.146-6.61
First three month ART adherence	Good	198	6	1	
	Fair/poor	30	10	8.95	2.624-33.7
Hemoglobin level	>10 gm/dl	150	5	1	
	≤10 gm/dl	78	11	2.270	0.620-8.3
Sever underweight	No	150	6	1	
	Yes	78	10	0.545	0.085-3.49
Sever wasting	No	141	5	1	
	Yes	71	11	7.040	1.267-39.13

6. Discussion

In this historical cohort study, we found prevalence of severe malnutrition at baseline based on weight for height Z score <-3 score was 36%. Overall nutritional status, 62.5% were stunted, 43.0% were underweight and 44.7% were wasted at baseline. Malnutrition was also high classified as severs underweight and sever stunting which was 34.2% and 38.6% respectively.

The cumulative proportion of survival was 98%, 97%, 94%, 92% and 84% at 6,12,24,60 and 96 months respectively. The mean survival time for this cohort using Kaplan Meier analysis was 89.34 months (95% CI 85.707-92.97). The cumulative incidence of mortality rate 21.02 per 1000 person years of observation (95% CI 12.8-34.3 per 1000 person years of observation).

After adjusted by multivariate cox proportional regression, the independent significant predictor of reduced surviving in children living with HIV/AIDS after initiation of ART remain residence of the children, age of the children, first three month ART adherence and sever wasting.

In this historical cohort baseline nutritional status showed that there are high prevalence of sever wasting, wasting, underweight and stunting which was high as compared with prevalence of malnutrition in EDHS 2011 for Ethiopia and SNNPR. However this finding is in line with the finding of study done in Zewditu memorial hospital that indicated with 61.1% underweight children, 55.6% stunting of children, 27.3% wasting of children at base line were (4, 9, 10). Our finding also has similar with finding in Uganda (25). This could be due to substantial impact of HIV infection on the nutritional status of infected people due to poor food intake as a result of poor appetite and difficulty eating, intestinal malabsorption because of chronic diarrhea and HIV caused intestinal cell damages, metabolic changes and increased nutrient requirements related to OIs.

In our study the cumulative incidence of mortality rate, cumulative proportion of survival and mean survival time for this cohort using Kaplan Meier analysis was lower in our study compared with study done in 2006 by Medicines Sans Frontie`res HIV/AIDS programs in 14 countries, the overall probability of survival (11). Our finding also has lower mortality rate compared study done in Ethiopia in AA zewditu and Bahir Dar (9, 10, 19) . This could be explained in two ways. Firstly, the difference in the study period as there were changes in the treatment and care of children on ART through time. Secondly our study include health centers which give ART service so health centers have most of simple cases as severe cases were refer to hospital.

In this study residence of children is one of the predictor of reducing survival of children on ART living in rural four times higher than urban children. This is similar with EDHS 2011 shows Mortality rates in urban areas are consistently lower than in rural areas in child mortality. This could be due to hygiene and sanitation, malnutrition is prevalent in rural, poor knowledge of on care of HIV and others (4).

In our study the only socio demographic predictor for survival was children age as < 18 months were more not surviving than age 18 month-5 year, 5-14 years of age. This is in line with study done in South Africa shows age of <3 years 2.6 times higher to die than the others (7). Our study also in line with study done in south Africa from this study age comparing ≥120 months with <18 months were risk factor for death (12). Study done in Malawi also in line with our result Children <18 months old were 2.15 times more likely to die as children aged at least 18 months (18). Our study also support WHO new 2013 guideline which says ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count (27) .

But our result is not congruent with result from Ethiopia done in Bahir Dar Felege Hiwot referral hospital and AA zewditu memorial Hospital. These studies ends that age is not the predictor in the multivariate cox regression. This could be due WHO guideline change for ART initiation that uses age as starting for ART. However, sex and other socio demographic characteristic was not predictors of mortality in in our study and another study from Ethiopia(9, 10).

