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Survival Time and Predictors of Death among Hiv infected Under Five Children After Initiation of anti Retro Viral Therapy in West Amhara Referral Hospitals, Northwest Ethiopia

Gebrie, Getu

BAHIR DAR UNIVERSITY

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BY GEBRIE GETU (BSc)

A RESEARCH THESIS REPORT TO BE SUBMITTED TO DEPARTMENT OF EPIDEMIOLOGY AND BIOSTATISTICS, SCHOOL OF PUBLIC HEALTH, COLLEGE OF MEDICINE AND HEALTH SCIENCES, BAHIR DAR UNIVERSITY, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN EPIDEMIOLOGY.

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Name of Investigator	Gebrie Getu (BSc) Tel: 251-918663516 Email: gebryegetu27@gmail.com
Names of Advisors	1. Mr. Anemaw Asrat (MPH, Associate professor), Department of Epidemiology and Biostatistics Academic Coordinator, Ethiopian Field Epidemiology Training Program School of Public Health College of Medicine and Health sciences Bahir Dar University Tel: 251-911751787, Email: anemawasrat@gmail.com anemawasrat@gmail.com/ Anemaw.Asrat@bdu.edu.et 2. Mr. Zelalem Mehari (MSc.,Assistant Professor of Biostatistics),Department of Epidemiologyand Biostatistics Assistant Registrar,School of Public HealthCollege of Medicine and Health Sciences Bahir Dar University Tel: 251-9111058918, Email: zelalem2011@gmail.com

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Acronyms and Abbreviations

AHR:..... Adjusted Hazard Ratio

AIDS:..... Acquired Immune Deficiency Syndrome

ART:..... Antiretroviral Therapy

ARV:..... Anti Retro Viral

AZT:**.....** Zidovudine

CD4:..... Cluster of Differentiation 4

CI:..... Confidence Interval

CPT:..... Cotrimoxazole Preventive Therapy

HAART:..... Highly Active Antiretroviral Therapy

HIV..... Human Immunodeficiency Virus

IPT:..... Isoniazid preventive Therapy

LMICs:..... Low and Middle Income Countries

MTCT:..... Mother to Child Transmission

NVP:..... Nevirapine

OIs:..... Opportunistic Infections

PLHIV:..... Patient living with Human Immunodeficiency Virus

PYO:..... Person Years Observation

SSA:..... Sub Saharan Africa

TB:..... Tuberculosis

WHO:..... World Health Organization

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ABSTRACT

Background: Acquired Immune deficiency syndrome is an infectious diseases caused by human immunodeficiency virus (HIV) which primarily targets an individual's immune system. In Ethiopia, nearly 24% of HIV-related deaths occur in children under the age of five; however studies regarding survival time of HIV-positive under five children after anti-retroviral therapy initiation are limited with poor evidence of predictors of death.

Objective: To assess survival time and predictors of death among HIV infected under five children after initiation of anti-retroviral therapy in West Amhara Referral Hospitals, Northwest Ethiopia, 2021.

Methods: A multicenter institution based retrospective follow up study was conducted in 432 HIV-positive under five children on anti-retroviral therapy selected by simple random sampling from January 2010 to December 2019. A standardized data extraction tool was employed which was adapted from anti-retroviral therapy entry and follow-up forms. The event of interest for this study is death whereas absence of experience of death is censored. Data was entered into Epi-Data version 3.1 then export to STATA version 14. Kaplan Meier curve was used to estimate the survival probability. Cox regression model was used to identify independent predictors of death.

Result:-Among 415 records included in the final analysis, 25(6.02%) of the individuals were died. The incidence rate of death was found to be 2.87 per 1000 child-months (95%CI: 1.94 - 4.25). The cumulative survival probabilities of children after 6, 12, 24, and 36 months were 0.97, 0.95, 0.92 and 0.85 respectively. HIV-infected under-five children who lived in rural area (AHR 3.32:-95% CI 1.17- 9.39), with poor adherence to anti-retroviral therapy (AHR=3.36; CI: 1.06, 10.69), without Isoniazide prophylaxis (AHR=3.15; CI: 1.11, 8.94) and with anemia (AHR: 3.05, 95% CI: 1.16, 8.03) were at higher risk of death.

Conclusion and recommendation:-Death of HIV-infected under-five children on anti-retroviral therapy is high within the first one year after enrolment. The risk of death was higher for those who are rural resident, had poor adherence, lack Isoniazide prophylaxis and present with anemia. Therefore, clinicians shall emphasize for those lived in rural area, Isoniazide prophylaxis, present with poor adherence, anemia and in early phase of anti-retroviral therapy.

Key words: Anti-Retroviral Therapy, Under-Five Children, Death, Northwest Ethiopia

1. INTRODUCTION

1.1 Background

Human Immunodeficiency Virus/Acquired Immune Deficiency Syndromes (HIV/AIDS) remains one of the leading causes of death among children under the age of five (1).AIDS is an infectious diseases caused by HIV, which primarily targets an individual's immune system (2). HIV/AIDS is a life-threatening communicable disease with poor prognosis (3). Antiretroviral Therapy (ART) is medication treatment that helps patients infected with HIV to survive longer and healthier. Survival time is the length of time persons were followed from the moment they started ART until they died, lost to follow up, or alive at the end of the follow up time (4).

HIV infection rates among children have been dramatically rising in recent years. The majority of under-five children living with HIV are infected via mother-to-child transmission (MTCT); during pregnancy, childbirth or breastfeeding. It is believed that more than 90% of all HIV infections in children are transmitted through MTCT(5).

Children and adults have different HIV natural histories and clinical presentations with children having a faster disease progression in infancy and a preference for recurring, common viral and bacterial infections over opportunistic illnesses. Undeveloped immune systems as well as the effects of viral replication and inflammation on somatic and neuro-developmental growth are blamed for the faster progression. The opportunistic infections that emerge from immunological weakness in HIV-positive children under the age of five are frequently primary infections rather than reactivation diseases resulting in higher mortality (2, 6, 7).In Ethiopia, the first case of HIV was reported in 1984. Since then, HIV/AIDS has become a major public health concern in the country, resulting millions of people have died (8).

Untreated infants infected with HIV in their first year of life have a significant mortality rate, making early HIV testing, timely result and treatment beginning critical (7). All children under the age of five who visit a health facility should be offered HIV testing and counseling. Infants born to HIV-positive mothers who are at high risk of contracting the virus should be given dual prophylaxis with Zidovudine (AZT) twice daily and Nevirapine (NVP) once daily throughout the first six weeks of life regardless of whether they are breastfed or formula fed (7).

In terms of research, no other modern infectious disease has had such a disastrous effect on the world's youngest and most fertile citizens. However, as horrific as these mortalities are, HIV/AIDS' impact does not end with the victims. Because individuals dying of AIDS are mostly people in their prime who are often parents, one of the most well-known effects of the epidemic is the large number of children orphaned by it (8).

1.2 Statement of the problem

Globally HIV is still a major public health concern, although it is particularly prevalent in low and middle-income countries (LMICs).AIDS continues to be the greatest cause of death among children(5). Worldwide under-five children mortality due to HIV/AIDS accounted for 1.4% in 2015 and over 120,000 children died due to AIDS-related illnesses in 2016, this equates to 328 deaths every day. In fact, HIV-positive children aged 0–4 years are more likely to die than HIV-positive patients of any age (9). According to studies in Africa have shown that children taking antiretroviral therapy have a short survival time (4).

Perinatally infected children have high rates of treatment failure and drug resistance, which can make long-term treatment more difficult and lead to more serious co morbidities and early mortalities (10). HIV exposure at birth has a greater impact on child morbidity and mortality especially in the first year of life and reduces children's survival (11).

Despite significant improvements to antiretroviral treatment accessibility, the death of children on ART remains a persistent problem in Sub-Saharan African (SSA) countries (12). In HIV-infected children in developing nations, the rate of disease progression and death is high(13).Children under the age of five continue to be a major health issue in SSA. HIV/AIDS is one of the main reasons for the region's relatively slowly drop in under-five mortality (14).

HIV/AIDS has taken the lives of millions of people and left hundreds of thousands of children orphaned. Ethiopia's government took a number of initiatives to prevent the disease from spreading further, as well as to improve HIV care, treatment and support for those living with HIV(7). The country has met the majority of the Millennium Development Goals (MDGs) relating to HIV/AIDS. The rate of HIV/AIDS death, on the other hand, has been slow to diminish. Between 1990 and 2016, the annualized HIV/AIDS mortality rate reduction was only 0.4%(15). HIV infection remains a major global and national health problem that requires

substantial action to achieve the Sustainable Development Goals (SDGs), which targeted to reduce HIV related death and ending HIV infections by 2030 (16).

In children, the disease progresses quickly and if treatment is not started, approximately half of affected children will die within the first year of infection. In Ethiopia, nearly 24% of HIV-related deaths occur in children under the age of five (17).

Despite better access to ART, young children continue to be at danger of dying early; innovative techniques to quickly diagnose and commence therapy are required (18). Though Highly Active Antiretroviral Therapy (HAART) has been available in Ethiopia for more than a decade, data on mortality rates of HIV-positive under five children after starting ART is limited (19).

