COLLEGE OF HEALTH SCIENCES

SCHOOL OF NURSING AND MIDWIFERY

INCIDENCE AND PREDICTORS OF LOST TO FOLLOW UP AMONG CHILDREN ON ANTIRETIROVIRAL THERAPY AT EAST AND WEST GOJJAM ZONE REFERRAL HOSPITALS, AMHARA REGIONAL STATE, 2018: A RETROSPECTIVE COHORT STUDY

BY: TAMENE FETENE (BSc)

A RESEARCH THESIS SUBMITTED TO ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCE, SCHOOL OF NURSING AND MIDWIFERY FOR THE PARTIAL FULFILMENT OF THE REQUIREMENTS FOR DEGREE OF MASTERS OF PEDIATRICS AND CHILD HEALTH NURSING

JUNE, 2018

ADDIS ABABA, ETHIOPIA

ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF NURSING AND MIDWIFERY

INCIDENCE AND PREDICTORS OF LOST TO FOLLOW UP AMONG CHILDREN ON ANTIRETIROVIRAL THERAPY AT EAST AND WEST GOJJAM ZONE REFERRAL HOSPITALS, AMHARA REGIONAL STATE, 2018: A RETROSPECTIVE COHORT STUDY

BY: TAMENE FETENE (BSc)

ADRESS: e-mail tamenefet732@gmail.com

ADVISORS: HABTAMU ABERA (ASS. PROFESSOR, PhD FELLOW)

BEREKET GEBREMICHAEL (BSc, MSc)

JUNE, 2018

ADDIS ABABA, ETHIOPIA

APPROVAL SHEET BY THE BOARD OF EXAMINERS

I, the undersigned MSc student, declare that I have submitted my original work on the title lost to follow up and its predictors among children on antiretroviral therapy at East and West Gojjam Zone referral hospitals, Amhara regional state, 2018 for examination.

Submitted by:

Tamene Fetene (BSc) _____ _____

Name of student Signature Date

This thesis by Tamene Fetene is accepted in its present form by the board of examiners as satisfying thesis for degree of masters in Pediatrics and child health nursing.

Approved by

EXAMINER:

Endale Gemechu (Ass. Professor): _____ _____

Name Signature Date

ADVISORS:

Habtamu Abera (Ass. Professor) _____ _____

Name of major advisor Signature Date

Bereket Gebremichael (BSc, MSc) _____ _____

Name of co -Advisor Signature Date

DEPARTMENT HEAD

Name _____ _____

Leul Derbe (MSc) Signature Date

Statement of Declaration

By my signature below, I declare and affirm that this thesis is my own work. I have followed all ethical principles of research in the preparation, data collection, data analysis and compilation of this thesis. Any scholarly matter that is included in the thesis has been given recognition through citation.

This thesis is submitted in partial fulfillment of the requirements for a master degree of pediatrics and child health nursing at the Addis Ababa University. The thesis will deposit in Addis Ababa University library and will made available to borrowers under the rules of the library. I solemnly declare that this thesis has not been submitted to any other institution anywhere for the award of any academic degree, diploma of certificate.

Brief quotations from this thesis may be made without special permission provided that accurate and complete acknowledgement of the source is made. Requests for permission for extended quotations from or reproduction of this thesis in whole or in part may be granted by the Head of the School or Department when in his or her judgment the proposed use of the material is in the interest of scholarship. In all other instances, however, permission must be obtained from the author of the thesis.

Name: Tamene Fetene Signature_____

Date _____

Advisors: Habtamu Abera (Ass. Professor) _____ _____

Name of major advisor Signature Date

Bereket Gebremichael (BSc, MSc) _____

Name of co advisor Signature Date

ACKNOWLEDGEMENTS

First of all, I would like to thank Addis Ababa University, School of Nursing and Midwifery for providing the opportunity to develop this research.

I would also like to express my thanks to Wolikite University for sponsoring me.

I would also to express my deep sincerely gratitude to my advisors Habtamu Abera (Ass.Proffessor, PhD fellow) and Bereket Gebremichael (BSc, MSc) for their invaluable commitment, support and guidance during the overall process of this research development.

In addition, I also interested to give lot of thanks to pediatrics and child health nursing staffs of Addis Ababa University for their kindness and valuable helps during title selection.

My heartfelt gratitude also goes to, chronic HIV care coordinators of Debremarkos referral hospital and Felegehiwot referral hospital for providing me necessary information

I would also interested to thanks to data collectors and supervisors for helping me a lot.

Last but not least, I would like to thank Mr. Animut Alebel (BSc, MSc) who has helped me a lot through his critical comments in the course of this paper

ABBREVIATIONS AND ACRONYMS

AIDS	Acquired immune deficiency syndrome
ART	Anti-retroviral therapy
ARV	Antiretroviral
CD4	Cluster of differentiation 4 cells, type of T lymphocytes
CD4%	Percentage of cluster of differentiation 4 cells
EFMOH	Ethiopian federal ministry of health
HAART	Highly Active Antiretroviral Therapy
HAZ	Height for age Z score
HIV	Human immune deficiency virus
Hgb	Hemoglobin
IRIS	Immune Reconstitution Inflammatory Syndrome
LTFU	Lost to follow up
OI	Opportunistic infections
SD	Standard deviation
UNAIDS	United Nations Program on HIV/AIDS
W/A	Weight for Age
WAZ	Weight for Age z score
WHO	World health organization

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Globally, 36.7 million people were living with HIV up to midd-2017 of which 2.1 million were children less than 15 years. Antiretroviral therapy is introduced to maintain maximal suppression of viral replication, to restore immune function, to reduce HIV-related morbidity and mortality and to prolong survival. However, effectiveness of highly active ART could vary from region to region because of the difference in the retention of patients on antiretroviral therapy.

Objectives: The main aim of the study is to asses incidence and predictors of lost to follow up among children on antiretroviral therapy at East and West Gojjam Zone referral hospitals, 2018.

Methods: Six years of retrospective follow up study was conducted among 561 children aged less than or equal to 14 years who were newly enrolled in HIV care clinic from 1st of January 2012 to December 31, 2017 after gating ethical clearance from institutional review board of Addis Ababa University. Data was entered into and cleared using Epi-Data version 3.1 and then was exported to STATA version 14 for further statistical analysis. Kaplan Meier survival curve was used to estimate the cumulative survival time and Log rank test was used to compare the survival time between different categories of the explanatory variables. Multivariable Cox proportional hazards model was fitted to identify predictors of lost to follow up (LTFU).

Results: Out of the 561 charts reviewed, 533 children records were included in the final analysis. A total of 46 new LTFU cases were observed during the 15288 Person months follow up period. Hence, the overall incidence rate of LTFU was 3.6 per 100 person years. Baseline age <1 year (AHR; 3.7, 95% CI: 1.08, 12.68), and 1-5 years (AHR:3.86, 95% CI:1.73,8.61),OIs at baseline (AHR:2.26,95%CI:(1.08,4.71),hemoglobin level<10gm/dl(AHR:3.57,95% CI:1.54,8.24),baseline malnutrition in the form of underweight(weight for age Z score (WAZ)<-2)(AHR:5.67,95%CI :2.11,15.21)were independent predictors of LTFU occurrence.

Conclusion and Recommendation: The first 18th months of ART initiation is the time of high LTFU .Baseline age <1 year and 1-5 years, WAZ<-2, OIs at baseline, not taking cotrimoxazole preventive therapy and Hgb <10gm/dl were an independent predictor of LTFU. Hence, Special emphasis and close follow up should be given to patients in the first 18th months of ART initiation and to those children having the above predictors.

Key words: Addis Ababa, ART, Ethiopia, Incidence rate, lost to follow up,

1 INTRODUCTION

1.1 Background

Human immune deficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS), continues to the world's serious health and development challenge. Globally, 36.7 million people were living with HIV up to mid- 2017 of which 2.1 million were children less than 15 years old. In the same year, 1.8 million people become newly infected with HIV and new HIV infections among children declined by 47% from 2010 to 2016. Of all, 20.9 million (54%) people were have access to antiretroviral therapy Globally [1, 2].Since the start of the epidemic, an estimated 78 million people have become infected with HIV and 35 million people have died of AIDS-related illnesses[3].

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[4]

In 2014, the Joint United Nations Programs on HIV/AIDS (UNAIDS) outlined ambitious targets to end the HIV epidemic by ensuring that 90% of people living with HIV know their diagnosis, 90% of those diagnosed receive sustained anti-retroviral therapy (ART), and 90% on ART achieve viral suppression by 2020.To reach these targets for children, children with HIV must be identified, linked to care, receive ART, retained in care, and finally achieve sustained virologic suppression. To meet these 90-90-90 targets, the Federal ministry of health (FMOH) adopted the targeted testing approach that aims to raise the proportion of people who know their HIV status to 90% in 2020 by increasing the community demand for testing and focusing on the most at-risk populations for better yield. In line with this first 90, efforts are also underway to put 90% of people diagnosed with HIV on ART at existing ART sites with further expansion. To meet the third 90, the FMOH is working to strengthen the regional laboratory with further expansion to perform viral count for patients who are on ART[5]
In 2015, the World Health Organization (WHO) revised its guidelines and recommended initiating treatment for all people diagnosed with HIV regardless of symptoms or clinical stage. This bold recommendation means that all children diagnosed with HIV should be offered

treatment, but just 43% of children aged 0-14 years worldwide had access to treatment in mid-2017 [6]. While this was an improvement compared to 21% in 2010, more than half the children in need of treatment do not have access[1, 6]. Access to ART is particularly low for children. Under 2013 WHO treatment guidelines, 89% of HIV positive children in West and Central Africa and 63% in East and Southern Africa eligible for treatment are not accessing to ART[7].

Ethiopia is one of the countries with the highest prevalence of HIV. The government launched fee-based ART in 2003 and free-based ART in 2005, and delivered as part of the comprehensive HIV/AIDS care [8]. According to EMOH annual performance report of 2017, the number of persons requiring ART stands at 718,498 and 65,088 were Children out of which 33 % are currently receiving treatment. Amhara region is with highest number of people living with HIV (PLHIV) requiring ART (204,481) by leading Oromia (185,516) and Addis Ababa (127,619)[5]. Despite, the rapid scale up of children ART coverage in Ethiopia (from 5% in 2010 to estimated 33% in 2016),children are still twice less likely to be on ART than adults [2, 5, 9].

There is a growing concern about the increasing rates of Lost to Follow up (LTFU) in HIV programs among people who are already on treatment[10]. The effectiveness of highly-active ART could vary from region to region because of the difference in the retention of patients on ART[11].

According to World Health Organization(WHO), LTFU is an administrative classification indicating that patients did not registered as death or transfer to another facility but cease to engage in the continuum of care because of their own wishes or beliefs or because of barriers to continued access to care (due to transportation, sigma, resources, etc.) and the period definition for LTFU for the patient once on ART is 90 days after the last scheduled appointment [12].

1.2 Statement of the problem

Highly Active Antiretroviral Therapy (HAART) improves the survival and quality of life of people living with HIV [13]. Due to this, there is remarkable scale-up of pediatric antiretroviral therapy globally and has resulted in increasing numbers of infants infected with HIV surviving to adolescence and beyond[14].Despite this, significant numbers of children drop out of care at various points along the treatment pathway[15].

ART Program coverage is improving in all regions of the world including Africa region, but significant numbers of children drop out of care at various points along the treatment cascade, from HIV diagnosis to long-term retention in care. Maximizing the multiple benefits of ART requires improving the uptake of HIV testing and counselling, linking people to care, enabling them to initiate ART early and supporting adherence and retention in care[14].

Although ART has become more widely available in resource-limited settings in recent years, lost to follow-up (LTFU) is a common unfavorable outcome in ART programs. It introduces bias in estimates of mortality at the level of the treatment program, that is, mortality in all patients starting ART at a given site. Efforts to improve program retention by tracing all or a sample of patients LTFU have been introduced in some programs, and mortality in patients LTFU was found to be substantially higher than in patients retained in the programs[16, 17].

In addition, as ART coverage increases, a rise in LTFU has been observed in many ART programs in Africa and is notably worse among children. It is, therefore, a major impediment to successful implementation of HIV care and treatment programs in Sub-Saharan Africa, with an estimated 20-40% of patients being LTFU and is associated with increased risk of ART failure, morbidity, mortality and hospitalizations[18].