In our study fair/poor of the first three month ART adherence of children were not surviving as good adherence with 8 times higher. According to WHO Retaining people receiving ART in care and ensuring good treatment adherence are critical determinants of successful ART outcomes. Our finding is similar with finding from British Non adherence over time (<95%) was strongly associated with higher risk of mortality (AHR: 3.13; 95% CI:1.95 to 5.05). This was also in line with study in Uganda which was good adherence reduces the hazard rate adherence to HAART was associated with survival (HR 0.46, 95% CI 0.47–0.50) (16, 21, 28). Due to fair/poor adherence of the ART leads to virologic, immunologic and clinical failure that is mediated mainly by two potentially reinforcing mechanisms. Fair/poor adherence to ART leads to failure to suppress viral replication, thus increasing the likelihood of developing HIV mutations that could lead to the development of drug-resistant viral strains. Secondly, Fair/poor adherence to ART fails to prevent

further viral destruction of the cellular immune system with consequent reduction in the level of CD4+ cells and development of opportunistic infections (29).

In this study we found the incidences of mortality rate for sever wasted children is 3.77 (95% CI 1.2-13.8) times higher than non-sever wasted children. Sever wasting is associated with survival, sever wasted children at baseline were seven times higher to die early than not sever wasted children with which is consistent with study done in AA zewditu memorial Hospital, but in study done in Bahir Dar nutritional predictors were not associated with survival.(9, 10, 19). Households of HIV-positive children under ART had lower economic status, less education, and greater proportions of unemployed caregivers. Such disadvantaged socioeconomic conditions further complicate under-nutrition among children. Despite the effectiveness of ART in ameliorating disease burdens, persistent socio-economic backwardness may ultimately retard the progress (25). The mechanism malnutrition might act to decrease survival is uncertain: the hypothesized reason is malnutrition impair immune reconstitution and there by prolong the period at which patient remain at increased risk of opportunistic infection.

However in contrary to another study presence of OI, WHO clinical stage, hemoglobin level, absolute CD4 value, Cotrimoxazole preventive therapy at baseline and delayed or regressing developmental history were significant predictors of mortality but not in our study (9, 10). This could be explained by in our study there are high missing value for example for hemoglobin and absolute CD4 value were have number of missing value and missing value analysis was done for these variables.

Strength and limitation of the study

Strength

- Study was carried out in a rural hospital and rural health centers
- Retrospective longitudinal study
- Gives an insight for researchers especially for prospective study.

Limitation

- Using secondary data have incomplete data
- Selection bias is possibly introduced during secondary data collection because patients with incomplete records were excluded
- Computing risk of death may overestimate the predictors.
- Mortality might be underestimated lost to follow up patient
- Important predictors of survival viral load and micronutrient deficiency were not considered.

7. Conclusion

Children on ART at baseline have high prevalence of malnutrition. The incidence of mortality for children infected with HIV and initiated ART was lower in this cohort. Malnutrition as Sever wasting was an important predictor of reducing survival of children on ART. Other independent predictors of mortality or reducing survival were residence, age of the child, first three month ART adherence registered by physician at baseline.

8. Recommendation

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

To hospitals and health centers with ART clinic

- A careful monitoring and follow up of patients with who came from rural, age less than 18 months are necessary particularly during the first 6 months of ART initiation.
- Malnutrition as sever wasted children on ART at baseline should be carefully assessed and treated accordingly and seek special follow up
- Careful follow up for poorly or fairly adhered patients and giving them drug counseling is crucial to improve survival
- Develop a way to control the completeness and reliability of base line and follow up data being collected especially hemoglobin and CD4 count or percentage.
- Preventive efforts should focus on high risk groups.

To Health science Researchers.

- Further study on prospective by controlling such as viral load and micronutrient deficiency.

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Annex

Annex-I QUESTIONNAIRE

Date----------/month----------/year----------

Name of data collector---------- signature----------

Name of supervisor----------signature----------

Part-I SOCIO DEMOGRAPHIC CHARACTERISTICS

No,	Questionnaire	Possible answers	skip
101	Age	(---------) years or (-------)months	
102	Sex	1. Male, 2. Female	
103.	Religion care giver	1. Protestant 2.Catholic 3.Orthodox 4.Muslim 5. Others specify----------	
104.	Ethnicity	1. Wolaita 2. Gamo 3. Amhara 5. Others specify---	
105.	Current status of parents.	1, both alive 2, mother alive but father dead 3, mother dead but father alive 4, both dead	
106.	Marital status of care giver	1. Single 2. Married 3. Divorced 4. Widowed 5. Separated	
107.	Age of care giver	(----------)years	
108.	Relation of care giver for the child	1, parent 2, sister/brother 3, uncle/aunt 4, grandparent 5, others specify	
107.	Educational status of care giver	1. Primary 2.Secondary 3. Tertiary 4. Not educated	
108	Occupational status of care giver	1. Farmer 2.Merchant 3. Government employee 4. Non-government employee	