Antiretroviral therapy is well known for reducing AIDS-related mortality while mortality has become a public health concern in Ethiopian (20).Even though visible efforts to improve HIV-infected child survival have resulted in significant reductions in mortality rates among children under the age of five, the presence of persistent and intolerably high numbers of child death indicates that more work needs to be done to address the specific survival needs of children in Ethiopia (21).

Well-organized and up-to-date information about the mortality rate of HIV-positive young children following the start of ART is highly recommended for providing appropriate treatment to HIV-positive young children (20, 22). Identifying baseline characteristics that predict mortality could help to enhance pediatric HIV care by allowing them to be modified (22).

WHO stage III or IV at the start of treatment; low body weight, severe anemia, and low CD4 cell count, type of ART treatment, cotrimoxazole prophylaxis, INH prophylaxis, gender, resource-poor locations, and poor adherence to HAART are all linked to mortality among HAART patients. This enables us to address modifiable risk factors that have been identified. However, the researcher's awareness of the availability of information on such topics in Ethiopia in under five children is limited. Under five mortality rates are a crucial output indicator for child health and well-being, as well as for social and economic development. It is a closely watched health indicator since it shows children's and communities' access to fundamental health interventions including infectious diseases medical treatment such as HIV/AIDS. Therefore, this study will be important to guide evidence based information for better treatment and prevention of HIV/AIDS

in resource-limited settings such as Northwest Ethiopia by assessing the survival time and predictors of death that have role in mortalities of HIV positive under five children after the initiation of ART.

1.3 Significance of the Study

- Results obtained from this study will potentially help health professionals for the Prevention and management of HIV/AIDS and inform a national program of research inclusive interventions. The study will also provide information for the hospitals in order to give attention for the management of HIV/AIDS and assist health facilities that provide ART services in focusing on factors that affect the treatment outcome throughout the patient's follow-up.

- It recognizes the potential impacts of HIV/AIDS on children to the national and international government and non-government service providers in Ethiopia to expand AIDS-prevention efforts and develop policies and programs to address children's HIV/AIDS-related needs. It can provide for policy makers and Nongovernmental Organizations (NGOs) with relevant information for future planning and interventions. The findings of the study can also be utilized to create and administer an effective HIV/AIDS program that focuses on key areas that can improve survival. It will also help many planners, implementers and aid organizations in the country and abroad to take evidence based actions, operating in this field to better their assistance and support, as well as offer them with extra program monitoring and evaluation tools.

- This study will also serve as a reference material for researchers for future other studies to be conducted on related topics. Finally, the findings of the study enable patients to be entertained by the best of their treatment outcomes while also improving their quality of life by raising awareness of elements that are harmful to their therapy.

2. LITERATURE REVIEW

2.1 Burden of HIV/AIDS

Globally, an estimated 37.9 [32.7–44.0] million people were living with HIV in 2018. Sub-Saharan Africa bears the brunt of the burden, accounting for over 71% of the global total(23). In Ethiopia, an estimated 722,248 people are infected with HIV. According to a 2017 CDC report, HIV/AIDS is Ethiopia's seventh leading cause of death, affecting children significantly (24).After a long period of decline, the incidence and prevalence of HIV infection among people in Ethiopia has begun to rise in recent years(25).

2.2 HAART and Estimates of Survival in under five children on ART

According to a retrospective cohort study conducted on mortality and clinical outcomes in HIV-infected children on Antiretroviral Therapy at 3 sites (Malawi, Lesotho, and Swaziland) in 2012 on ART, 4.5% of the participants were died. Of the total deaths, 77.9% occurred in the first year of treatment with a 12-month mortality rate of 3.5%. The overall mortality rate was 2.25 deaths/100 person-years (26).

According to a surveillance study conducted at all newly-diagnosed HIV-infected children ≤2 years of age in Johannesburg, South Africa in 2017, child mortality rate was found 19.5% of HIV/AIDS-positive young children (under the age of two) had died. The average death age was 9.1 months (18). According to a retrospective cohort study conducted on Morbidity and mortality in HIV-exposed under-five children from January 2009 to June 2011 at a demographic and health site in Karonga district of northern Malawi showed that Child mortality rate was found 16.6/1000 Person Years Observation (PYO) (11).

According to a retrospective cohort study conducted on time to death among HIV infected under-five children after initiation of anti-retroviral therapy and its predictors in Oromia Liyu Zone, Amhara Region, Ethiopia from 2014 to 2019, the mortality rate was found 5.59% and the incidence of death rate was 5.9 per 100 child-months and of the total deaths, 9.5% of them occurred within the first three months after initiation of HAART and 42.85% of them occurred within the first 12 months of ART initiation. In this study, the overall mean time to death among under-five children on ART was 19.7 months and the median follow up period for children under the age of five after starting ART was found 19 month. In this study, the cumulative probability

of survival of under-five children on ART after the last month of follow-up was 87.23% .The cumulative survival probabilities of children After 3, 6, 12, 24, and 36 months, were 0.99, 0.98, 0.97, 0.89, and 0.87 respectively(17).

According to an institution based retrospective cohort study conducted on Predictors of mortality among HIV exposed infants at University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia from July 2013 to December 2017 showed that the overall mortality rate of infants with HIV/AIDS was found to be 8.88 per 100 child-year (27).

2.3 Factors affecting survival

2.3.1 Socio demographic factors

Caregivers must recognize the necessity of keeping children in their care, particularly younger children. Children are often told later in life, making it difficult to convey the significance of follow-up. WHO recommends Children should be informed about the importance of follow up at an appropriate age (7).

According to a retrospective cohort study conducted on Morbidity and mortality in HIV-exposed under-five children in a rural Malawi from January 2009 to June 2011 showed that higher mortality rates were observed in children under one year compared to older age groups (11). According to the observational cohort study conducted on mortality risk factors among HIV exposed infants in rural and urban Cameroon between 2004 and 2012 showed that rural setting was not a risk factor for infant mortality (28). Another study done on Nutritional Status and Other baseline Predictors of mortality among HIV–infected Children initiating antiretroviral therapy in Tanzania Between October 2004, and December 2010,living in the rural district was risk factors for overall mortality(29).

According to a retrospective cohort study done on Predictors on mortality of human immunodeficiency virus infected children after initiation of antiretroviral treatment in Wolaita zone health facilities, Ethiopia from February, 2006 to March, 2014, living in rural area and age of children at starting of ART were predictor for survival. In this study children under the age of 18 months were more likely to die than children between 18 months to five years (22). According to an institution based retrospective cohort study conducted on Predictors of

mortality among HIV exposed infants at University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia from July 2013 to December 2017 , showed that infant mortality was found to be predicted by the death of at least one parent (27). Other institution based retrospective cohort study conducted on Survival time of human immunodeficiency virus infected children who started ART between 2008 and 2013 and who followed through April 2015 at University of Gondar Comprehensive Specialized Hospital, Gondar, Ethiopia showed that, age was linked to a higher risk of death(30).

According to a Tanzanian study on under-five mortality and maternal HIV status between 2003 and 2012 using AIDS Indicator Survey data the largest mortality risk (4.6 times greater) was seen among under-five children born to HIV-positive mothers than among under-five children born to HIV-negative mothers. One to two out of every three deaths of infants under the age of five born to HIV-positive mothers can be attributed to their mothers' HIV status, accounting for 3.7-11.3% of all under-five deaths in Tanzania. Due to prohibitive expenses, poor families were unable to obtain HIV testing and ART for their children. As a result, there were higher HIV-related deaths among children under the age of five(14).

2.3.2 Baseline clinical, laboratory and ART

HIV-positive newborns are vulnerable to a variety of opportunistic illnesses, such as pneumocystis pneumonia (PCP), tuberculosis (TB), and other bacterial infections that are associated with high death rates (7).

The retrospective cohort study conducted in Swaziland on Predictors of survival among HIV-positive children living with HIV who were initiated ART between 2004 and 2008, and followed up until 2014 who were started on ART early had a better chance of survival over time than those who were started later. Children who were nurished had 88% lower risk of dying than children who were chronically malnourished. The study show that ART pediatric services are helpful in raising HIV infected children's survival rates, and that early-initiated children have a high survival rate. Active tuberculosis (TB), malnutrition, and a delay in starting ART are still predictors of poor survival in HIV-positive children (31).

According to a retrospective cohort study conducted on Morbidity and mortality in HIV exposed under-five children in a rural Malawi from January 2009 to June 2011 showed that all-cause

morbidity rate was 337.6/1000 PYO and HIV-exposed children morbidity rate was 1.34 times higher compared to HIV-unexposed children. Integrated management of childhood illness (IMCI) pneumonia was the most common diagnosis (39.3%) in that cohort (11).

According to a surveillance study conducted at all newly-diagnosed HIV-infected children ≤2 years of age in Johannesburg, South Africa in 2017, the start of antiretroviral therapy was linked to a 71% reduction in the chance of mortality. Children with advanced HIV illness, especially those with CD4 levels below 20%, were at a higher risk of death, and WAZ-2 SD remained an independent predictor of death (18).