Furthermore, the long-term success of ART in children is critical, as they will require life-long therapy, without which HIV disease progresses more rapidly than in adults[17]. Without treatment, half will die by their second birthday and are more vulnerable to LTFU than adults because they rely on their parents or caregivers to gain access to healthcare services[19].

Different Studies also show the fact that significant number of children are LTFU.Studies done resource limited settings in Asia and Africa(90% in Africa) among <5 years of age children showed,69% LTFU occurred in the first 3 and 6 months of ART[20]. Retrospective cohort

analysis of children and adolescents in Uganda also showed that 37.61% children were LTFU and this resulted in overall LTFU of 126 per 1000 person-years[21].South African study shows differences in LTFU among children in ART programs and it ranges up to 14.2%[22].

In Ethiopia, the first time study conducted by Federal HIV/AIDS Prevention and Control office (HAPCO) from September 2003 to October 2007 on comprehensive analysis of the outcomes of HIV patients showed that,25% of the people who start HIV treatment are no longer receiving treatment after two years with large proportions of LTFU (14.5%) were during the first six months of ART and this high number of patients lost to treatment who need to be on ART is of great concern[23] and LTFU from ART treatment is reported as one of the predictors of treatment failure[24].Therefore for those on ART, uninterrupted ART and continual monitoring are essential for sustained viral suppression and optimal treatment outcomes[25].Ethiopia's national AIDS plan includes rapid scale up and decentralization of HIV care. But, high rates of LTFU particularly among young children, require urgent attention and innovative solutions to ensure that all HIV-infected children ensue lifelong benefits of the ART scale-up[26].

There are different predictors of LTFU. Some of them are the child's age, CD4 count at ART initiation, WHO stage III/IV, CD4% < 10%, WAZ $\leq$ 2,shorter duration of time on ART, hemoglobin <8 g/dl, religion of the caregiver and educational status of care giver [27-31]. Some of the reasons children are lost to follow up also include lack of caregiver contact information, stigma and counselling challenges, the burden on people to return for results, and the weak follow-up within clinics[32].

To improve health care and reduce patients' LTFU, the factors that affect LTFU of the patients on antiretroviral therapy need to be identified and taken into account[33]. The study of LTFU and other treatment outcomes in HIV care has been also used to monitor and improve program effectiveness, using patient retention as a measure of quality of care[34]. However, little is known about the time to LTFU and predictors among children after ART initiation in low resource settings including Ethiopia. Furthermore, as my review, no published data is found on similar topic in Amhara region. So, a better understanding of the predictors associated with LTFU could be helpful to design interventions to reduce LTFU and improve clinical outcome of patients who initiate ART. Consequently, the aim of this study is to describe the LTFU after ART initiation in a cohort of children attending ART and identifying its predictors.

1.3 Significance of the study

The final result of the study will be helpful for health professionals in identifying techniques to retain children on ART in the service. It will also serve as a base line data for researchers who will be interested to perform their research on lost to follow up and its predictors. It will also be helpful for health policy makers in understanding predictors and time to LTFU and in designing possible interventions to retain children in care.

2 LITERATURE REVIEW

2.1 Incidence of the lost to follow up among children on ART

Even if HIV seriously affected Sub-Saharan Africa, it is a major public health problem throughout the world. Studies have been conducted in developed as well as in developing countries to determine the incidence and predictors of loss to follow up among HIV positive children on ART. In developed countries, a study done in Thailand between 2008 and 2013 among Children who initiated ART at age<15 years, 11% were lost to follow-up, for a lost to follow-up rate of 2.9 per 100 person-years[35].

In South African study, among a total of 4,266 children, 7.6% were lost to follow-up in the first year on ART. With a total of 3832.8 child-years of follow-up, and the overall incidence of LTFU in the first 12 months was 8.4 per 100 child-years. The incidence of LTFU was highest in the first 3 months on ART with a period incidence rate of 13.6 per100 child-years. While overall incidence of LTFU in the second year on ART was 5.0 per 100 child-years[36].

In addition, different institution based retrospective cohort studies have been conducted in resource-limited settings to determine the incidence of lost to follow up among HIV positive children on ART. Of which, one comparative analysis among children in Asia and Africa, followed for a median length of 18 months ,the crude estimated 18-month LTFU rate was 23.5% in West-Africa,16.4%in East-Africa, 10.8% in Southern-Africa, 4.3% in Asia[37]. Retrospective cohort study in Nigeria with mean duration of 27.7 months follow-up time showed Loss to follow-up was 19.0% during the follow-up period, with 3.6% of patients lost within the first six months of ART initiation[27].

Another retrospective cohort study done in Uganda routinely collected between 2003 and 2012, 37.61% were LTFU and this resulted in overall LTFU incidence of 126 per 1000 person-years throughout the entire study period[21].Another study from Tanzania revealed that (34%) were LTFU giving an incidence rate of 18.2 per 100 child-years of follow up over a median follow up of 16.7 months[38]. Another cohort study done in done in Zimbabwe with observation for 5571 person years,(8.4%) individuals' LTFU, resulting in an overall LTFU rate of 4.92 per 100 person-years and median follow-up time before LTFU was 1.01 years [39].

Another retrospective cohort study done about mortality and lost to follow-up among children enrolled in Côte d'Ivoire's National Antiretroviral Therapy Program shows over 4585 person-years of follow-up, 664 children were lost through attrition; 237 children died and 427(9.3%) became LTFU and much of the documented LTFU [149 (35%) of 427 events] occurred within days 0–90 of ART[30]. Another study done in Malawi over 12 months shows infants and young people had LTFU rate of 24.7 and 19.3 per 100 person-years, respectively[40]

In Ethiopia, few institutions based retrospective cohort studies conducted to determine the incidence of lost to follow up among HIV positive children on ART. Retrospective study from an Ethiopian public hospital clinic among 383 patients(53 were children) who started second line ART, 14.3 % children met criteria for LTFU with a median follow up of 22.2 months [41]. Another retrospective cohort study done at ART clinic of Mizan-Aman general hospital among patients(6% were children) living with HIV/AIDS and attending an ART clinic between 2005 and 2013, , the cumulative incidence of LTFU was 8.8 per 1000 person-months with median follow-up of 25 months [42].Another retrospective comparison between pediatric patients managed in health center and hospital clinic, conducted in Oromia region showed that 34% of children were LTFU, with greater proportion in hospital clinic, which is 36%[43]

2.2 Predictors of lost to follow up among HIV positive children on ART

2.2.1 Baseline socio demographic predictors

Age of the child is considered as predictor of loss to follow up in different studies. Studies from Tanzania[38], Democratic Republic of Congo[29] and Nigeria[27], children age ≤2 years more likely to become LTFU than older children. Comparative analysis on Outcomes of antiretroviral therapy in children in Asia and Africa shows that age<1 year, were significantly associated with higher LTFU [37]. Another study done in Malawi national ART programs shows infants and young people had also the highest rates for LTFU over 12 months 24.7 and 19.3 per 100 person-years, respectively, while children 6 to 14 years were most likely to remain in care, followed by children aged 2–5 years[40].

In Thailand study, patients with baseline age<5 years , age 9-<12 years, and age≥12 years were at greater risk of loss to follow-up than those aged 5-<9 years at ART initiation[35].

Age 0-1 year also significantly associated with LTFU while age 1-5 years is associated with increased risk of LTFU in study done in Ethiopia [43]

Male children are more likely to be LTFU, according to study in South Africa [36].As indicated in study of Brazil, children whose caregivers had low level of education were also among the factors found to be significantly correlated with LTFU [31].

Children whose biological mother was their primary care giver had the highest risk of LTFU. Having a grandmother, other relatives or non-family care-givers as primary caregivers at baseline was significantly associated with a lower risk of LTFU[36]. Religion of the caregiver and residency are also reported as risk factor to lost to follow up in democratic Republic of Congo[29].

2.2.2 Base line Clinical and laboratory predictors

Study done in Côte d'Ivoire showed compared with children with CD4% >20% at ART initiation, children with CD4% <10% had increased risk of LTFU[30].In Democratic republic of Congo, children with a CD4 cell count≤200/μL and those with a CD4 cell count between.>200–<350/μL were likely to experience higher risk of loss to follow up compared to children with CD4 count≥350/mL[29]. Children with severe immunosuppression, were more likely to lost to follow-up than children with no suppression [27]. CD4 cell count below 350 cells/mm3 were associated with increased risk of LTFU in another study done in Ethiopia[43].

Findings also reported that children with WHO stages III and IV at base line [28],WHO stage IV at base line[37], severe anemia (hemoglobin <8 g/dl)[30, 44] had higher incidence of LTFUP. In Ethiopia, children with WHO stage IV were reported as having high risk of loss to follow up[26].

2.2.3. ART and other medication predictors

Any cotrimoxazole use in prior to ART initiation was associated with improved 2-year outcomes[45] . Comparative analysis on outcomes of antiretroviral therapy in children in Asia and Africa shows that, none nonnucleoside reverse transcriptase inhibitors(NNRTI) based ART regimen, was significantly associated with higher rate of loss-to-follow-up[37].

Duration of stay on ART also had significant associated with LTFU. Most LTFU has been reported in the immediate period after enrolment into care and treatment. Research done in

Johannesburg, South Africa, LTFU after 2 years is significantly higher compared to in the first 1 year [36].

2.2.4 Nutritional predictors

Malnutrition has been positively linked with LTFU among children. Study done in Kampala, Uganda shows Children who are less than two standard deviations (-2SD) less than the weight-for-age and weight-for-height which is one of the AIDS defining signs have been associated with LTFU [28]). Severely underweight children (WAZ <-3) were over three times more likely to become LTFU than well-nourished children([30].Sever wasting is reported significant predictor of loss to follow up in Ethiopia[43]

2.3 Conceptual framework

The following conceptual framework shows association between independent variables with dependent variable which is developed after reviewing many literatures [30, 35, 36, 38, 41-43]. According to these literatures, Socio-demographic, ART and other medications, baseline nutritional status and baseline clinical and laboratory variables affect LTFU of children in continuum of HIV care.

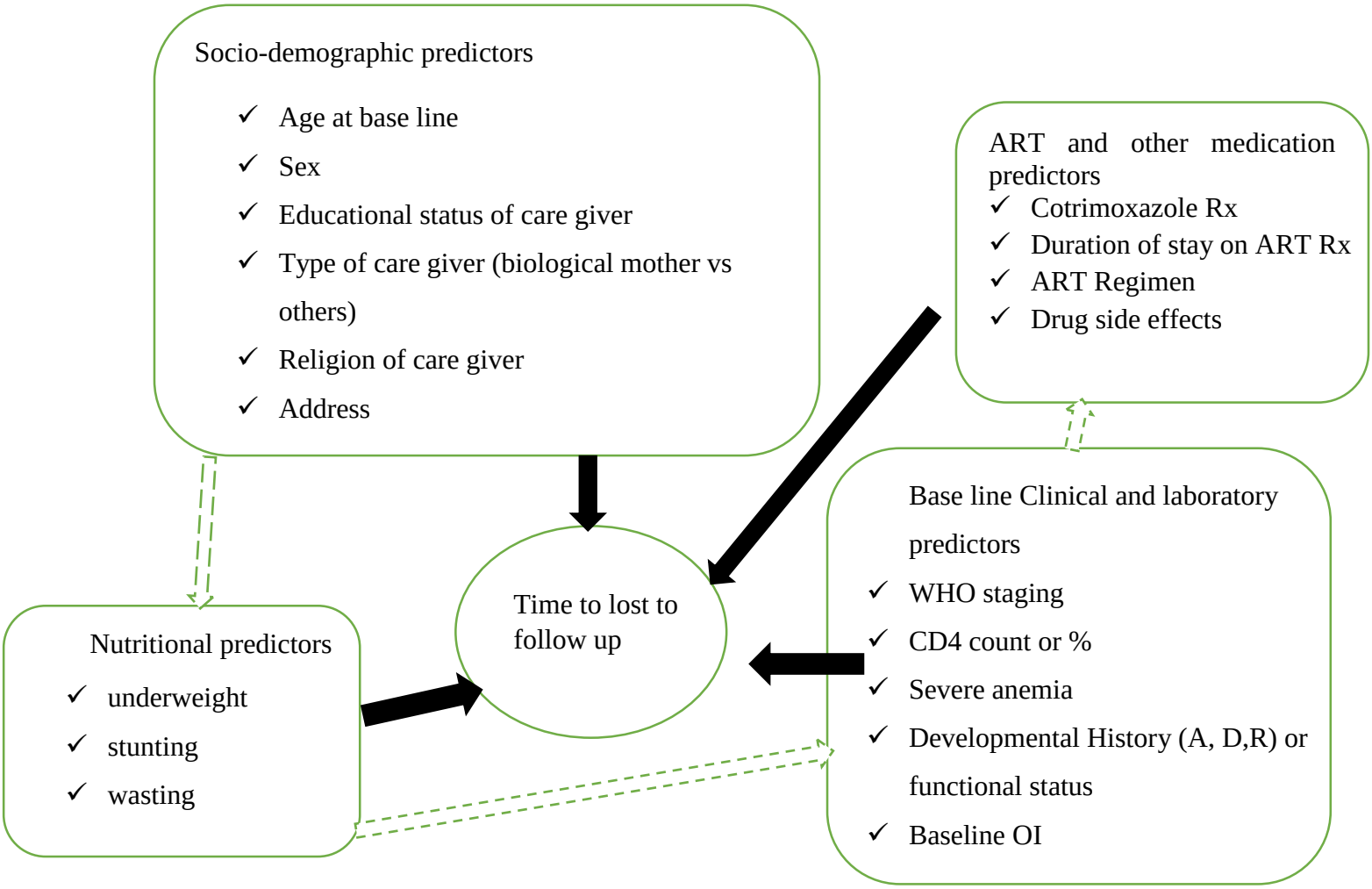

Figure 1: Conceptual framework for the incidence and predictors of lost to follow up among children on antiretroviral therapy at East and West Gojjam zone Referral Hospitals, Amhara Regional State, 2018

3 OBJECTIVES

3.1 General Objective

The main aim of the study was to assess the incidence and predictors of lost to follow up among children on antiretroviral therapy at East and West Gojjam zone referral hospitals from 2012 to 2017.