		5. Day laborer 6. Driver 7. Commercial sex worker 8. Jobless 5. Other 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. Diarrhea 9. Pneumonia 10. Herpes simplex 11. Kaposi sarcoma 12. Toxoplasmosis 13. Encephalopathy 14. Wasting syndrome 15.Herpes zoster 16. Other specify-------	
202.	Weight at base line	(----------) kg	
203.	Height/length at base line	(----------) cm	
204	MUAC at baseline	(……)cm	
205	Nutritional status at base line	Normal …….. Under-nutrition (wasting, stunting, severe wasting, underweight, severe underweight	208
206	If child was malnutrition, was it took treatment?	1. yes 2. no	
207	Functional status at base line	1. Working 2.Ambulatory 3. Bed ridden	
209.	WHO clinical staging of HIV at base line	1. Stage II 2.Stage III 3. Stage IV	

210.	Past TB test	1. No 2. Not determined 3. Positive 4. Negative	
211	Past TB treatment	1. No 2.2SRHZ/4RH 3.2HRZES/1HRZE/4HRE 4.2HRZE/4RH	
212.	Past medication	1. No 2. Cotrimoxazole 3.INH 4. Other specify-------	
213.	CD4 count or CD4% at base line	(---------) date----------/-------/---	
214.	Hgb count at base line	----------	
215	If CD4 count or CD4% is lower at base line when become normal?	_____months	
216.	TLC count at base line	----------	
Part- III	ART treatment		
301.	ART eligibility criteria	1. CD4<350 , 500 2. WHO stage IV 3. WHO stage II and III with TLC<1200	
302.	OI prophylaxis given	1. Not given 2. Cotrimoxazole 3. INH 4. Fluconazole 5. Others specify----------	
303.	Regimens given at follow up time	1. 4a=d4t-3TC-NVP 2. 4b=d4t-3TC-EFV 3. 4c=AZT-3TC-NVP 4. 4d=AZT-3TC-EFV 5. 2nd line regimens 6. 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	
406.	Follow up data		

Variable	Base line	3 month	6 month	12 month	24mnth	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8yrs	Recent
CD4% or count												
Hgb												
Weight in kg												
Height/length cm												
MUAC												

406.	Recent functional status	1. Working 2. Ambulatory 3. Bedridden	
407.	Recent WHO staging	1. Stage II 2.Stage III 3. Stage IV	
408.	TB prophylaxis	1. No 2. Yes	
409.	TB screened	1. No 2. Negative 3. Positive	
410.	TB treatment	1. No 2. Yes	
411.	Opportunistic infections	1. No 2. Zoster 3. Pneumonia 4. Pulmonary TB 5. EPTB 6. Oral trush 7. genital/oral ulcer 8. Diarrhea 9.Cryptococcal meningitis 10.CNS toxoplasmosis	

		11. PCP 12. Others specify------	
412.	Cotrimoxazole	1. Given 2. Not given	
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. unable to pay 10. Depression 11. 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 12. Others specify----------	
416.	Reason for regimen change	1. Not change 2. Toxicity/SE 3. New drug available	

		4. Drug out of stoke 5. Clinical failure 6. New TB 7. Other specify----------	
417.	Reason for stopping regimen	1. Not stopped \ 2. toxicity/SE 3 .Treatment failure 4. Poor adherence 5. Drug out of stock 6. Lack of finance 7. Other patient decision 8.Planned treatment interruption 9. Other specify----------	
418.	Recent CD4 count	(-------date--------/---------/------)	
419.	Recent TLC count	(----------)	
420.	Recent Hgb count	(----------)	
421	Current status	1.alive 3 lost follow up 2. Dead 4 transfer to	
422.	If dead when after initiation of ART	(----------) month	
423	If lost follow up or transfer to other facility	(……)month	