According to a prospective cohort study of HIV-infected treatment-naive children was conducted between September 2007 and September 2010 at the HIV clinic at Macha Hospital in rural Southern Province, Zambia showed that factors associated with mortality included, anemia and lower weight-for-age z-score at study enrollment(32).Another study done on nutritional Status and other baseline predictors of mortality among HIV–infected Children initiating antiretroviral therapy in Tanzania between October 2004, and December 2010,baseline risk factors for overall mortality included severe anemia, severe immune suppression, history of tuberculosis, opportunistic infections , living in the poorest district and advanced WHO stage(29).

A systematic review and meta-analysis conducted on mortality and its predictors among children on antiretroviral treatment in 2020 showed that the death rate of children with HIV on ART was high. lower CD4 cell count, anemia, WHO clinical staging (III/IV), and under nutrition were significantly associated with the higher mortality of children on ART while cotrimoxazole preventive therapy, on the other hand, had a significant impact on mortality reduction (20).

According to a retrospective cohort study conducted on survival time and its predictors among HIV-infected children after antiretroviral therapy in public health facilities of Arba Minch town, Gamo Gofa Zone, Southern Ethiopia from January 2009 to December 2016 showed that nutritional status, absolute CD4 count below threshold, poor antiretroviral medication adherence, isoniazid prophylaxis, and co-trimoxazole prophylaxis were all independent predictors of survival time (4). Another retrospective cohort study conducted in Wolaita zone health facilities, fair/poor adherence to ART for the first three months, as well as severely wasted children at baseline, was predictors of reduced survival. The death rate for severely malnourished children on ART was 3.77% (22).

According to a retrospective cohort study conducted on time to death among HIV infected under-five children after initiation of anti-retroviral therapy and its predictors in Oromia Liyu Zone, Amhara Region, Ethiopia on the period from January 2014 to June 2019 showed that baseline nutritional status, WHO clinical stage of the child during ART enrolment, adherence status of the child to drugs, and isoniazed (INH) prophylaxis during the child's ART enrolment were the primary factors that determined time to death of under-five children with HIV/AIDS on ART (17).

According to an institution based retrospective cohort study conducted on predictors of mortality among HIV exposed infants at University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia from July 2013 to December 2017 , Infant with death of at least one parent, growth failure (development failure), presence of sign and symptom of HIV infection (opportunistic infections) and low birth weight were found to be predictors of infant mortality (27). And also the other institution based retrospective cohort study conducted on Survival time of human immunodeficiency virus infected children who started ART between 2008 and 2013 and who followed through April 2015 in University of Gondar Comprehensive Specialized Hospital, Gondar, Ethiopia, showed that a low CD4 count at the initiation of ART, advanced WHO clinical stages, and a low hemoglobin level (less than 7gm/dl and between 7 and 8.5gm/dl) are all linked to a higher risk of death. And also HIV-infected children who were at advanced WHO clinical stage III & IV were also associated to an elevated rate of mortality (30).

Conceptual Frame Work

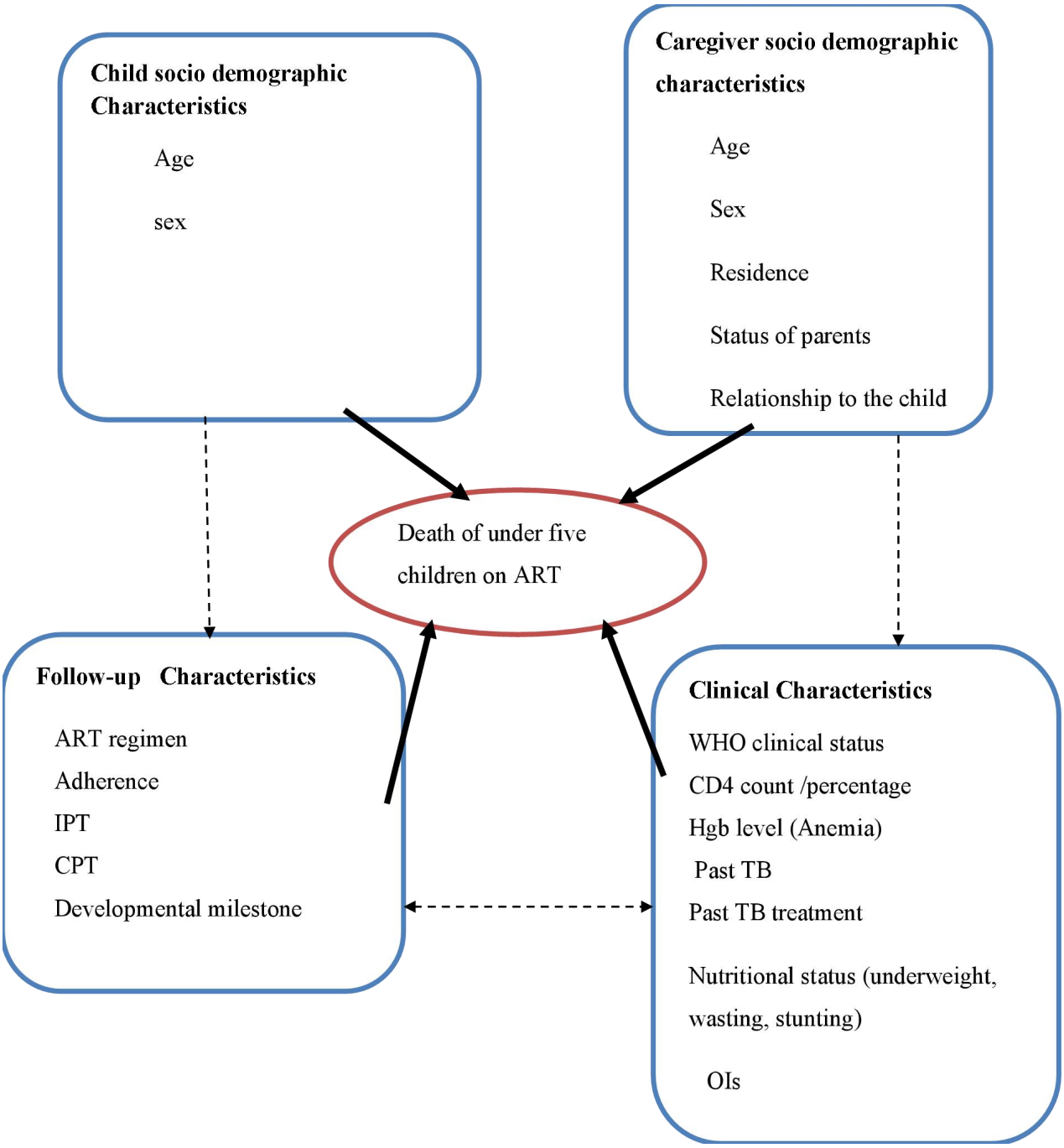


Figure 1: conceptual framework constructed after reviewing different litterateurs for survival time and predictors of death among under five Children after initiation of ART, Northwest Ethiopia, 2021.

3. OBJECTIVES

3.1. General Objective

To assess survival time and predictors of death among HIV infected under five children after initiation of anti-retroviral therapy in West Amhara Referral Hospitals, Northwest Ethiopia, 2021.

3.2. Specific Objectives

- To estimate the incidence of death rate at any time among HIV infected under five children after initiation of ART in West Amhara Referral Hospitals, Northwest Ethiopia, 2021.
- To estimate the cumulative probabilities of survival at different time points among HIV-infected under five children after initiation of anti-retroviral therapy in West Amhara Referral Hospitals, Northwest Ethiopia, 2021
- To identify predictors of death among HIV infected under five children after initiation of anti-retroviral therapy in West Amhara Referral Hospitals, Northwest Ethiopia, 2021

4. METHODS AND MATERIALS

4.1. Study design

A multicenter institution based retrospective follow up study was conducted in West Amhara Referral Hospitals, Northwest Ethiopia.

4.2. Study area and period

Institution based retrospective follow up study was conducted on under five children who initiated ART on the period from 2010 to 2019 in West Amhara Referral Hospitals ART center.

West Amhara Referral Hospitals which give ART in the follow up period were University of Gondar Comprehensive Specialized Hospital (UoGCSH), Felege Hiwot Comprehensive Specialized Referral Hospital (FHCSRH), Debre Tabor Referral Hospital (DTRH) and Debre Markos Referral Hospital (DMRH).

University of Gondar Comprehensive Specialized Hospital is located in North Gondar administrative zone, Amhara National Regional state, Ethiopia which is about 738 km Northwest of Addis Ababa (the capital city of Ethiopia). According to the 2007 population and housing census report, the total population size of Gondar town was estimated to be 206,987(33). Currently, Gondar town has one public Comprehensive Specialized Hospital, one private general hospital, five government Health Centers and more than fifty private clinics. University of Gondar Comprehensive Specialized Hospital is a teaching Hospital which serves more than five million people of the North Gondar zone and peoples of the neighboring zones. The HIV care service of the Hospital was initiated in 2005 and has 7 outpatient rooms, one voluntary testing and counseling room, one pharmacy, and one laboratory. In the clinic 2 general practitioners, 2 Health Officer, 8 BSc nurses, 2 masters nurses, 2 masters of infectious disease and HIV medicine, and 20 supportive staff that means case managers and adherence supporters are working there. Adult ART clinic, Pediatric ART clinic, VCT clinic and PMTCT clinic are the specialty clinics in the Hospital. Since 2005 in which the hospital started ART, about 285 under five children were enrolled of which 198 HIV-infected under five children were receiving active ART follow up between January 2010 to December 2019.