3.2 Specific Objectives

To estimate incidence rate of lost to follow up among children on ART at East and West Gojjam zone referral hospitals, 2018

To identify predictors of loss to follow up among children on ART at East and West Gojjam zone referral hospitals, 2018

4 METHODS AND MATERIALS

4.1 Study area and period

The study was conducted in the two referral hospitals (Debre Markos referral hospital and Felege Hiwot referral hospital) of East and West Gojjam zones in Amhara regional state. Debre Markos referral hospital is the only referral hospital in East Gojjam zone and found in Debre Markos, the town of East Gojjam administrative Zone. Whereas, Felege Hiwot referral hospital is the only referral in west Gojjam zone and found in Bahir Dar, the town of Amhara regional state. These hospitals are found in Northern direction 565 Kilometers and 299 Kilometers far from Addis Ababa (capital City of Ethiopia) respectively.Debre Markos referral hospital is located 256 Kilometer from Bihar Dar. According to information obtained from administrative offices of these hospitals, Debre Markos and Felege Hiwot referral hospitals serve for more than 3.5 million and 5 million population in their catchment area respectively. Apart from other services, both referral hospitals provide chronic HIV care (ART) services. Currently, 326 and 352 children had ART follow up in Debre Markos referral hospital and Felege Hiwot referral hospital respectively[46, 47].

The study period was conducted from March 1 to 30, 2018 among records of children registered from 1st of January 2012 to December 31, 2017. This period is selected in order to have a nearest six years of follow up study periods and more or less full implementation of standardized formats, documentation and recording system in regular manner will much improved in nearest years. This is critical as the study was based on secondary data and it was also important to make sure that important variables for the study should be available for enrolled subjects in the study.

4.2 Study design

A six year institution based retrospective cohort study was employed among 561 records of children who were enrolled on antiretroviral therapy at East and West Gojjam zone referral hospitals starting from 1st of January 2012 and were followed till December 31, 2017.

4.3 Population

4.3.1 Source Population

All HIV Positive medical records of children who had ART follow up from January1st, 2012 to December 31, 2017 at East and West Gojjam zone referral Hospitals.

4.3.2 Study population

The study population consists of medical records of children enrolled for ART from January1st, 2012 to December 31, 2017 at East and West Gojjam zone referral hospitals and whose chart is available during data collection time.

4.4 Inclusion and Exclusion criteria

4.3.1 Inclusion criteria

The inclusion criteria was children who are less than or equal to 14 years old and who were enrolled on ART starting from study period to end of study.

4.3.2 Exclusion criteria

The exclusion criteria was children's chart with incomplete intake forms (at least sociodemographic data and baseline predictors)

4.5 Sample Size determination and sampling procedure

For the first objective, a single population proportion formula was used to calculate the sample size by considering the following statistical assumptions.

P = proportion of LTFU among children on ART is 18%, from study done in Ethiopia [43].

Z α/2 = the corresponding Z score of 95% CI,d= Margin of error (5%) and N= Sample size

$$\mathbf{N} = \frac{(\mathbf{Z}_{\frac{\boldsymbol{\alpha}}{\mathbf{2}}})^{\mathbf{2}} \times \mathbf{p}(\mathbf{1}-\mathbf{p})}{(\mathbf{d})^{\mathbf{2}}}$$

N= $(1.96)^2$ *0.18*0.82/ $(0.05)^2$ = 227 then after adding 10 % contingency rate the final sample size was 250.

For the second objective, the sample size was determined using double population proportion formula by considering low care giver education level and WHO clinical stage I and II and as the major predictor variables based on study done in Kenya[48]in order to calculate the required sample size. Moreover, WHO clinical stage I and II is considered as independent predictor since it gives the maximum sample size (Table 1). Finally, it was calculated by using **Epi info version 7 statistical package**.

$$n_1 = \frac{\left[Z_{\alpha/2}\sqrt{\left(1+\frac{1}{r}\right)P(1-P)} + Z_{\beta}\sqrt{\frac{P_1(1-P_1)+P_2(1-P_2)}{r}}\right]^2}{(P_1-P_2)^2}$$

Table 1 : Sample size calculation to assess the incidence of LTFU and its predictors among HIV positive children on antiretroviral therapy in East and West Gojjam zone referral hospitals, Northwest Ethiopia, 2018

Variables	Assumptions	Total sample size	After adding 10%
Low care giver education level	P1=23.4% P2=13.3%	498	548 [48]
WHO clinical stage I&II	P1=18.75% P2=9.7%	510	561[48]

- ✓ **P1:** is percent of exposed with the outcome
- ✓ **P2:** is percent of non-exposed with the outcome
- ✓ **$Z_{\alpha/2}$:** is taking CI 95%,
- ✓ $Z_{B:}$80% power
- ✓ And **r** is the ratio of non-exposed to exposed 1:1
- ✓ Then the largest sample size (N= 561) was selected as the final sample size for the study.

4.5.1 Sampling procedure

The study was conducted at Debre Markos referral hospital and Felege Hiwot referral hospital. Then to select the study participants from each hospitals, the sample size was proportionally allocated. After that, medical records of children who started ART between january1st, 2012 to December 31, 2017 were isolated. From the isolated cards in each hospitals, simple random sampling technique, computer-generating method was used to select the study participants. Finally, the selected medical charts were followed for six years (Figure 2)

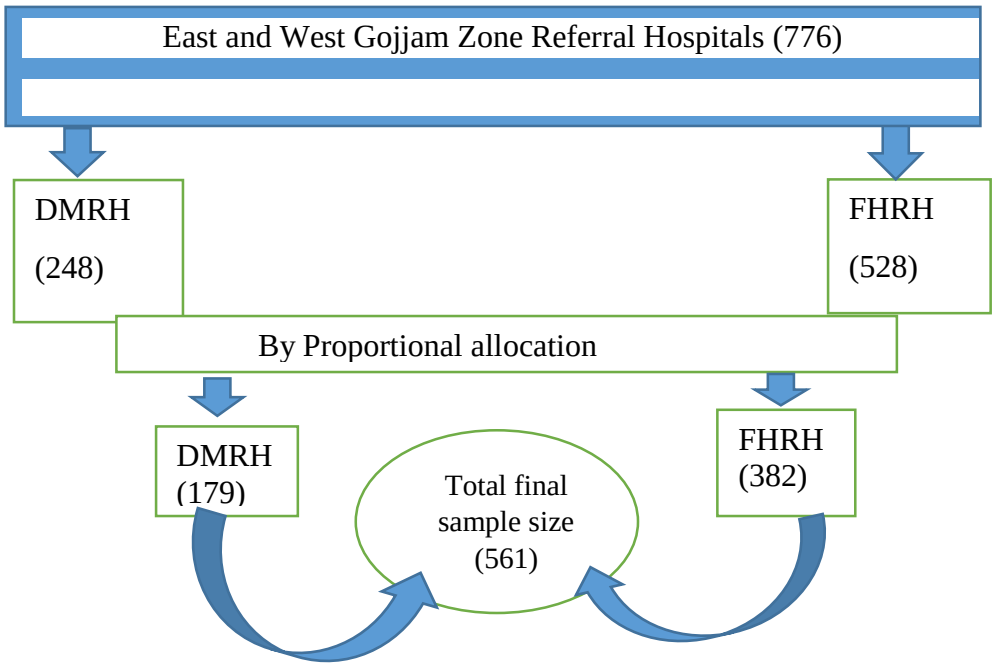

Figure 2: Schematic presentation of sampling procedure to assess the incidence of lost to follow up and its predictors among children on antiretroviral therapy in east and west Gojjam zone referral hospitals, 2018.

4.6 Study variables

4.6.1 Dependent variable

Time to lost to follow up

4.6.2 Independent variables

Socio-demographic characteristics (age at ART initiation, sex, religion of care giver, educational status of care giver, place of residence)

Base line Clinical and laboratory predictors (WHO staging, CD4 count or % at ART initiation, severe anemia, OIs, functional status).

ART and other medication predictors (provision of cotrimoxazole prophylaxis therapy (CPT), duration of stay on ART treatment, type of ART Regimen, drug side effects).

Nutritional predictors (underweight, stunting, wasting)

4.7 Operational definitions

LTFU: Was defined as no visit in the past 3 months for ART patients and not documented as dead or transferred out to another HIV clinic.

Transferred out: Those patients who were transferred to other health care facilities.

Event: LTFU of children after the initiation of ART.

Censored: Individuals who died while on ART or individuals transfer out to other health institutions after beginning of the study or individuals on ART at the end of the study were considered as censored.

Baseline CD4 count: Was taken as the CD4 cell count nearest to ART initiation, using a window of three months before ART initiation. If there is no pre-treatment laboratory test, however, results obtained within one month of ART initiation were considered as baseline values.

Duration on ART: Was defined as the time between the start date of ART and the date of last contact with the health facility.

Malnutrition: If the child has either of one Height/age< -2, or Weight/age<-2 or weight/Height <-2 standard deviation according to WHO 2006 curve

Functional status: Was described as working, ambulatory, bedridden.

Working: Go to school, do normal activities or playing.

Ambulatory: Able to perform activities of daily living.

Bedridden: Not able to perform activities of daily living.

4.8 Data collection procedures

4.8.1 Data collection tool and procedure

A data extraction tool was developed from the standardized ART entry and follow up form that is currently used by the ART clinics of the study hospitals. The patient records had been first observed and appropriate data extraction format had been prepared in English. Data collectors were used the data collection tool to collect the information from children's charts. Charts was retrieved using the children's registration number which was found in data base in the electronic

system and one data clerk in each hospitals was support them by identifying the charts. Necessary data was extracted by reviewing children's ART cards. Lost to follow up was confirmed by reviewing medical registration in the hospital, or registration by ART adherence supporter. The most recent laboratory test results before starting ART was used as a baseline value. If there is no pre-treatment laboratory test, results obtained within one month of ART initiation will be used as a baseline. When two results obtained within a month, the mean value was used.

4.8.2 Data quality control

Data about LTFU was collected from patents' charts. The data was collected by four-experienced BSC nurses (two from each hospitals) who have been trained on comprehensive HIV care and involved in the patient follow up care. Pretest was done at Finote selam hospital on 28 charts and modification of checklist was made. One supervisor in each hospital was closely supervise the entire data collection process. A one day training was given for both data collectors and supervisors in each hospital concerning the data collection tool and data collection process. Data quality was also assured by designing proper data abstraction tool and through continuous supervision. Codes ware given to checklists. All collected data was checked for completeness by data collector and supervisor every day. Consistency was examined through random selection of cards by the principal investigator and cross check for their similarity. Problems encountered during the study period was discussed with principal investigator and was solved.

4.9 Data processing and analysis

Data was entered using Epi-Data version 3.1 and analysis was done using STATA 14 statistical software. WHO AnthroPlus version 1.04 and ENA for smart software's were used to generate Z scores (WAZ, HAZ and WHZ/BIAZ) to define nutritional status. Data was cleaned and edited before analysis. Cox proportional hazard model assumption was checked using schoenfeld residual test and variables having P-value >0.05 were considered as fulfilling the assumption. Children' cohort characteristics for continuous data were described in terms of central tendency (mean or median) and dispersion (standard deviation or inter quartile range) and in frequency distribution for categorical data.

Finally, the outcome of each subject were dichotomized into censored or LTFU. The Kaplan Meier survival curve was used to estimate survival time after initiation of ART and log rank tests was used to compare survival curves. Bivariate Cox-proportional hazards regression model was fitted for each explanatory variables. Moreover, those variables having p-value ≤ 0.25 in the bivariate analysis were fitted to the multivariable Cox-proportional hazards regression model. Hazard ratio with its 95% confidence interval and p-values was used to measure strength of association and identify statistical significant result. Variables having P-value < 0.05 were considered as statistically significant association.

4.10 Ethical consideration

Ethical issues with in the study were taken into consideration when carrying out this study. Ethical clearance was obtained from institutional review board of Addis Ababa University, college of health sciences, school of nursing and midwifery. A formal letter was submitted to Debre Markos and Felege Hiwot referral hospitals and permission was assured. As this is a retrospective study, informed consent from individual patients were not requested. Since the study was done through reviewing of medical records, the individual patients may not be subjected to harm as much as the confidentiality is kept. To keep the confidentiality all collected data was coded and locked in a separate room before entered in to the computer. After entered to the computer the data was locked by password, names and unique ART numbers was not included in data collection format and the data was not disclosed to any person other than principal investigator .All information collected from patients cards were kept strictly confidential and names of patients were not included in the checklist.

4.11 Dissemination of results

The findings of this study was presented to Addis Ababa University, school of Nursing and Midwifery. In addition, it was disseminated to East and West Gojjam zone referral hospitals, Amhara regional state, Northwest Ethiopia where the study was conducted. The findings will be also attempted to be published in a journal for wider dissemination of the information.

5 RESULT

5.1 Sociodemographic characteristics of Children on ART

Among HIV positive children (age 0-14 years), who were enrolled from January 1, 2012 to December 31, 2017, 561 records were reviewed. Of these 533 (95%) of records were remaining in the final analysis while 28 (4.99%) were not included in the final analysis due to missing data from the files. Among 533 patients remaining in the final analysis, more than half 309 (57.97) of study participants were males and more than two third 376 (70.54%) of them were from urban area. The mean age of the cohort at ART initiation was 7.12 years with SD $\pm$ 3.99 years. The majority of study participants (83.11%) were living with their parents and nearly half (51.13%) of caregivers of the child were married (Table 2).

Table 2: Baseline socio-demographic characteristics of Children on ART at East &West Gojjam Zone referral hospitals, Amhara regional state, Northwest Ethiopia, 2018,(N=533)

Variables	Frequency	Percent
Sex		
male	309	57.97
Female	224	42.03
Total	533	100
Age		
<1year	17	3.19
1-5 year	156	29.27
>/=5 year	360	67.54
Total	533	100
Residence		
Urban	376	70.54
Rural	157	29.46
Total	533	100
Marital status of caregiver		
Single	87	16.35
Married	272	51.13
Divorced	88	16.54
Widowed	85	15.98
Total	533	100
Relation of Caregiver to the child		
Parent	443	83.11
Sister or brother	18	3.38
Uncle or aunt	19	3.56
Grandparent	37	6.94
Others	16	3.00
Total	533	100

5.2 Baseline clinical, laboratory and ART information of Children on ART

Two third 256 (66.79%) of the children started ART in mild WHO clinical disease stage of HIV (II or I). During the ART initiation, 124 (23.26%) of the children had opportunistic infection. Of which 57(10.69%) had pneumonia followed by tuberculosis 53(9.94%) and diarrhea 48 (9%) (Figure 5).Majority of the children 145(83.81%) had appropriate developmental status on ART initiation. Nearly two third 356(68.73 %) of the children had CD4 count or percent above the threshold for severe immunodeficiency. Three fourth 397 (74.48%) of the children have been taking cotrimoxazole preventive therapy. About 86 (16.14 %) of the child were anemic at ART initiation (Table 3).

Table 3: Baseline clinical, laboratory and ART information of Children on ART at East &West Gojjam zone referral hospitals, Amhara regional state, Northwest Ethiopia, 2018,(N=533**)**

Variables	Frequency	Percent
OI at baseline		
No	409	76.74
Yes	124	23.26
Total	533	100
Functional status for age>/= 5 years(N=360)		
Working	166	46.11
Ambulatory	183	50.83
Bedridden	11	3.05
Total	360	100
Developmental History for age <5 years(N=173)		
Appropriate	145	83.81
Delayed	25	14.45
Regressive	3	1.73
Total	173	100
CD4 count or percent		
Above the threshold	356	66.79
Below the threshold	161	30.20
Missing	16	3.00
Total	533	100
Hemoglobin level		
≥10 gm/dl	418	78.42
<10 gm/dl	86	16.14
Missing	29	5.44
Total	533	100
ART eligibility criteria		
CD4<350	169	31.71
WHO stage II and III with TLC<1200	182	34.15
WHO stage IV	37	6.94
Without criteria	145	27.20
Total	533	100
Cotrimoxazole preventive therapy		
Yes	397	74.48
No	136	25.52
Total	533	100
Side effect during follow up		
Yes	67	12.57
No	466	87.43
Total	533	100

Regarding baseline WHO clinical staging of HIV, 222 (41.65%) of children were WHO stage II while only 42(7.88%) were WHO stage IV (Figure 3)

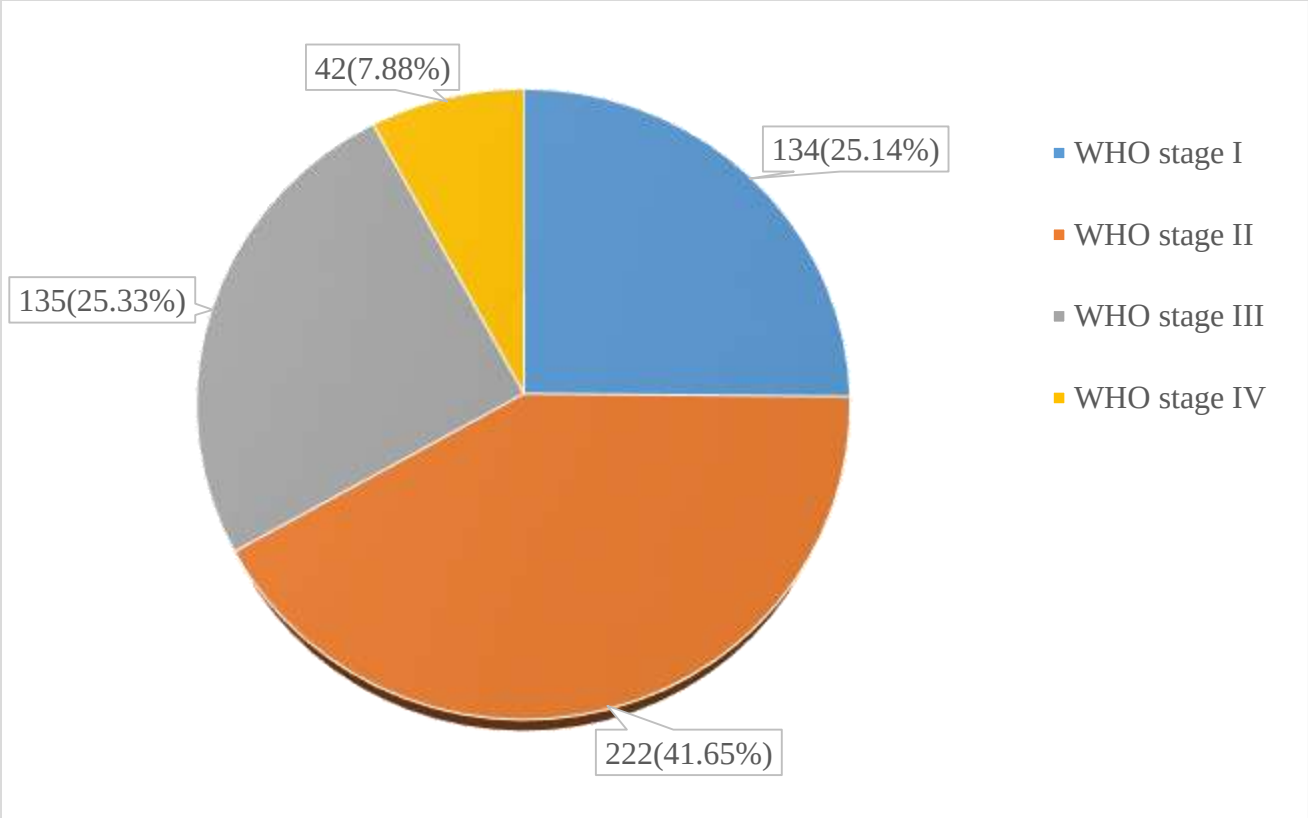

Figure 3 : Baseline WHO clinical staging of HIV positive children on ART in East &West Gojjam zone referral hospitals, Amhara regional state, Northwest Ethiopia, 2018

Regarding baseline ART regimen given for HIV positive children, 151(28.33%) of children have taken a drug of 4c (AZT-3TC-NVP) followed by 114(21.39%) of children have taken a drug of 4d (AZT-3TC-EFV). (Figure 4)

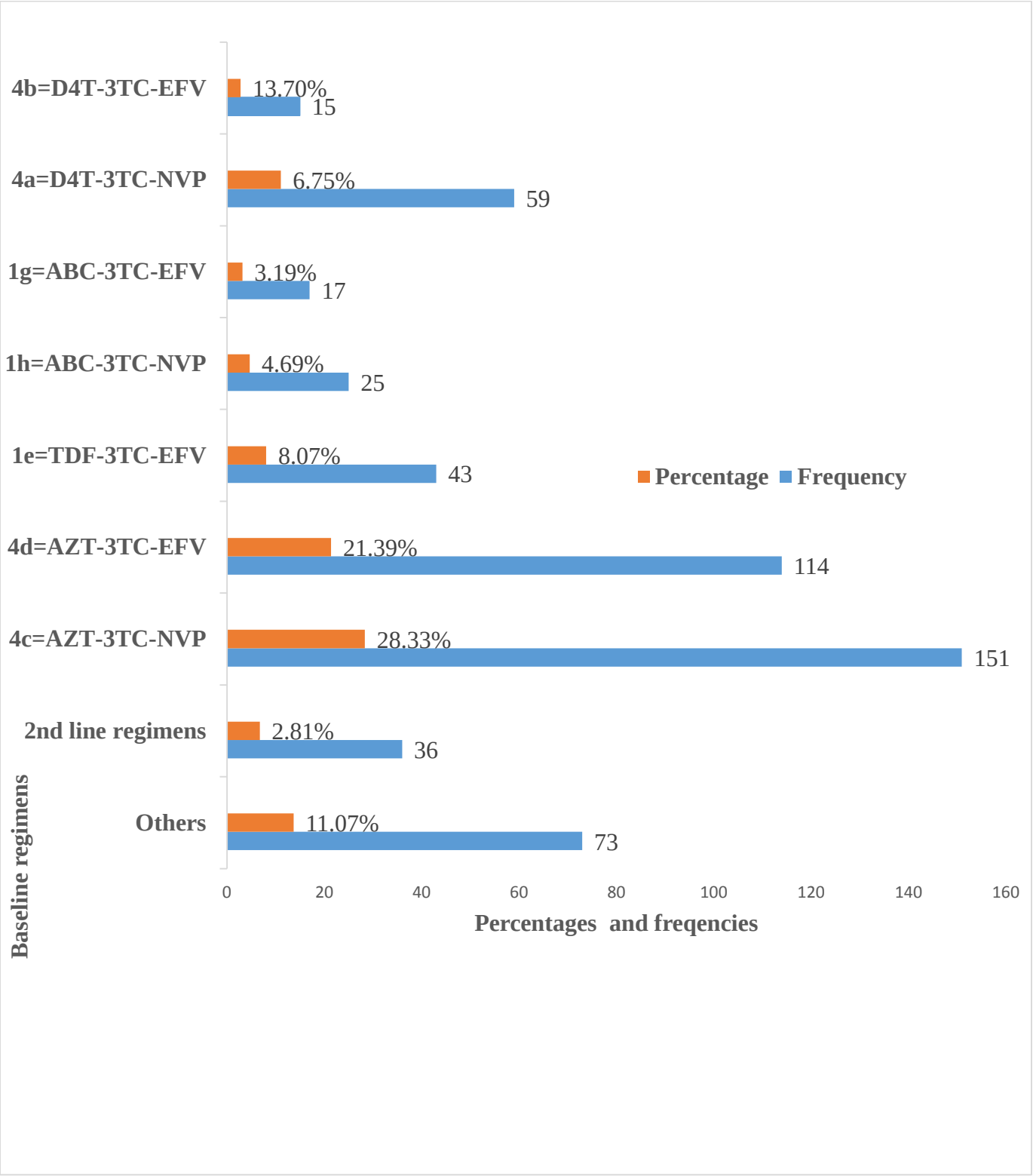

Figure 4:Baseline ART regimen given for HIV positive children on ART at East &West Gojjam zone referral hospitals Amhara regional state, Northwest Ethiopia, 2018

Regarding baseline opportunistic infection, 57(10.69%) had pneumonia followed by 53(9.94%) Tuberculosis and 48(9%) had Diarrhea (Figure 5).