Debre Tabor Referral hospital is the largest hospital in South Gondar which is located 660 km far from Addis Ababa, the capital city of Ethiopia. It provides outpatient, inpatient and operation theatre department. The hospital has been provided service for a population of 2.4 million including ART services. The ART case-team in the hospital comprised trained physicians, nurses, pharmacists, laboratory technicians, data clerks and ART education adherence counselor. To date, a total of 120 HIV infected under five children commenced ART at this site of which, 92 HIV-infected under five children are receiving active ART during the follow up period.

Bahir Dar city is the administrative capital of Amhara regional state and located 565km north-west of Addis Ababa, Ethiopia's capital. According to Bahir Dar city administration plan report for 2019/2020 fiscal year, the total population of Bahir Dar town administration was 345,088 (34). Felege Hiwot Referral Hospital is found in Bahir Dar city of Amhara regional state which gives a service for Amhara region and serving over 12 million people from the surrounding area. In ART clinic 2 general practitioners, 3 Health Officer, 7 BSc nurses, 3 masters nurses, 2 masters of infectious disease and HIV medicine, and 22 supportive staff that means case managers and adherence supporters are working there. Adult ART clinic, Pediatric ART clinic, VTC clinic and PMTCT clinic are the clinics in the Hospital. To date, a total of 297 HIV infected under five children commenced ART at this site of which, about 210 HIV-infected under five children are receiving active ART follow up between January 2010 to December 2019.

Debre Markos town is located 300 km far from Addis Ababa, the capital city of Ethiopia and 265 km far from Bahir Dar, the capital city of Amhara Region. According to the 2007 national census, Debre Markos has a total population of 62,497, of whom 29,921 were men and 32,576 were women(33). Debre Markos Referral Hospital is the only referral hospital in East Gojjam Zone providing services for more than 3.5 million peoples in the zone and neighboring zones. The hospital has been providing HIV-care and ART follow-up services since 2005. Currently, the ART clinic of this hospital has one medical doctor, five nurses, three data clerks, one porter, one cleaner, five case managers, and six adherence supporters. To date, a total of 225 HIV infected under five children commenced ART at this site of which, about 148 HIV-infected under five children are receiving active ART follow up between January 2010 to December 2019.

All Referral Hospitals have antiretroviral therapy (ART), psychiatry, internal medical, gynecologic and obstetric, pediatric, radiologic, laboratory, pharmacy and ophthalmology

services. These hospitals were selected because they provide ART follow-up and care services for a large proportion of HIV-positive patients in the region. Together four hospitals provide inpatient and outpatient services for more than 20 million people living in the Amhara Region and neighboring regions.

4.3. Source and study population

All under-five children with HIV infection ever enrolled in pediatrics ART clinic and initiated ART in West Amhara Referral Hospitals providing ART services.

4.4. Sample

Under 5 years old children with HIV infection and initiated ART who were selected by computer generation method and who fulfill the inclusion criteria during data collection time.

4.5 Eligibility Criteria

4.5. 1. Inclusion criteria

All under-five HIV positive children who were enrolled in Pediatric ART Clinic from 2010 to 2019 in the study hospitals who took ART medication for at least three months were included.

4.5.2. Exclusion Criteria

Under-five children with incomplete records of age and ART initiation date during the data collection period were excluded.

4.6 Sample size determination

The sample size was calculated and the maximum sample was taken as follows.

Using the following formula for survival analysis for the first objective from previous study (17)

$$E = \frac{4\,(Z_{\alpha/2} + Z_{\beta})^2}{(ln\ HR)^2}$$

$$n = E/\ P\ (e)$$

Where: $Z\ \alpha/2 = 1.96$ which is 95% confidence level

Z_{β}: the power of this study, the value of power 85% at Z_{β} is 1.0364

E= required number of the events (death) for this study

P (e) = probability of events (death) from the previous study

HR = the least hazard ratio of the previous study which is 3.55

n = Total sample size

After this substitute each value on the formula

$$E = \frac{4(1.96+1.0364)^2}{(ln\ 3.55)^2}$$

$$E = \frac{4(8.978)}{(1.27)^2}$$

$$E = 35.9/1.6$$

$$E = 22.4 = 22$$

$$P(e) = \frac{\text{Number of death}}{\text{Total sample size}} \text{ from the previous study (17)}$$

$$P(e) = 21/376 = 0.056$$

Then $n = E/P(e)$

$$n = 22/0.056$$

$$n = 392.85 = 393$$

After adding 10% for incomplete data 39, then final sample size becomes 393+39=432

The sample size was also determined from factors in previous study by using Medcalc software for survival analysis (log rank test) by assuming: 95% confidence interval, power 85% and ratio of exposed to non- exposed (the ratio of sample size in group 1 to group 2) 1:1. Survival rate in group 1 (unexposed group) and Survival rate in group 2 (exposed group) are calculated from the previous study among the statistical significant variables (17). Baseline nutritional Status, Adherence status of the child, Baseline WHO Clinical stage and INH prophylaxis are the significant variables.

Table 1: The factors and their corresponding sample size using med calc software

No	Variables	Survival rate in group 1	Survival rate in group 2	CI	Power	Sample size for both groups	Sample size with 10% for incompleteness
1	Baseline nutritional Status	0.9899	0.6579	95%	85%	58	64
2	Adherence status of the child	0.975	0.6786	95%	85%	68	75
3	Baseline WHO Clinical stages	0.9965	0.7826	95%	85%	88	97
4	INH prophylaxis	0.9779	0.8933	95%	85%	312	343

The sample size was also calculated by using stata software version 14 with Log - rang test comparing two survival rates. The two-population proportion formula approach with the following assumptions is applied which is 95% confidence level (Z α/2= 1.96), power 85% (Zβ = 0.85) and unexposed to exposed ratio 1:1. Percent of censored (outcome) in exposed group (p1) and Percent of censored (outcome) in unexposed group (p2) are computed from the previous study among the statistical significant variables. Baseline nutritional Status, Adherence status of the child, Baseline WHO Clinical stage and INH prophylaxis are the significant variables(17).A 10% incompleteness is added to it to obtain the final sample size. Based on this information the factors and their corresponding sample size are demonstrated in the table 2 below.

Table 2: The factors and their corresponding sample size using stata SE version 14 software.

No	Variables	Survival probability in unexposed group	Survival probability in exposed group	CI	Power	Sample size for both groups with 10% withdrawals
1	Baseline nutritional Status	0.9899	0.6579	95%	85%	64
2	Adherence status of the child	0.975	0.6786	95%	85%	76
3	Baseline WHO Clinical stages	0.9965	0.7826	95%	85%	96
4	INH prophylaxis	0.9779	0.8933	95%	85%	346

Therefore the final sample size of this study is 432 because it is the largest of all.

4.7. Sampling Technique and Procedure

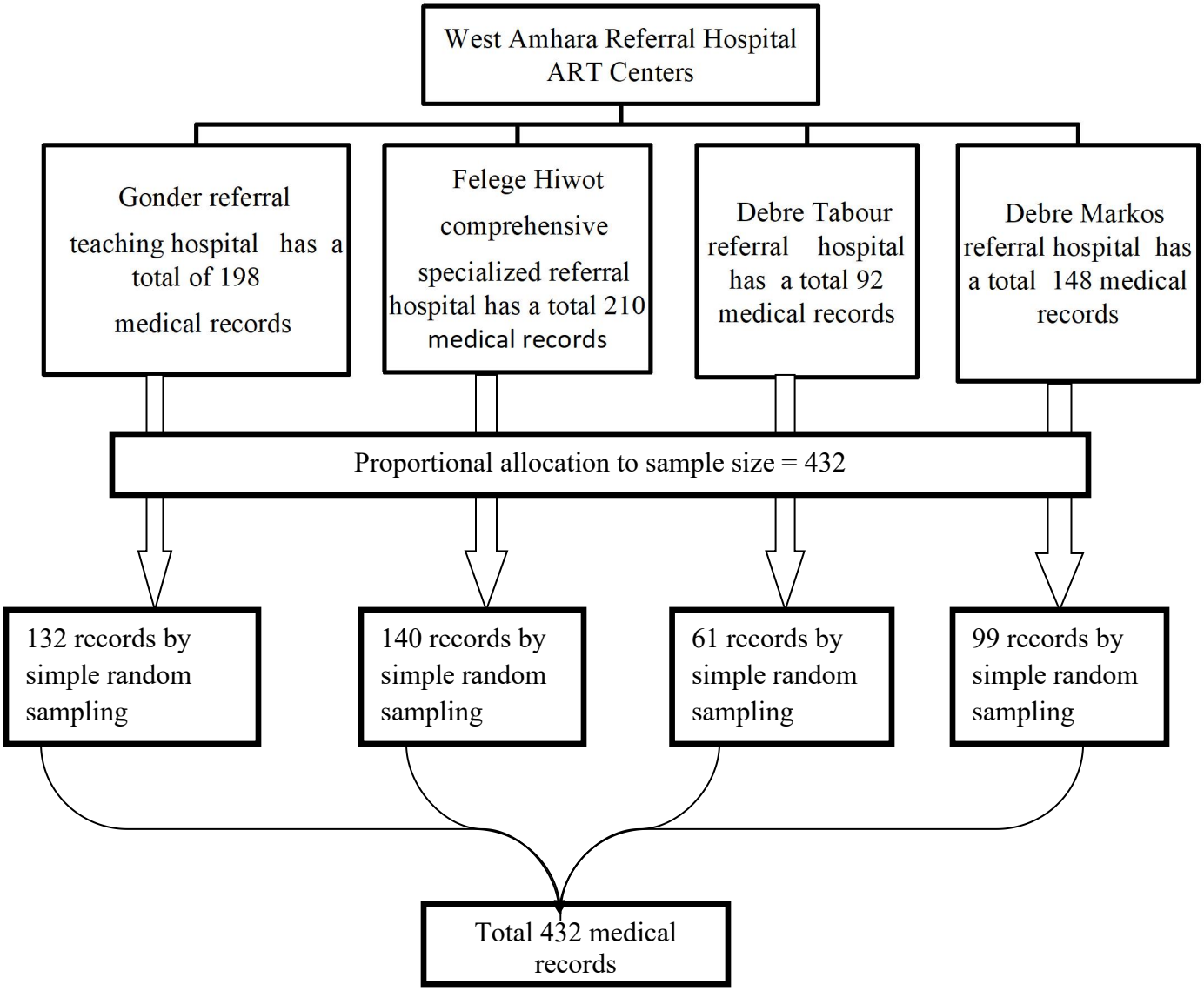
Stratified sampling technique was used to proportionally allocate samples into the four referral hospitals to their size of the population and then simple random sampling was used to select the samples from each hospitals. Sampling frame was prepared for all referral hospitals independently from patients' medical registration numbers. Patients' medical registration number was collected from Health Management Information System (HMIS) ART registration book and then entered to Micro soft excel and then copy paste into SPSS version 23. SPSS was used to generate random numbers for patients' medical registration numbers. The required folders were selected among the medical registration numbers for each institution independently.