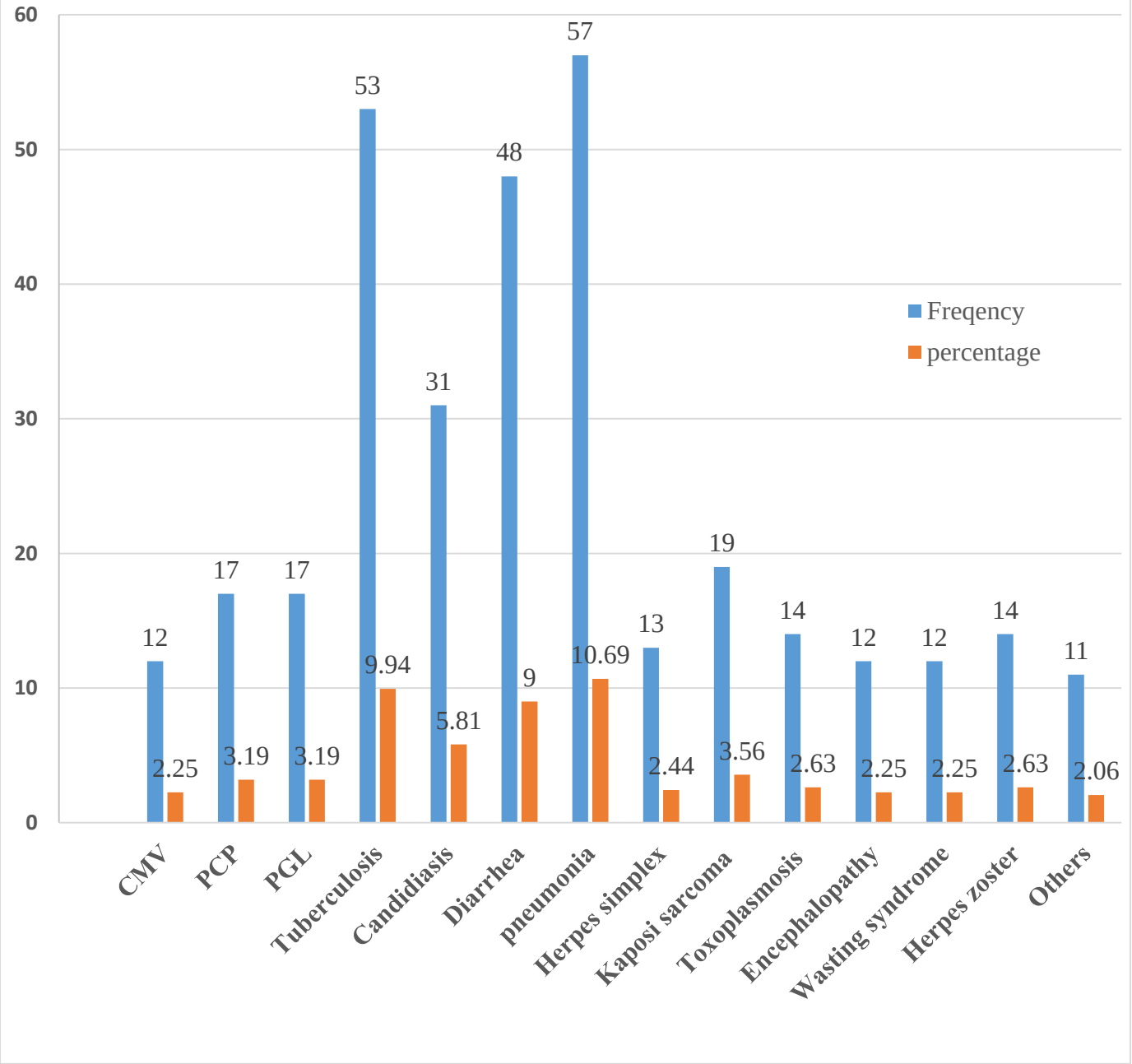

Figure 5: Baseline opportunistic infection of HIV positive children on ART at East &West Gojjam zone referral hospitals Amhara regional state, Northwest Ethiopia, 2018

5.3 Nutritional information of Children on ART

Regarding to the nutritional status of the child, (6.38 %), (5.44 %) and (4.88 %) of children have sever wasting, Stunting and underweight respectively (Table 4).

Table 4 : Baseline nutritional information of Children on ART at East &West Gojjam zone referral hospitals, Amhara regional state, Northwest Ethiopia, 2018,(N=533)

Variables	Frequency	Percent
Wasting		
Normal	471	88.37
Moderate wasting	28	5.25
Sever wasting	34	6.38
Stunting		
Normal	455	85.37
Moderate stunting	49	9.19
Sever stunting	29	5.44
Underweight		
Normal	454	85.18
Moderate underweight	53	9.94
Sever underweight	26	4.88

5.3 Incidence of lost to follow up after initiation of ART

With a median follow up time of 29 months with IQR (42-11 months) from the 533 cohort of children on ART, 356(66.79%) were alive, 46 (8.63 %) were lost to follow up, 40 (7.5 %) were died and 91 (17.07%) were transferred out. Lost to follow up incidence rate was calculated using Person-months of follow up as a denominator for the entire cohort. Five hundred thirty-three study participants were followed for different periods for maximum of six years and gives 15, 288 person-months observation. Within the follow up period, 46 new lost to follow cases were observed. Hence, the overall lost to follow up incidence density rate (IDR) in the cohort was 0.3 per 100 child-months observation (3.6 per 100-child years observation). Regarding the time of lost

to follow up 3 (6.52 %) 10 (21.73%), 21 (45.65%) and 29 (63.04%) of LTFU occurred within the first three, six, twelve and eighteen months of ART initiation respectively. The cumulative probabilities of survival at 3, 6, 12, 24 and 72 months of ART initiation were found to be 0.976, 0.964, 0.953, 0.948 and 0.882 respectively(Figure 6). The mean survival time of the entire cohort was found to be 65.10 months with (95% CI: 63.25-66.99 months).

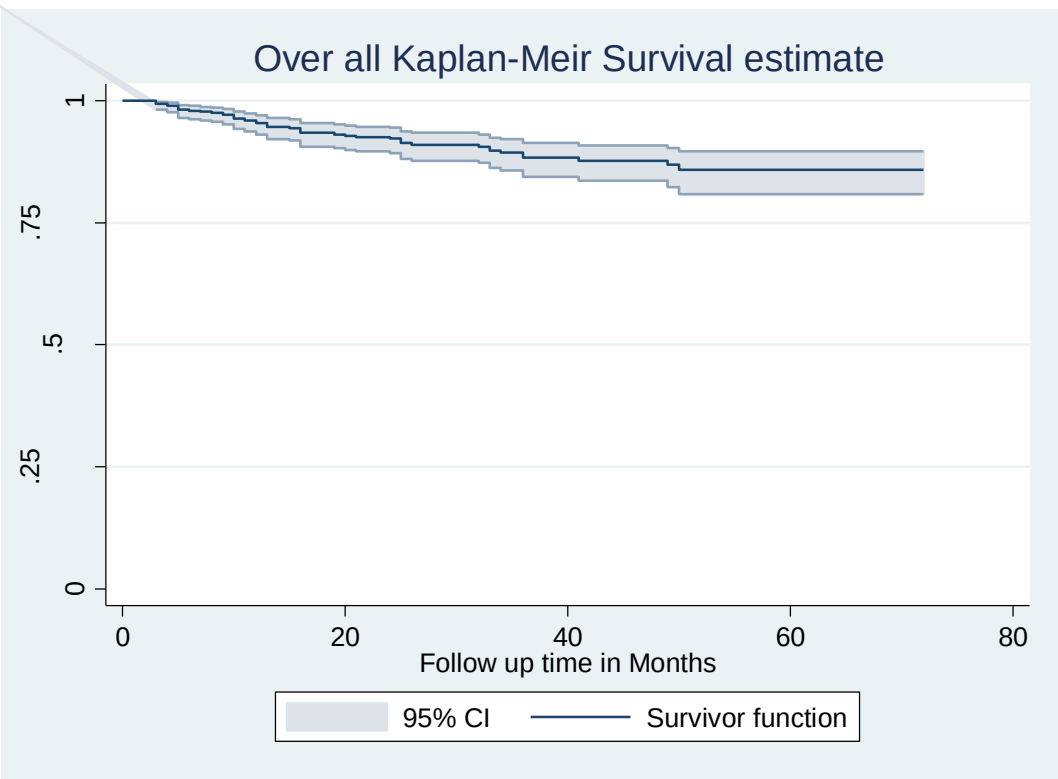

Figure 6: The overall Kaplan-Meier survival curve with 95% confidence intervals of children on ART at East &West gojjam zone referral hospitals Amhara regional state, Northern Ethiopia, 2018

5.4 Predictors of Lost to follow up

To test equality of survival curves of different categorical explanatory variables, Cochran-Mantel Haenszel Log rank test was performed. The test statistics showed that there is a significant difference in survival function for different categorical variables. These variables include: hemoglobin count (< 10 gm/dl and >= 10 gm/dl), those who are taking cotrimoxazole preventive therapy and those who did not take and having OI at baseline and did not have OI at baseline.

In this historical cohort those study participants who had a low hemoglobin level (<10gm/dl) have lower survival time as compared to those who had a high hemoglobin level (>=10gm/dl). The mean survival time for those having a low hemoglobin level was 46.72 months with SD ± 3.57 months and the mean survival time for those having hemoglobin level >= 10gm/dl was 67.6 months with SD ± 0.87 months. The survival time difference between the groups was found statically significant with P-value < 0.001(Figure below)

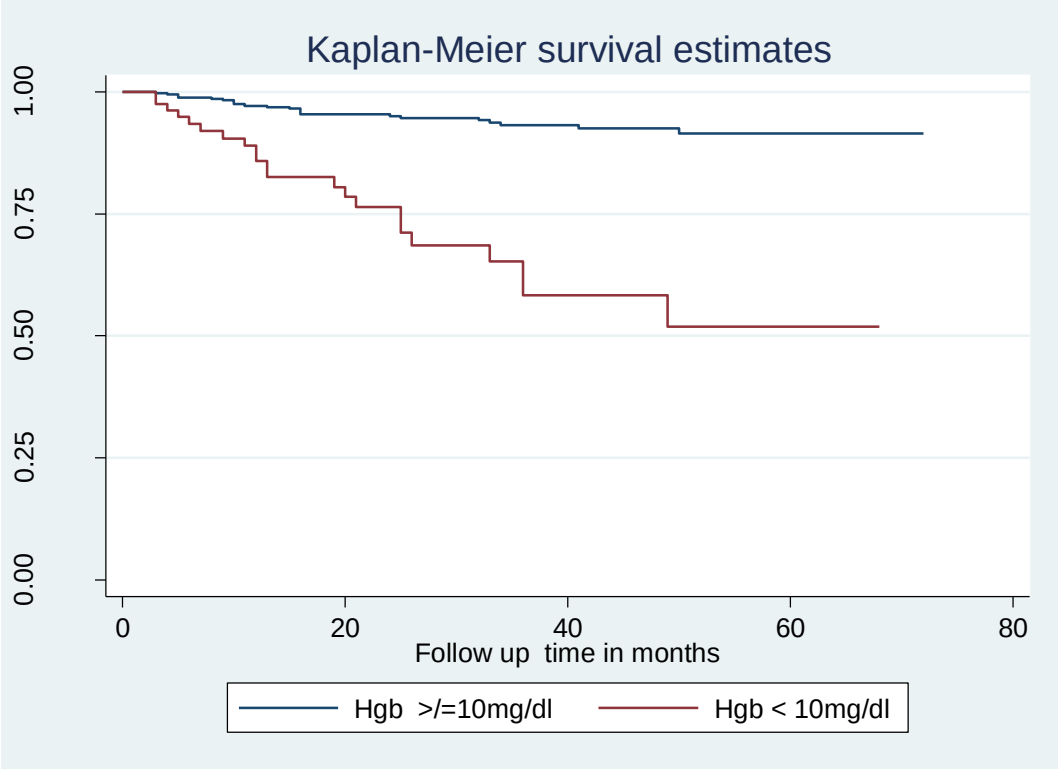

Figure 7: Kaplan-Meier survival estimate of lost to follow up free survival proportion based on baseline hemoglobin cell count at enrolment at East &West gojjam zone referral hospitals, 2018

The mean survival time for those who have been taking cotrimoxazole preventive therapy (CPT) was found to be 66.89 months with SD ± 0.96month as compared to those who were not taking cotrimoxazole preventive therapy with a mean survival time of 57.68 months with SD ± 2.51months. This difference is statistically significant with p-value= 0.003 (Figure 8)

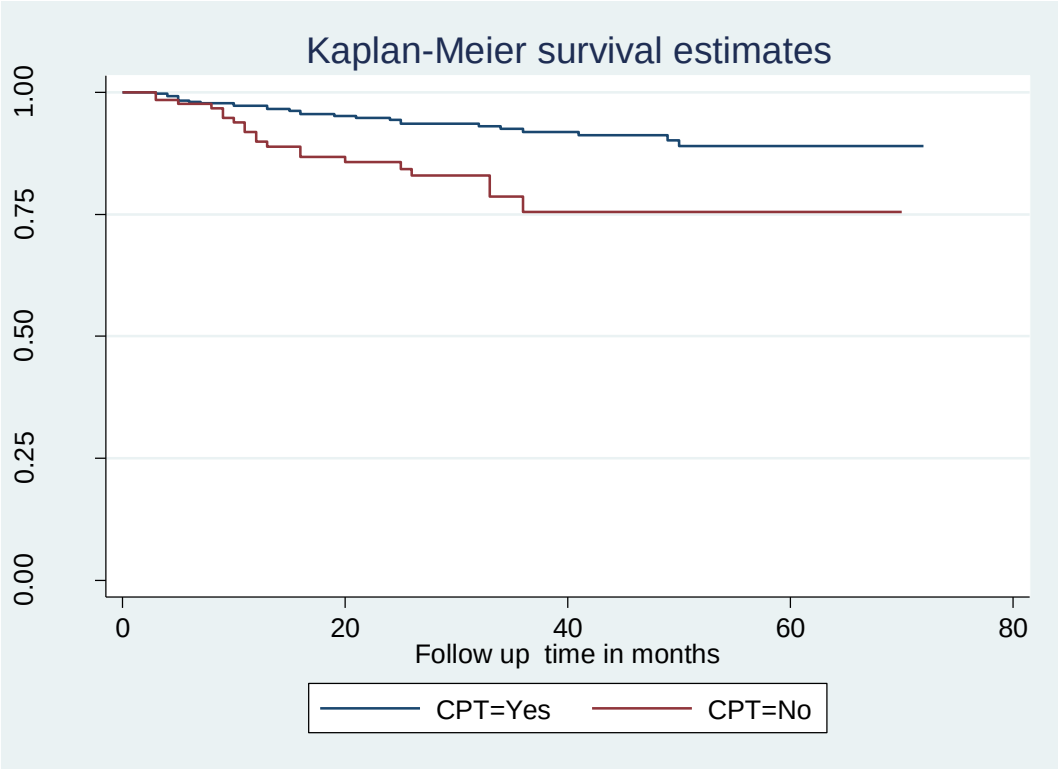

Figure 8: The Kaplan-Meier survival curves compare survival time of HIV positive children on ART with different categories of cotrimoxazole preventive therapy in East &West gojjam zone referral hospitals, Amhara regional state Northwest Ethiopia, 2018.

The mean survival time for those who had OI at baseline was 57.854 months with SD±2.58, but it was 66.58 months with SD±0.98 for those who did not have OI at baseline this difference was statistically significant with p-value < 0.0006 (Figure below)

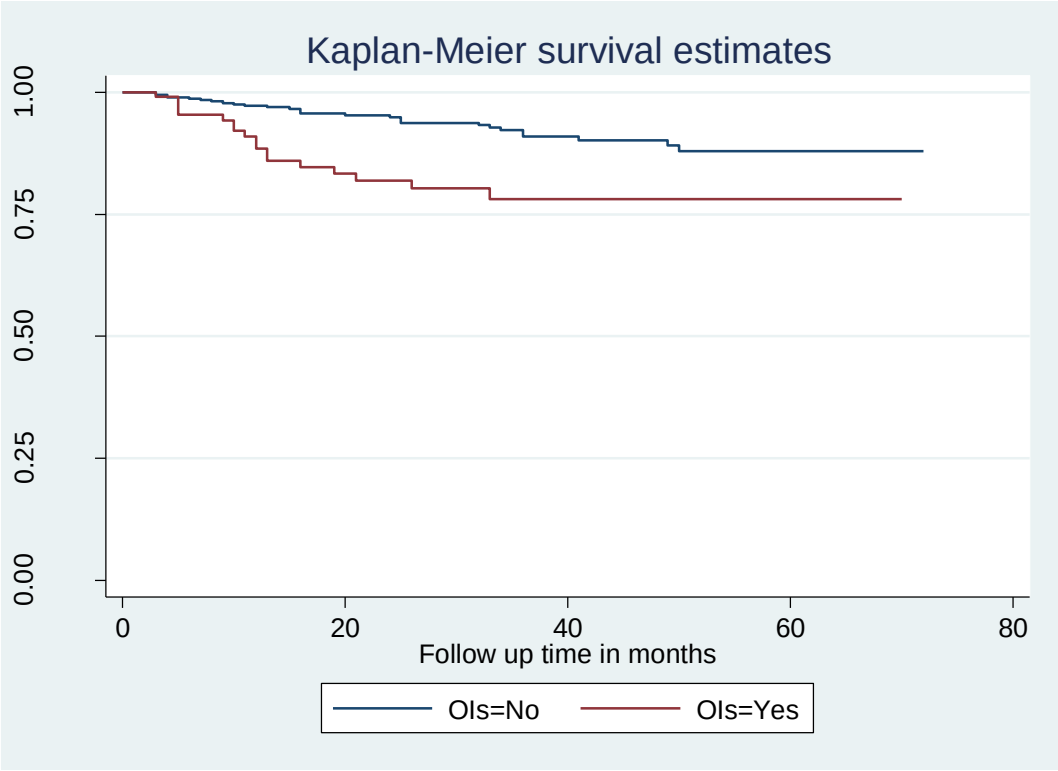

Figure 9: The Kaplan-Meier survival curves compare survival time of HIV positive children on ART with different categories of baseline opportunistic illness in East & West gojjam zone referral hospitals, Amhara regional state, Northwest Ethiopia, 2018.

The relationship between the baseline variables and the risk of LTFU was analyzed using bivariate Cox proportional Hazard regression model. The result of bivariate analysis showed that, factors including being age< 1 year and 1-5 years, living in rural area, Hgb level <10 mg/dl, presence of opportunistic infections at base line, not taking cotrimoxaxole prophylaxis, being WHO clinical stage of HIV (III&IV), being underweight (moderate and severe), stunting (moderate and severe) and wasting (moderate and severe) were found to be the predictors of LTFU. However, other Socio demographic, clinical and laboratory variables were not found to be the predictors of LTFU, as a result they were not fitted to multivariate analysis. In multivariate Cox proportional hazard adjusted model, five factors were the predictor's of lost to follow up. The result of multivariate analysis revealed that children who have age <1 year were 3.7 times more likely to LTFU than those age >/= 5 years (AHR;3.7, 95% CI: 1.08,12.68) .Children who have age 1-5 years were also 3.86 times more likely to LTFU as compared to children with age>/= 5 years(AHR:3.86, 95%

CI:1.73 ,8.61).Children who had opportunistic infections(OIs) at baseline at baseline were 2.26 times more likely to LTFU as compared to those who did not have OI at baseline (AHR:2.26,95% CI:(1.08, 4.71). Children having a hemoglobin level less than 10 gm/dl were 3.57 times more likely LTFU as compared to those having hemoglobin level greater than or equal to 10 gm/dl (AHR: 3.57, 95% CI: (1.54,8.24. Furthermore, children who are underweight (Moderate & severe) were 5.67 times more likely to LTFU as compared to those who are normal (A HR: 5.67, 95% CI: 2.11, 15.21) (Table 5)

Table 5: Cox regression analysis of predictors of lost to follow up among children on ART at East and West Gojjam zone referral hospitals, Amhara regional state, North West Ethiopia, 2018.

Variables	Survival status		CHR (95%CI)	AHR (95%CI)	p-value
	Censored N (%)	LTFU N (%)			
Age					
<1yer	13(2.43)	4 (0.75)	4.28(1.48 , 12.37)	**3.70(1.08,12.68)**	**0.037**
1-5 year	138 (25.89)	18 (3.37)	1.95 (1.06 3.60)	**3.86(1.73 ,8.61)**	**0.001**
>=5 year	336 (63.03)	24(4.5)	1	1	
Residence					
Urban	336 (63.03)	40 (7.5)	1	1	
Rural	151(28.33)	6 (1.12)	0.36(0.15, 1.87)	0.45 (0.18, 1.09)	0.077
OI at baseline					
Yes	106 (19.88)	18 (3.37)	2.72 (1.50,4.92)	**2.26(1.08, 4.71)**	**0.030**
No	381 (53.53)	28 (5.25)	1	1	
Taking CPT					
Yes	371(69.6)	26(4.87)	**1**	**1**	
No	116(21.76)	20(3.75)	2.78(1.54,5.01)	**2.72(1.24,5.97)**	**0.012**
WHO clinical staging					
Stage I&II	335(62.85)	21 (3.94)	1	1	
Stage III&IV	152(28.51)	25 (4.69)	2.63 (1.47, 4.71)	0.76 (0.33, 1.74)	0.526
Hemoglobin level					
<10 gm/dl	64(12.01)	22 (2.79)	6.28 (3.49 11.31)	**3.57 (1.54,8.24)**	**0.003**
≥10 gm/dl	395(74.10)	23 (4.28)	1	1	
Missing	28(5.25)	1(0.18)	0.61(0.08,4.54**)**	0.47(0.61,3.59)	0.469
Weight for height					
Normal	445(83.48)	26 (4.87)	1		
Wasting	42 (7087)	20(3.75)	6.24 (3.48,11.19)	1.37 (0.63, 2.94)	0.417
Height for age					
Normal	432 (81.05)	23(4.31)	1	1	
Stunting	55 (10.31)	23 (4.31)	7.18 (4.02, 12.8)	1.61 (0.68, 3.82)	0.277
Weight for age					
Normal	436 (81.80)	18 (3.37)	1	1	
Underweight	51(9.56)	28(5.25)	13.9(7.66,25.25)	**5.67(2.11,15.21)**	**0.001**

Significantly associated predictors are shown with bold.

CHR: Crude Hazard Ratio; **AHR**: Adjusted Hazard Ratio; **CI**: Confidence Interval

P-value is from Cox-regression model adjusted for all predictors in the final model

6 DISCUSSION

In this historical cohort study, the aim is to determine the incidence of lost to follow up (LTFU) and its predictors among HIV positive children on ART. At the end of six years of follow up, 46 (8.63 %) were LTFU, 40 (7.5 %) were died and 91 (17.07%) were transferred out to other health facility and about 356 (66.79%) were alive. In this study, the overall incidence of LTFU was found to 0.3 per 100 child-months observation (3.6 per 100-child year's observation) and cumulative incidence was 8.63%.