Then the calculated sample size was allocated into the four Referral Hospitals ART centers proportional to their size of the population using the formula;

$$\text{Sample in a hospital} = \text{total sample} \times \frac{\text{Population in the hospital}}{\text{Source population}}$$

Finally, 140 medical records was taken from Felege Hiwot Comprehensive specialized Hospital, 132 medical records was taken from Gonder Referral teaching Hospital, 61 medical records was

taken from Debre Tabor Referral hospital and 99 medical records was taken from Debre Markos Referral hospital (Fig 2).



Footnote: proportion was calculated as follows: the total number of HIV-infected < 5 children on ART at a given hospital between January 2010 to December 2019 Multiplied by my calculated sample size (432), then divided by the total number of HIV-infected < 5 children started ART in the four referral hospitals between January 2010 to December 2019 (648).

Figure 2 Schematic presentation of sampling procedure to estimate survival time and predictors death among HIV-infected under five children on ART in West Amhara Referral Hospitals ART center, Northwest Ethiopia, from January, 2010 to December, 2019.

4.8 Data Collection Tool and Procedure

After reviewing some HIV-infected children charts a standardized data extraction checklist was carefully developed. Data were extracted from the document by using structured checklist those adapted and prepared based on the charts. Those under five children with HIV who initiating ART from January 2010 to December 2019 and have follow up within the selected hospitals were retrieved. The data extraction tool was prepared for the collection of socio-demographic, clinical, laboratory, treatment and outcome related information that were important for the assessment. Data were collected by four BSc nurse under the supervision of two BSc nurses. Initially, the medical charts of eligible HIV-positive under five children on ART were gathered from the card room using the patient's medical registration number. Then, basic socio-demographic, clinical, and treatment-related variables of HIV-infected under five children were extracted from those selected charts. The most recent laboratory test results and clinical findings prior to ART initiation were considered as a baseline value; however, variables like a history of treatment failure, history of regimen change, level of adherence, and history of OIs were taken on a follow-up basis. Besides, relevant patient data that was not available on the patients' chart was retrieved from the ART smart care file. Lastly, the consistency between records and collected data was confirmed by principal investigator through randomly selected reviews of previously extracted medical records.

4.9. Study Variables

4.9.1. Dependent variable

Death of the child at any time t

4.9.2. Independent variables

Sociodemographic Factors: These are - **child**:-Age and sex

Care giver: - age, sex, residence, relationship of care giver to the child and Status of parents

Baseline Clinical, laboratory and Immunological Factors : These are predictors such as WHO clinical stage, TB and its treatment, Hemoglobin level, CD4 count/percentage, ART regimen, Nutritional status (Underweight, wasting, stunting), OIs ,eligibility criteria for HAART

Follow up Clinical and Immunological Factors: Cotrimoxalzole preventive therapy (IPT) and Isoniazed Preventive Therapy (IPT), ART regimen change, treatment failure, child adherence to ART, History of OIs are independent variable of the study.

4.10. Operational Definitions

Advanced WHO clinical stages: When HIV-infected children under the age of five are enrolled in ART, their clinical stages are stage III and IV (35).

Anemia: The hemoglobin level is less than 10 gm/dl (4)

Event: The event of interest for this study is death of HIV infected under five children after initiation of ART due to HIV and its complications and opportunistic infections.

Censored: When a child is lost-to-follow-up, transferred out, or dies for reasons unrelated to the study (dies due to another cause) and lives longer than the follow up period (not died at the end of their fifth year).

Time to event: The time interval (months) between ART initiations till the occurrence of death.

Survival time: The number of months a child was followed from the moment he or she began ART until mortality, was lost to follow up, transfer out or was still being followed up on

Survival: Absence of experience of death

Follow-up period (time): The time from the beginning of the study (January 1/ 2010) to an event (death), loss to follow up, withdrawal from the study, not died at the end of their fifth year until December 31/2019 and who additionally followed through data collection time for about 20 months follow up time (for an average of a 20 months follow up time)

Incidence of death: The rate of child death during the follow-up time to the total person-months of observation.

Mild WHO clinical stages: are stage I and II baseline clinical stages of HIV-infected under-five children during ART enrolment (35)

Under nutrition was defined as the child having either of Height for Age (H/A) Z-score < -2, or Weight for Age (W/A) Z-score < -2 or weight for height (W/H)Z-score < -2 standard deviations (SD) (36).

Moderate underweight was defined as children having W/Age Z-score < -2 SD(36).

Severe underweight was defined as children having W/Age Z-score < -3 SD(36).

Moderate stunting was defined as children having H/ Age Z-score < -2 SD(36).

Severe stunting was defined as children having H/Age Z-score < − 3 SD (36).

Moderate wasting was defined as children having W/ H Z-score < − 2 SD(36).

Severe wasting was defined as children having W/H Z-score < − 3 SD (36).

Opportunistic infections: When HIV infected child developed any form of OIs after ART initiation during the follow-up period(37).

Treatment Failure: Clinical failure: After 6 months of effective therapy, a new or repeated clinical event showing advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with the exception of tuberculosis). **Immunologic failure:** A persistent CD4 count of less than 200 cells/mm3 or < 10% (Persistent is to mean at least 2 CD4 measurements below the threshold).**Virologic failure:** if two consecutive viral load measures with adherence support between measurements are greater than 1000 copies/ml within a 3-month interval(7).

Loss to follow-up: children have missed their follow-up or drug pick-up appointments for three months and above(16).

Transferred out: Those children who were transported to different medical facilities (16).

Incomplete card: considered when the indicator of the dependent variable and/or 5% of the independent Variable is not registered

Child developmental status: classified as appropriate (able to attain milestones for age), delayed (failure to attain milestones for age); and regression (loss of what has been attained for age) (38).

CD4 counts or percentage (%): Below the threshold was considered if the child had CD4 cell counts < 1500/ mm^3 or 25% for age < 12 months, CD4 cell counts < 750/ mm^3 or < 20% for age 12–35 months, CD4 cell counts < 350/mm^3 or < 15% for age 36–59 months(39).

Adherence :Good (>95%) – if the percentage of missed doses is ≤2 doses of 30 doses or ≤3 doses of 60 doses; **Fair:** (85–94%) – if the percentage of missing doses is between 3 and 5 doses of 30 doses or 4–9 doses of 60 doses; **poor:** (<85%) if missed doses are 6 doses of 30 doses or 10 and above doses of 60 doses, as documented by the ART physician(40).

4.11. Data Quality Control

Training and orientation for the supervisors and data collectors were given for one day about sample size, data extraction, ethical issues and way of supervision. The collected data were reviewed and checked for its completeness before data entry and incomplete data were discarded. EpiData was used for data entry to prevent data entry errors.

4.12. Data processing and Analysis procedure

Descriptive analysis was carried out to present the magnitude of each study variables. The Kaplan-Meier survival curve was used to estimate survival time after initiation of ART, and log rank tests were used to compare the survival curves. The probability of survival within each time interval and cumulative probability of survival for each subsequent time intervals was estimated using life table.