Regarding cumulative incidence, this finding is consistent with studies done in South African[36] which was (7.6%), in Zimbabwe [39] which was 8.4%, Côte d'Ivoire[30] which was 9.3%. However, this finding is lower than the study done in Ethiopia [43] which was 34%, in Thailand [35]which was 11%, in Uganda [21] which was 37.61% and in Tanzania [38]which was 34%. To the contrary, this finding is much higher than the study done in Asia [37]which was 4.3%.

Regarding the overall incidence rate of LTFU, it was found to be 3.6 per 100-child year's observation. This finding is in line with the study done in South African [36]which was 5.0 per 100 child-years and in Zimbabwe([39] which was 4.92 per 100 person-year. Whereas this finding is much lower than previous studies including study done in in Uganda [21] which was 12.6 per 100 person-years and in Tanzania [38] which was 18.2 per 100 child-years observation. On the contrary, this finding showed higher incidence density rate as compared with previous study done in Thailand [35]which was 2.9 per 100 person-years.

This gap might be due to different reasons. One possible reason for variation in overall incidence rate of LTFU might be difference in sample size. For example, the study in Zimbabwe (N=2273), in Tanzania (N=6236) and in Thailand (N=4618 from 497 hospitals). Another possible explanation is that some studies include pre ART patients (has tendency to have high incidence rate) in their study. For example, study in Tanzania includes pre Art patients. The other possible explanation might be the characteristics of the population included under our follow up. In this study, the majority of the study participants initiated ART at WHO clinical stage (I&II). It is well known that those children who were initiated ART at early phase had a longer retention time as compared to their counterparts. Additional, possible explanation might be the difference in the study period as

there are changes in treatment and care of children on ART through time given that the studies in Uganda, Thailand and Tanzania were conducted 6 years, 5 years and 7 years ago respectively.

Concerning the time of LTFU, 10(21.74%), 21(45.65%) and 29 (63.04%) of the LTFU occurred within the first 3rd, 12th and 18th months of ART initiation respectively. In this study, LTFU before 18 months after ART initiation was higher than LTFU 18 months after ART initiation with an incidence rate of 2.28 per 100 child-years observation and 1.32 per 100 child year's observation respectively. The result of this study is congruent with the study done in South Africa, which showed that LTFU before 18 months after ART initiation was higher than LTFU 18 months after ART initiation[36]. Similarly, the result is consistent with other studies which have been conducted in Nigeria which showed most of the LTFU occurred in the first 6 months following ART initiation[27]and in cot'divor which showed most of the LTFU occurred in the first 3 months following ART initiation[30].This high LTFU at early ART initiation in this study may be attributed to the fact that immune reconstitution inflammatory syndrome (IRIS) occurred in the early initiation of HAART.

Baseline age was found to be a significant predictor of LTFU among HIV positive children on ART. In this study those having age <1 year are 3.7 times more likely to LTFU as compared to children having age >/= 5 years. This finding is consistent with other previous studies which have been conducted in Ethiopia [43], comparative analysis done among African and Asian children [37], study in Congo [29], Nigeria [27] and Malawi [40]. Children with age 1-5 years also 3.86 times more likely to LTFU as compared to children having age >/= 5 years. This finding is also consistent with other previous studies which have been conducted in Ethiopia [43]. Similarly this study supported by study done in Thailand [35].This reduced probability of remaining in care for the youngest children may reflect that the significant number of young children LTFU reflects the high mortality rate (may lead to unregistered death) among children in this age group. This is largely because children starting ART before 2 years of age are more likely to have rapid disease progression[49] . The fact that age below 1 year was identified as a predictor for LTFU in our population suggests that several children LTFU may have died. Mortality was found to be the cause of LTFU among 40% of adult patients on ART in southern Ethiopia[50].

Presence of opportunistic infection at the time of ART initiation was found to be another important predictor of LTFU. Accordingly, children who have an opportunistic infection at ART initiation

are 2.26 times more likely to LTFU as compared to those who did not have an opportunistic infection on ART initiation. This finding is supported by a study done among children receiving ART in Tanzania, which demonstrated that diarrhea(one of opportunistic infection) at enrollment was associated with an increased risk of LTFU by 20% compared to children without diarrhea[35]. This might be because opportunistic infections may increase the risk of LTFU in the first few months after initiating ART due to IRIS, a paradoxical worsening or recurrence of opportunistic infection symptoms as a result of rapid immunological recovery.

Any cotrimoxazole use in prior to ART initiation was associated with improved two year ART outcomes. In this findings, children who did not take cotrimoxazole preventive therapy are 2.72 times more likely to LTFU as compared to children who take cotrimoxazole preventive therapy. This finding is supported by study done in Mozambique [45] and in Tanzania[35].This may be because cotrimoxazole gives benefit to children in HIV care as suggested by clinical trial results that HIV-infected children benefit from continued co-trimoxazole use (protecting against both malaria and non-malarial disease), even when on ART[51]. This may be justifiable reason that children on ART benefit from cotrimoxaxole use.

Baseline hemoglobin level (10< gm/dl) was found a significant predictor of LTFU among HIV positive children on ART. In this study, those having a low hemoglobin level (<10 gm/dl) are 3.57 times more likely to LTFU as compared to those having hemoglobin level greater than or equal to 10 gm/dl. This finding is consistent with other previous studies which have been conducted in *Cote* d'Ivoire [30]. These May be because Anemia is one of the markers of advanced disease and can increase unregistered death (LTFU). Amazingly, 49.7 % of study participants have been taking the drug of 4c (AZT-3TC-EFV) or 4d (AZT-3TC-NVP) which contains AZT drug and Anemia is one of the most common complication after taking this Drug, which can further complicate continuum of care in ART.

This study also found that malnutrition in the form of underweight (moderate &severe) was also an independent predictor of LTFU. Children who are underweight (moderately or severely) at the time of ART initiation were 5.67 times more likely to lost to follow up as compared to those who were not wasted at the time of ART initiation. This finding is consistent with other previous studies that have been conducted in Ethiopia [43] and in South Africa[36]. This may be because it is well known that anthropometric parameters are associated with patients' outcomes

7 LIMITATIONS AND STRENGTHS OF THE STUDY

The potential limitations of this study is that,since the data were collected from medical records, charts were lost for some patients were not included under the study and missing values for some of the variables were inevitable. Therefore, those study subjects whose charts were not included in the study and with missing value may undermine the result if it is related with LTFU.

Despite the above potential limitations, the study has the following strengths. The study was conducted for a long follow up (six years) period which increases period of observation, and enabled to know the long term impact of chronic HIV care and highly active antiretroviral therapy on LTFU. Data were collected by nurses who have been trained in comprehensive ART care and this has an important role in the quality of data.

8 CONCLUSION

This study showed that the overall incidence rate was 3.6 per 100 child years observation. The first 18^{th} months of ART initiation is the time of high LTFU. Children who have age <1 year and age 1-5 years, baseline malnutrition in the form of underweight (WFA<-2), opportunistic infections at baseline, children who were not taking cotrimoxazole preventive therapy and anemia (Hgb <10gm/dl) were an independent predictor of LTFU among HIV positive children on ART in East and West gojjam zone referral hospitals, Amhara regional, Northwest Ethiopia.

9 RECOMMENDATION

Based on the findings of this research, the following recommendations were forwarded;

1. To governmental and nongovernmental organizations

    - Chronic HIV care clinics need to be strengthened more to develop a way to control the completeness and reliability of base line data being collected especially hemoglobin and CD4 count or percentage and to reduce LTFU further.

2. To health care providers working ART clinics of East and West Gojjam zone referral hospitals

    - Close follow-up and monitoring should be given to children who have baseline age <1 year and age 1-5 years, baseline malnutrition in the form of wasting (WFA<-2), opportunistic infections at baseline, children who were not taking cotrimoxazole preventive therapy and anemic (Hgb <10gm/dl).
    - A special emphasis and close follow up should be given to patients in the first 18^{th} months of ART initiation, since this is the time of high LTFU.

3. To researchers

    - Status of children after LTFU and further predictors for LTFU from ART needs to be studied with another strong (prospective) study design.
    - Future interventions on targeted HIV care and treatment programs will be required to increase retention of children attending ART clinics.

REFERENCES

1. UNAIDS., Fact sheet - Latest statistics on the status of the AIDS epidemic.Accessed from http://www.unaids.org/en/resources/fact-sheet. 2017.
2. UNAIDS., Countyr fact sheet/2016,Accessed from http://www.unaids.org/en/regionscountries/countries/ethiopia. 2016.
3. UNAIDS:, Endind AIDS:Progress towards the 90-90-90 targets.available from http://www.unaids.org/en/resources/documents/2017/20170720_Global_AIDS_update_2017. 2017.
4. FHAPCO, Federal Ministry of Health. Guidelines for Paediatric HIV/AIDS Care and Treatment in Ethiopia. July 2008.
5. EFMOH., Ethiopian Federal Ministry of Health,Health sector transformation plan-I, Annual performance report. 2017.
6. UNAIDS:, Fact sheet on children HIV.Retrived from http://www.unaids.org/sites/default/files/media_asset/FactSheet_Children_en.pdf. 2016.
7. WHO&UNAIDS, Access to antiretroviral therapy in Africa: status report on progress towards the 2015 targets. Geneva, Switzerland: Joint United Nations Programme on HIV. AIDS. 2013:1-12. 2013.
8. FMOH, National Comprehensive HIV Care and Treatment Training for Health care Providers unpublished report. June, 2014.
9. UNAIDS, Etiopia HIV Epidemic available from http://www.unaidsrstesa.org/wp-content/uploads/2015/05/UNAids-Profile-Ethiopia.pdf 2014.
10. Ahmed, I., et al., Predictors of loss to follow-up before HIV treatment initiation in Northwest Ethiopia: a case control study. BMC public health, 2013. **13**(1): p. 867.
11. Abebe, N., et al., Predictors of mortality among HIV positive adults on antiretroviral therapy in Debremarkos Referral Hospital, Northwest Ethiopia. Journal of AIDS and HIV Research, 2014. **6**(1): p. 19-27.
12. WHO., Retention in HIV programmes: defining the challenges and identifying solutions: meeting report, 13-15 September 2011. 2012.

13. Koye, D.N., T.A. Ayele, and B.M. Zeleke, Predictors of mortality among children on Antiretroviral Therapy at a referral hospital, Northwest Ethiopia: a retrospective follow up study. BMC Pediatr, 2012. **12**: p. 161.
14. Weiler, G., Global update on HIV treatment 2013: results, impact and opportunitiesInternational AIDS Soiety (IAS) Kuala Lumpur, Malaysia. http://www. WHO. int/hiv/events/2013/1_weiler_report_ias_v5. pdf
15. Weiler, G., Global update on HIV treatment 2013: results, impact and opportunities,International AIDS Soiety (IAS) Kuala Lumpur, Malaysia. http://www. WHO. int/hiv/events/2013/1_weiler_report_ias_v5. pdf
16. Brinkhof, M.W., et al., Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. Bulletin of the World Health Organization, 2008. **86**(7): p. 559-567.
17. Brinkhof, M.W., M. Pujades-Rodriguez, and M. Egger, Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. PloS one, 2009. **4**(6): p. e5790.
18. Rosen, S., M.P. Fox, and C.J. Gill, Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. PLoS medicine, 2007. **4**(10): p. e298.
19. Avert, Information on Children HIV and AIDS,Retrieved from https://www.avert.org/professionals/hiv-social-issues/key-affected-populations/children. 2016.
20. Sauvageot, D., et al., Antiretroviral therapy outcomes in resource-limited settings for HIV-infected children< 5 years of age. Pediatrics, 2010. **125**(5): p. e1039-e1047.
21. Massavon, W., et al., Attrition and loss to follow-up among children and adolescents in a community home-based care HIV programme in Uganda. Pediat Therapeut, 2013. **3**(183): p. 2161-0665.1000183.
22. Fenner, L., et al., Early mortality and loss to follow-up in HIV-infected children starting antiretroviral therapy in Southern Africa. Journal of acquired immune deficiency syndromes (1999), 2010. **54**(5): p. 524.
23. Assefa, Y., et al., Rapid Scale-Up of Antiretroviral Treatment in Ethiopia: Successes and System-Wide Effects. PLoS Medicine, 2009. **6**(4): p. e1000056.

24. Yassin, S. and G.G. Beedemariam, Magnitude and predictors of antiretroviral treatment failure among HIV-infected children in Fiche and Kuyu hospitals, Oromia region, Ethiopia: a retrospective cohort study. Pharmacology research & perspectives, 2017. **5**(1).
25. Kalibala, S., N. Jani, and G. &Kassa, Algorithms for HIV care and treatment in Ethiopia. 2016.
26. Melaku Z, L.S.e.a., outcomes among HIV-infected children initiating HIV care and antiretroviral treatment in Ethiopia(Tropical medicine and international health, 2017. **22**(4): p. 474-84.
27. Ojikutu, B., et al., The association between quality of HIV care, loss to follow-up and mortality in pediatric and adolescent patients receiving antiretroviral therapy in Nigeria. PLoS One, 2014. **9**(7): p. e100039.
28. Massavon, W., et al., Factors determining survival and retention among HIV-infected children and adolescents in a community home-based care and a facility-based family-centred approach in Kampala, Uganda: a cohort study. Isrn aids, 2014. **2014**.
29. Ditekemena, J., et al., Antiretroviral treatment program retention among HIV-infected children in the Democratic Republic of Congo. PloS one, 2014. **9**(12): p. e113877.
30. Auld, A.F., et al., Temporal trends in mortality and loss to follow-up among children enrolled in Cote d'Ivoire's national antiretroviral therapy program. The Pediatric infectious disease journal, 2014. **33**(11): p. 1134-1140.
31. Da Cruz Gouveia, P.A. and G.A.P. da Silva, Predictors of loss to follow-up among children registered in an HIV prevention mother-to-child transmission cohort study in Pernambuco, Brazil. BMC public health, 2014. **14**(1): p. 1232.
32. UNICEF and U.W. , UNFPA. Children and AIDS: fourth stocktaking report. New York, NY: UNICEF, 2009.
33. FHAPCO., Federal Ministry of Health. Guidelines for Management of opportunistic infections and the antiretroviral treatment in adolescents and adults in Ethiopia, July 2007.Addis Ababa, Ethiopia. .
34. Assefa, Y., et al., Outcomes of antiretroviral treatment program in Ethiopia: retention of patients in care is a major challenge and varies across health facilities.BMC health services research, 2011. **11**(1): p. 81.

35. Teeraananchai, S., et al., Attrition and Mortality of Children Receiving Antiretroviral Treatment through the Universal Coverage Health Program in Thailand. The Journal of Pediatrics, 2017.
36. Sengayi, M., et al., Predictors of loss to follow-up among children in the first and second years of antiretroviral treatment in Johannesburg, South Africa. Global health action, 2013. **6**(1): p. 19248.
37. Leroy, V., et al., Outcomes of antiretroviral therapy in children in Asia and Africa: a comparative analysis of the IeDEA pediatric multiregional collaboration. Journal of acquired immune deficiency syndromes (1999), 2013. **62**(2): p. 208.
38. McCormick, N.M., et al., Implementation and Operational Research: Risk Factors of Loss to Follow-up Among HIV-Positive Pediatric Patients in Dar es Salaam, Tanzania. Journal of acquired immune deficiency syndromes (1999), 2015. **70**(3): p. e73-83.
39. Kranzer, K., et al., Loss to follow-up among children and adolescents growing up with HIV infection: age really matters. Journal of the International AIDS Society, 2017. **20**(1).
40. Weigel, R., et al., Mortality and loss to follow-up in the first year of ART: Malawi national ART programme. AIDS (London, England), 2012. **26**(3).
41. Wilhelmson, S., et al., Retention in care among HIV-positive patients initiating second-line antiretroviral therapy: a retrospective study from an Ethiopian public hospital clinic. Global health action, 2016. **9**(1): p. 29943.
42. Berheto, T.M., D.B. Haile, and S. Mohammed, Predictors of loss to follow-up in patients living with HIV/AIDS after initiation of antiretroviral therapy. North American journal of medical sciences, 2014. **6**(9): p. 453.
43. Hagströmer, O., et al., Decentralised paediatric HIV care in Ethiopia: a comparison between outcomes of patients managed in health centres and in a hospital clinic. Global health action, 2013. **6**(1): p. 22274.
44. Collaboration, K.-A.-L., Low risk of death, but substantial program attrition, in pediatric HIV treatment cohorts in Sub-Saharan Africa. JAIDS Journal of Acquired Immune Deficiency Syndromes, 2008. **49**(5): p. 523-531.
45. Vermund, S.H., et al., Poor clinical outcomes for HIV infected children on antiretroviral therapy in rural Mozambique: need for program quality improvement and community engagement. PloS one, 2014. **9**(10): p. e110116.

46. Felege Hiwot referral hospital ART clinic monthly report (2017).
47. Debre Markos referral hospital ART clinic monthly report(2017).
48. M., W., Magnitude and factors associated with loss to follow up among children attending the HIV clinic at kangundo level four hospital,Nairobi,Kenya.University of Nairobi. 2016.
49. Prendergast AJ, Penazzato M, Cotton M, et al. Treatment of young children with HIV infection: using evidence to inform policymakers. PLoS Med. 2012;9:e1001273.
50. Mulissa Z, Jerene D, Lindtjorn B. Patients present earlier and survival has improved, but pre-ART attrition is high in asix-year HIV cohort data from Ethiopia. PLoS One 2010; 5:e13268.
51. Jani IV, Sitoe NE, Alfai ER, Chongo PL, Quevedo JI, et al. Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in primary health clinics,2011: an observational cohort study. Lancet 378: 1572–1579.

ANNEX

Annex I Information Sheet

Title of the Research Project: Incidence and predictors of lost to follow up among children on antiretroviral therapy at East and West Gojjam zone referral hospitals, Amhara Regional State, 2018

Name of Investigator: Tamene Fetene (B.Sc.)

Name of the Organization: AAU

Name of the Sponsor: AAU

Introduction: This information sheet is prepared for East and West Gojjam zone referral hospitals administration and hospital HIV care clinic coordinating offices. The aim of the form is to make the above concerned offices clear about the purpose of research, data collection procedures and get permission to conduct the research.

Purpose of the Research Project: To determine Incidence and it's predictors of lost to follow up among children on ART in East and West Gojjam zone referral hospitals.

Procedure: In order to achieve the above objective, information which is necessary for the study will be taken from HIV care medical record follow up forms.

Risk and/or Discomfort: Since the study will be conducted by taking appropriate information from medical chart, it will not inflict any harm on the patients. The name or any other identifying information will not be recorded on the questionnaire and all information taken from the chart will be kept strictly confidential and in a safe place. The information retrieved will only be used for the study purpose.

Benefits: The research have no direct benefit for one whose document/ record is included in this research. But the indirect benefit of the research for the participant and other clients in the program is clear. This is because if program planners are preparing predicted plan there is a benefit for clients in the program of getting appropriate care and treatment services. Of all, the research work has a paramount direct benefit for health care planners and managers, especially for those on HIV prevention, treatment and support program planning and management.

Confidentiality: To reassure confidentiality the data on the chart will be collected by those individuals who are working on the HIV care clinic in the facility and information will be collected without the name of the clients. The information collected from this research project will be kept confidential and will be stored in a file. In addition, it will not be revealed to anyone except the principal investigator and it will be kept in key and locked system with computer password.

Person to contact: This research project will be reviewed and approved by the institutional review board of College of Medicine and Health Science, AAU. If you want to know more information, you can contact the committee through the address below. If you have any question you can contact any of the following individuals (Investigator and Advisors) and you may ask at any time you want.

1.Tamene Fetene, AAU University ,College of Medicine and Health Science, Department of Child health and pediatric Nursing: principal investigator.

Cell phone: +251-918554420

E-mail: tamenefet732@gmail.com

2. Habtamu Abera (RN, Bsc, Msc, assi.proffessor), AAU University, College of Medicine and Health Science, School of Nursing and midwifery: Main-Advisor.

Cell phone: +251-910218513

E-mail: habtamu.abera64@gmail.com

3. Bereket Gebremicheal(BSc, MSc) AAU University, College of Medicine and Health sciences , School of Nursing and midwifery: Co- Advisor.

Cell phone: +251-9 12660125, E-mail:bdpapi3@gmail.com

Annex II Checklist

This tool is prepared for the collection of socio-demographic, clinical, laboratory, treatment and outcome related information that are important for the assessment of Incidence and predictors of Lost to follow up among children on antiretroviral therapy at East and West Gojjam Zone Referral Hospitals, Amhara Regional State, 2018. All this information will be retrieved from the clients ART and pre-ART registration book and from individual patient card without mentioning the name of clients. This information will be collected by health care providers (BSc Nurses) possibly working in the ART clinic of the hospitals. **Contact information** Tamene Fetene Cell phone+251918554420, Habtamu Abera Cell phone: +251-910218513, Bereket Gebremichael Cell phone: +251-9 12660125

Data collection date----------month----------Year----------

Name of the Hospital ----------

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

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

Code no----------

Part-I Socio demographic Characteristics

No.	Socio demographic of child and caregiver	Possible answers	Skip
101	Age	(--------) years or (-------)months	
102	Sex	1. Male 2. Female	
103.	Religion care giver	1. Orthodox 2. Muslim 3. Catholic 4. Protestant 5. Others specify-----	
104.	Residence	1.Urban 2.Rural	
105.	Marital status of care giver	1. Single 2. Married 3. Divorced 4. Widowed 5. Separated	
106.	Age of care giver	(----------)years	

107.	Relation of care giver for the child	1.Parent 2.Sister/brother 3. Uncle/aunt 4. Grandparent 5. 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. 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	Functional status at baseline for age ≥ 5 years	1. Working 2. Ambulatory 3. Bedridden	
205	Developmental at baseline status for age <5 years	1. Appropriate 2. Delayed 3. Regressed	
206	WHO clinical stage at base line	1. Stage I 2. Stage II 3.Stage III, 4 .Stage IV	
207	Hgb count at base line	----------	
208	CD4 count or CD4% at base line	(---------) date----------/-------/--	
209	If CD4 count or CD4% is lower at base line when become normal?	_____months	
210	Past TB test	1. Not determined 2. Negative	

		3.possetive	
211	Past TB treatment	1.No **2**.2SRHZ/4RH 3.2HRZES/1HRZE/4HRE 4.2HRZE/4RH	
212	Past medication	1. No 2.Cotrimoxazole3. INH 4. Other specify……..	
Part- III	**ART treatment and other Medications information**		
301	ART eligibility criteria	1. CD4<350 2. WHO stage IV 3. WHO stage II and III with TLC<1200 4.No Criteria	
302	Starting date of ART	(----------/----------/---------)	
303	OI prophylaxis given	1.Not given 2. Cotrimoxazole 3. INH 4. Others specify----------	
304	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 5.1e=TDF-3TC-EFV 6 1h=ABC-3TC-NVP 7.1g=ABC-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	(---------- months)	
405	Recent CD4 count	(----------)	
406	Recent Hgb count	(----------)	

407	Opportunistic infections during follow up	1. No 2. Herpes zoster 3. Pneumonia 4. TB 5. Oral thrush 6. Diarrhea 7. Cryptococcus meningitis 8 Others specify------	
408	Cotrimoxazole preventive therapy	1.given 2.not given	
409	Recent ARV adherence	1. Good 2. Fair 3. Poor	
410	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. Depression 10. Others specify-----	
411	Drug side effect	1. No 2. Nausea 3. Diarrhea 4. Fatigue 5. Headache 6. Numbness 7. Rash 8. Anemia 9. Fat change 10. Nightmare 11. Dizziness 12.Others specify-------	
412	Does the regimen changed	1.No 2.Yes	
413	If yes, reason for regimen change	1. Toxicity/SE 2. New drug available 3. Drug out of stoke 4. Clinical failure 5. Immunologic failure 6. Virologic failure 7. New TB 8.Other specify	

414	Does the regimen stopped	1.No 2.Yes	
415	If yes reason for stopping regimen	1. Toxicity/SE 2. Treatment failure 3. Poor adherence 4. Drug out of stock 5. Other patient decision 6. Planned treatment interruption 7. Other specify----------	
416	Current status	1. Alive 2. Dead 3 .Lost follow up 4. transfer to other health facility	
417	If lost to follow up when after initiation of ART	(----------) month	
418	If dead or transfer to other facility when after initiation of ART?	(----------) month	