The goodness of fit for cox regression model was checked by Cox-Snell residual plot. Graphical tests such as (Log-log survival probability plot, Schoenfeld residual plot) and Schoenfeld residual global proportional hazard test were used to assess the proportional hazard assumption of the model. The parallelism of lines in Log _log survival probability plot, the presence of almost a constant smoother line on the Schoenfeld residual plot and P-value of > 0.05 on Schoenfeld residuals Proportional hazard (PH) test were used to ascertain whether proportional hazard assumption is satisfied or violated. Bivariable (simple) Cox proportional hazard model was used to identify candidate variables for multivariable Cox regression. Multivariable (multiple) Cox proportional hazard model was used to identify factors associated with time to death of HIV infected under five children. Variables having p-value less than 0.25 in the bivariable analysis were considered in the multivariable cox regression analysis. Finally, the adjusted hazard ratio (AHR) with 95 % CI was computed and variables with a p-value less than 0.05 in the multivariable Cox regression analysis was considered as significant predictors of death. In addition, the outcome status was calculated by dividing the total number of occurrences during the follow-up period by the total number of observations. The incidence density was measured with person months of observation.

4.13. Ethical Consideration

Ethical approval for this study was obtained from Bahir Dar University College of medicine and health science Ethical Review Board. Permission letters were obtained from each hospital administration of the four participating entities. Since the study was a review of medical records, individual patients were minimally at risk for harm as confidentiality was likely to be achievable. To maintain confidentiality, collected data were coded and locked in a separate room. After entry into the computer, all data were locked by pass word; as well, names and unique ART numbers were not included in the data collection forms.

5. RESULT

5.1 Socio-demographic characteristics of included participants

After reviewing 432 HIV-infected children records, 415 records were included in the final analysis as, 17 records were excluded due to incompleteness. About half 210 (50.6%) of study participants were females, the majority of participants 285(68.67%) were from urban areas and 350 (84.34%) children were living with their parents. The baseline median age of the participant was 34 months (IQR: 21-48 months); with the median age of caregiver was reported as 31 years (IQR: 27-37 years) and the majority of parents 327 (77.35%) were both alive.

Table 3 Baseline socio-demographic characteristics of HIV infected under five children receiving ART in West Amhara Referral Hospitals between January 2010 and December 2019

Variables	Category of variables	Outcome Status		Frequency (N=415)	Percent (%)
		Dead (Count, %)	Censored (Count, %)		
Sex of the Child	Male	14(6.83%)	191(93.17%)	205	49.40%
	Female	11(5.24%)	199(94.76%)	210	50.60%
Age of the child in months	<12 months	3(9.68%)	28(90.32%)	31	7.47%
	12-59 months	22(5.73%)	362(94.27%)	384	92.53%
Statusof parents	Both alive	17(5.30%)	304(94.70%)	321	77.35%
	mother alive but father dead	2(6.45%)	29(93.55%)	31	7.47%
	Mother dead but father alive	3(18.75%)	13(81.25%)	16	3.86%
	Both dead	3(6.38%)	44(93.62%)	47	11.33%
Sex of caregiver	Male	7(7.37%)	88(92.63%)	95	22.89%
	Female	18(5.63%)	302(94.4438%)	320	77.11%
Age of care giver in years	18-30	9(4.79%)	179(95.21%)	188	45.3 %
	31-40	9(5.66%)	150(94.34%)	159	38.31%
	41-50	3(6.82%)	41(93.18%)	44	10.60%
	>50	4(16.67%)	20(83.33%)	24	5.78%
Residence	Urban	11(3.86%)	274(96.14%)	285	68.67%
	Rural	14(10.77%)	116(89.23%)	130	31.33%
Relationship of caregiver for the child	Parent	19(5.43%)	331(94.57%)	350	84.34%
	Sister/brother	2(18.18%)	9(81.81%)	11	2.65%
	Uncle/aunt	1(4.76%)	20(95.24%)	21	5.06%
	Grandparent	2(8.7%)	21(91.3%)	23	5.54 %
	Others	1(10%)	9(91%)	10	2.41 %

5.2 Baseline and follow up Clinical, Immunological, laboratory and Treatment-related Characteristics

Of the total 415 under five children, more than half 261 (62.89 %) of the study participants had baseline opportunistic infections. In the study participants regarding to the developmental milestone 360 (86.75%), 47(11.32%) and 8(1.93%) were appropriate, delayed and regressed respectively.

Regarding the WHO clinical staging, lower than half 192(46.27%) of the study participants had advanced baseline WHO clinical Stage (3 and 4). About half 212 (50.85%) were screened for tuberculosis (TB) in the past (before starting of ART). Among them 26(6.27%) were positive for TB screening and all of them were took TB treatment.

The eligibility criteria for initiation of HAART were mainly by both CD4+ cell count or percent and WHO clinical stage 178 (42.89%) followed by test and treat strategy 113(27.23%).Moreover, more than half 231 (55.66 %) of the children had CD4 counts below the threshold. Furthermore, 51 (12.29%) of the participants had anemia at ART initiation. Eighty -three (20%) of the participants on ART had history of treatment failure.

During the study follow up period 319 (76.87%) and 57 (13.73%) of the participants have good and fair adherence, respectively. 39 (9.40%) of the study participants were with poor adherence, of them 8(32%) had died at the end of the follow up period. Throughout the follow-up time, 178 (42.89%) of the study participants developed OIs. Regarding prophylaxis use, 372(89.64%) of the participants were ever on Co-trimoxazole Preventive Therapy (CPT), whereas, 198(47.71%) were ever on Isoniazid Preventive Therapy (IPT). Regarding baseline nutritional status, 18.07%, 17.83, and 18.07% of HIV Infected under five children were severely underweight, stunted, and wasted (Table 4).

Table 4 Baseline and follow up Clinical, Immunological, laboratory and Treatment-related Characteristics of HIV infected under five children receiving ART in West Amhara Referral Hospitals between January 2010 and December 2019

Variables	Category of variables	Outcome Status		Frequency (N)	Percent (%)
		Dead (Count, %)	Censored (Count, %)		
Opportunistic infection	Yes	22(8.43%)	239(91.57%)	261	62.89 %
	No	3(1.95%)	151(98.05%)	154	37.11%
Developmental status	Appropriate	21(5.83%)	339 (94.17%)	360	86.75%
	Delayed	3(6.38%)	44(93.62%)	47	11.32%
	Regressed	1(12.5%)	7(87.5%)	8	1.93%
WHO clinical stage	Mild(stage I &II)	5(2.24%)	218(97.76%)	223	53.73%
	Sever (stage III &IV)	20(10.42%)	172(89.58%)	192	46.27%
Past TB test	Not determined	11(5.39%)	193(94.61%)	204	49.16%
	Positive	2(7.69%)	24(92.31%)	26	6.27%
	Negative	12(6.49%)	173(93.51%)	185	44.58%
Past TB treatment	Yes	2(7.69%)	24(92.31%)	26	6.27%
	No	23(5.91%)	366(94.09%)	389	93.73 %
CD4 count or percent	Below the threshold	20(8.66%)	211(91.34%)	231	55.66%
	Above the threshold	5(2.72%)	179(97.28%)	184	44.34%
Hemoglobin level	Anemic(< 10 g/dl)	12(23.53%)	39(76.47%)	51	12.29%
	Non-anemic (≥10 g/dl)	13(3.57%)	351(96.43%)	364	87.71
ART eligibility criteria	Immunologic/CD4	1(2.33%)	42(97.77%)	43	10.36%
	WHO stage	2(2.47%)	79(97.57%)	81	19.52%
	Both WHO& Immunologic	20(11.24%)	158(88.76%)	178	42.89%
	No criteria/Test and start	2(1.77%)	111(98.23%)	113	27.23%

Treatment failure	Yes	11(13.25%)	72(86.75%)	83	20%
	No	14(4.22%)	318(95.78%)	332	80%
Type of treatment failure (N=83)	Immunologic	6 (15%)	34(85%)	40	48.2%
	Virologic	1(4.76%)	20(95.24%)	21	25.3%
	Clinical	4(18.18%)	18(81.82%)	22	26.5%
ART adherence in the 1st 3 months	Good	11(3.45%)	308(96.55%)	319	76.87%
	Fair	6(10.53%)	51(89.47%)	57	13.73%
	Poor	8(20.51%)	31(79.49%)	39	9.40%
History of OIs during follow up time	Yes	19(10.67%)	159(89.33%)	178	42.89%
	No	6(2.53%)	231(97.47%)	237	57.11 %
Regimen change	Yes	13(9.35%)	126(90.65%)	139	33.49%
	No	12(4.35%)	264(95.65%)	276	66.51%
CPT	Given	20(5.38%)	352(94.62%)	372	89.64%
	Not Given	5(11.63%)	38(88.37%)	43	10.36%
IPT	Given	6(3.03%)	192(96.97%)	198	47.71%
	Not Given	19(8.76%)	198(91.24%)	217	52.29 %
Underweight	Normal	10(3.86%)	249(96.14%)	259	62.41%
	Moderate (WAZ < −2)	6(7.41%)	75(92.59%)	81	19.52%
	Severe (WAZ < −3)	9(12%)	66(88%)	75	18.07%
Stunting	Normal	11(3.87%)	273(96.13%)	284	68.43%
	Moderate (HAZ < −2)	7(12.28%)	50(87.72%)	57	13.73%
	Severe (HAZ < −3)	7(9.46%)	67(90.54%)	74	17.83%
Wasting	Normal	10(3.65%)	264(96.35%)	274	66.02%
	Moderate (WHZ < −2)	5(7.58%)	61(92.42%)	66	15.90%
	Severe (WHZ < −3)	10(13.33%)	65(86.67%)	75	18.07%

The commonest regimens given at the start of ART in the cohort were 4c= AZT-3TC-NVP which is 165(39.76%) followed by 4b= d4t-3TC-EFV 76(18.31%) from the total (figure 3).

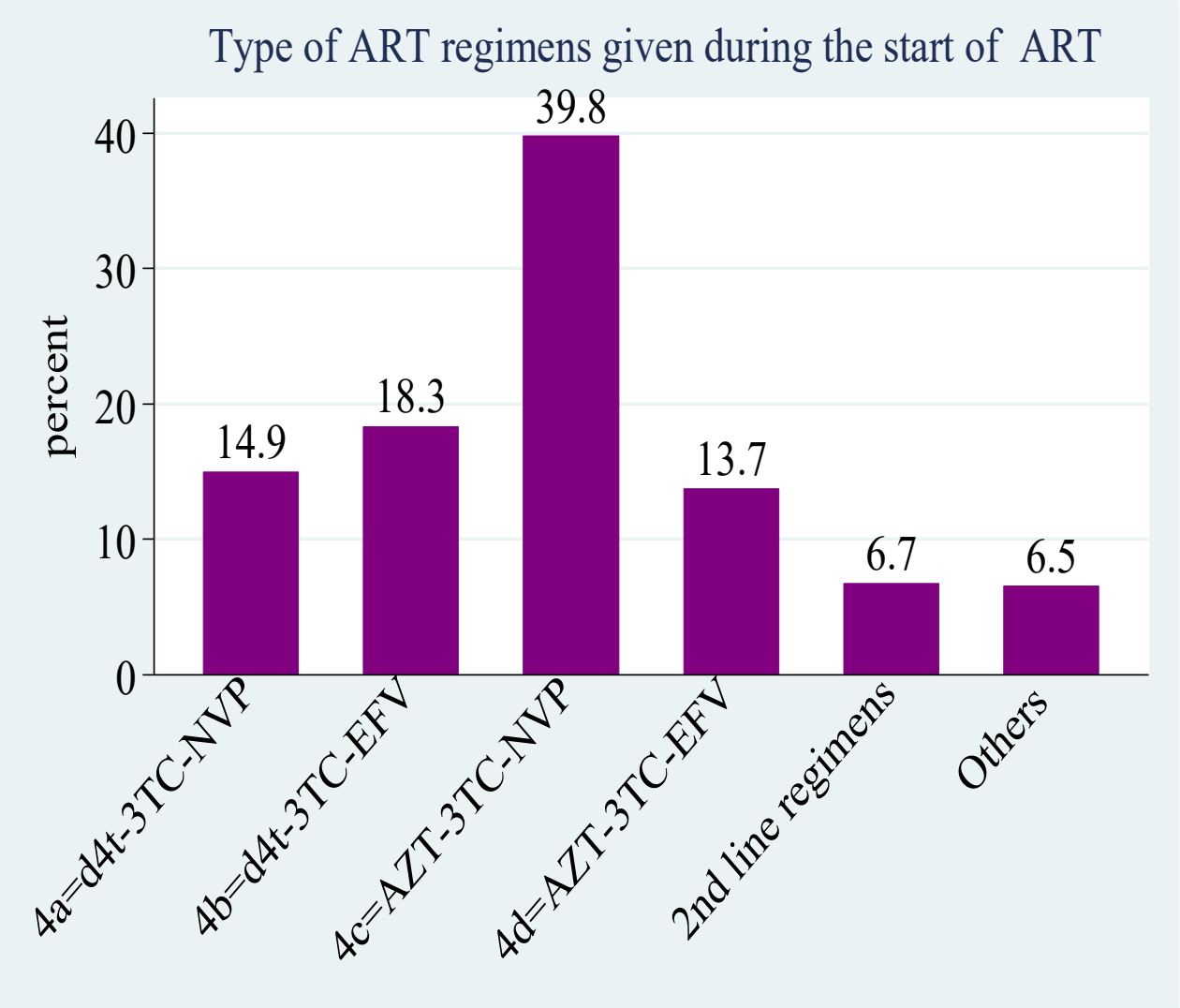


Figure 3 ART regimen given for under five children started ART in West Amhara Referral Hospitals between January 2010 and December 2019

One-third (33.5%) of HIV-infected under five children had a history of ART regimen change during the follow up time. Of this, 48(34.5%) were due to drug toxicity/side effect followed by immunological failure 30(21.6%) (Figure 4).

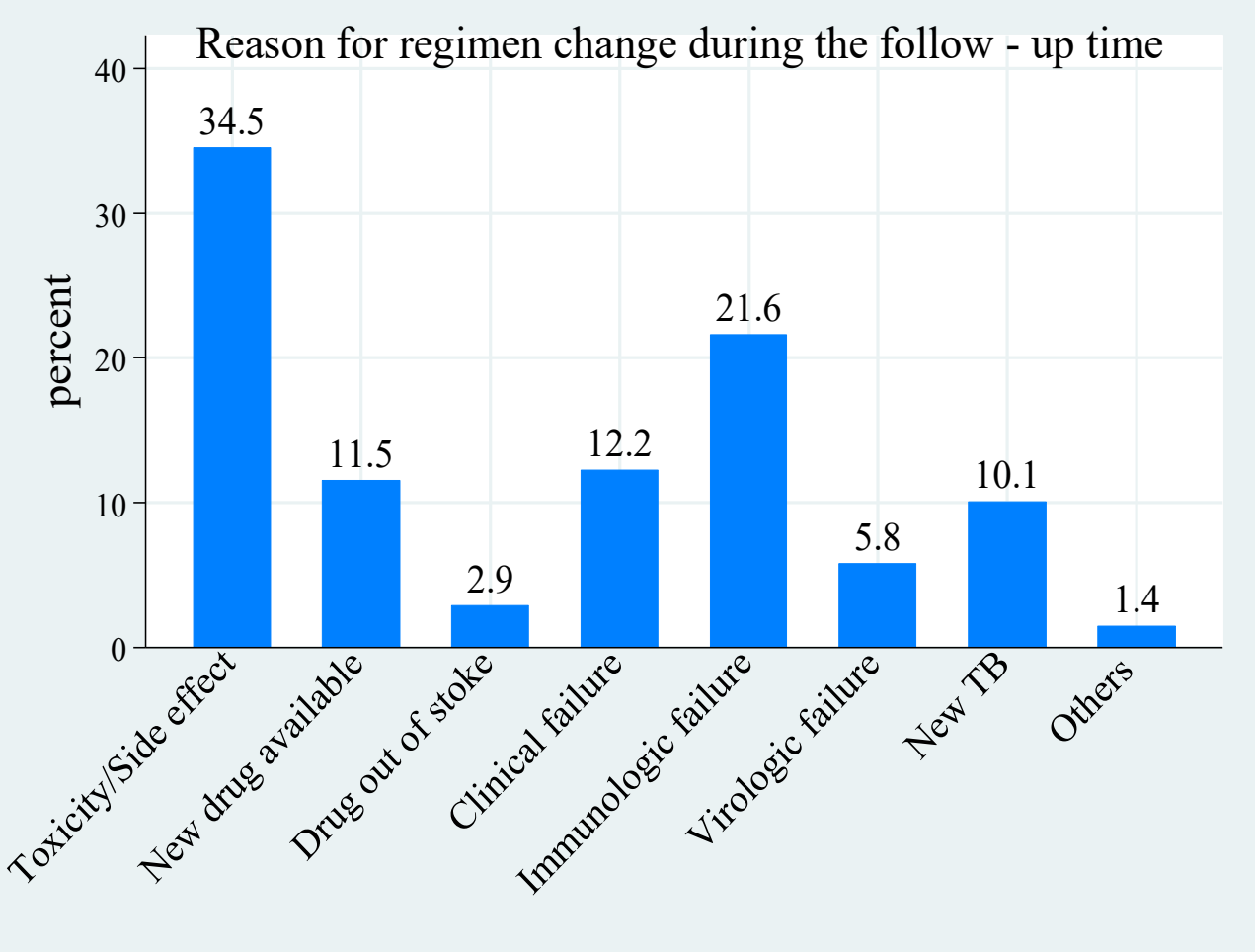


Figure 4 Reason for ART regimen change during the follow-up time for under five children started ART in West Amhara Referral Hospitals between January 2010 and December 2019

About 42.89% of HIV-positive under five children had opportunistic infections (OIs) during the follow up time. Of these, 39.3, 38.5, and 25.3% of the children had diarrhea, pneumonia, and candidiasis respectively (Fig.5)

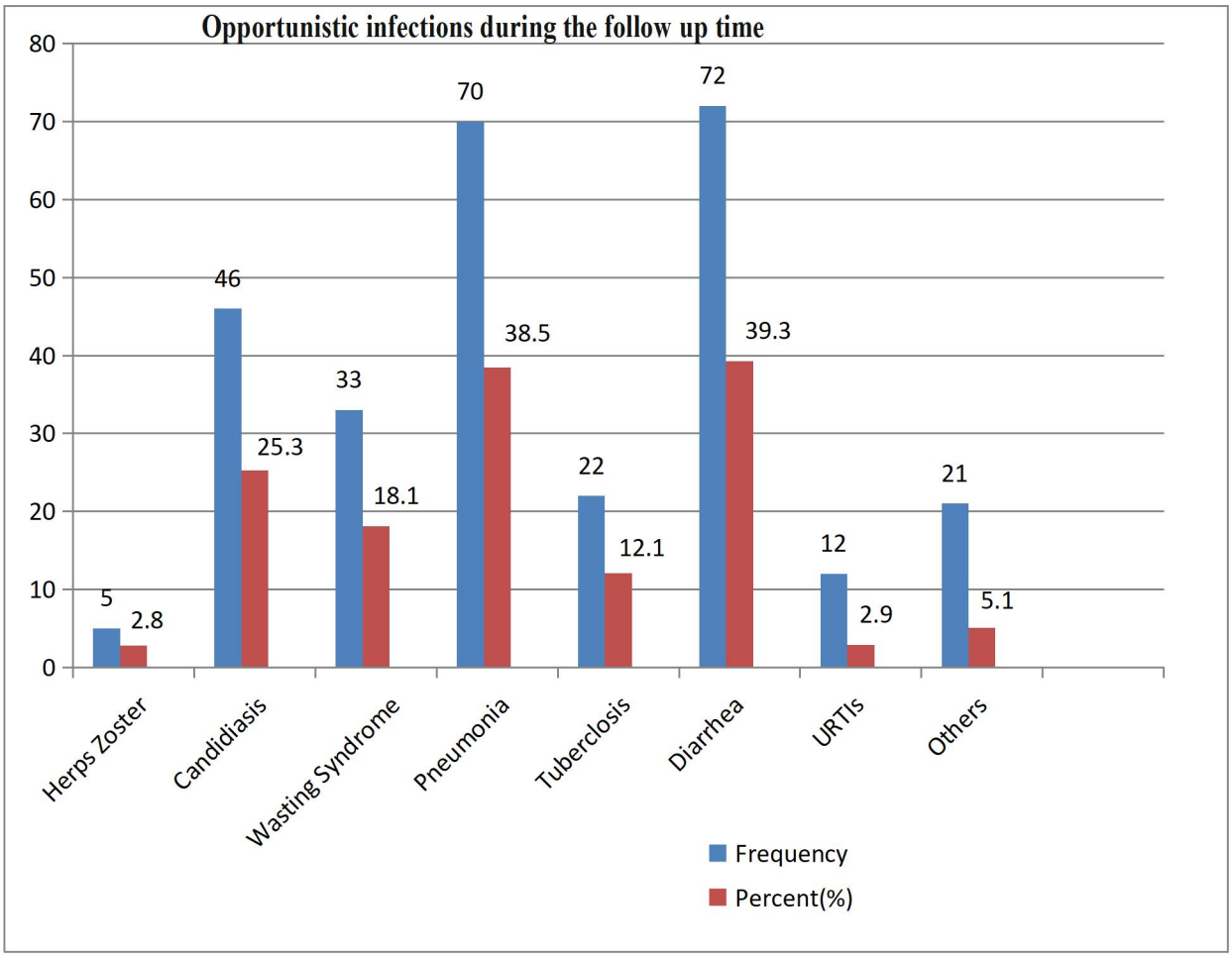


Figure 5 opportunistic infections during the follow up time of HIV-infected under five children receiving ART in West Amhara Referral Hospitals from January 2010 and December 2019

5.3 Survival characteristics after initiation of ART

After initiation of ART, HIV-infected children were followed for 3 months to 48 months which provides a total of 8700.5 person-month (725.04 person-year) of observation. At the end of follow up period, 325 (78.31) of the children were alive, 18 (4.34%) were lost to follow up, 47 (11.33%) were transferred out to other health facilities, 25 (6.02%) were reported dead due to HIV/AIDS (Fig.6).

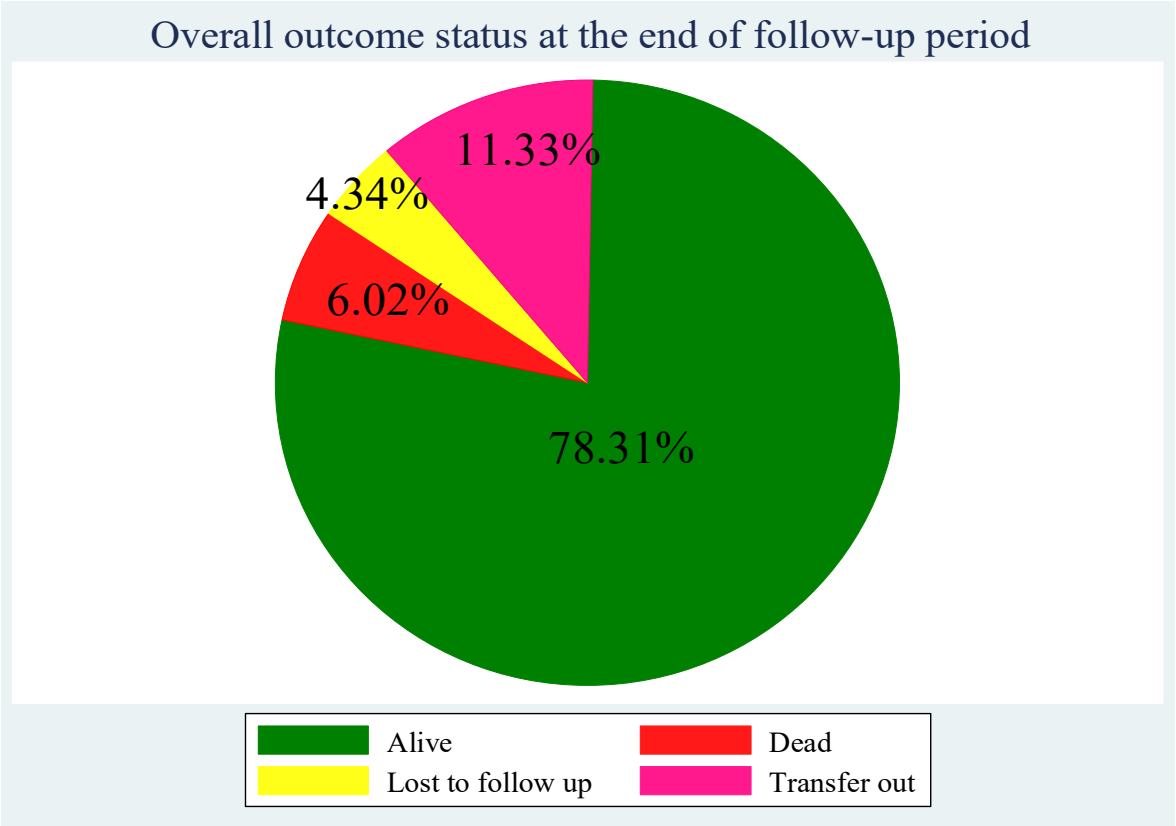


Figure 6 Outcome Status for HIV infected under five children receiving ART in West Amhara Referral Hospitals between January 2010 and December 2019.

The median follow up period for children under the age of five after starting ART was found 19 month (IQR=11 - 32).The median time to death was 14 months (IQR =10 - 23). The cumulative probability of survival of under-five children on ART after last month of follow-up was 85% (95%CI; 76.42 - 91.25). The cumulative survival probabilities of children after 6, 12, 24, and 36 months were 0.97, 0.95, 0.92 and 0.85 respectively (Table 5).

Table 5 Life table of the probability of survival within each time interval and cumulative probability of survival for each subsequent time intervals

Life Table[a]

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	Std. Error of Cumulative Proportion Surviving at End of Interval	Probability Density	Std. Error of Probability Density	Hazard Rate	Std. Error of Hazard Rate
0	415	16	407.000	3	.01	.99	.99	.00	.001	.001	.00	.00
6	396	126	333.000	7	.02	.98	.97	.01	.003	.001	.00	.00
12	263	45	240.500	6	.02	.98	.95	.01	.004	.002	.00	.00
18	212	57	183.500	3	.02	.98	.93	.02	.003	.001	.00	.00
24	152	29	137.500	2	.01	.99	.92	.02	.002	.002	.00	.00
30	121	62	90.000	2	.02	.98	.90	.02	.003	.002	.00	.00
36	57	31	41.500	2	.05	.95	.85	.04	.007	.005	.01	.01
42	24	23	12.500	0	.00	1.00	.85	.04	.000	.000	.00	.00
48	1	1	.500	0	.00	1.00	.85	.04	.000	.000	.00	.00

Interval		Beg. Total	Deaths	Lost	Survival	Std. Error	[95% Conf.	Int.]
0	6	415	3	16	0.9926	0.0042	0.9773	0.9976
6	12	396	7	126	0.9718	0.0088	0.9480	0.9847
12	18	263	6	45	0.9475	0.0130	0.9150	0.9678
18	24	212	3	57	0.9320	0.0156	0.8939	0.9568
24	30	152	2	29	0.9185	0.0181	0.8747	0.9474
30	36	121	2	62	0.8981	0.0227	0.8433	0.9344
36	42	57	2	31	0.8548	0.0369	0.7642	0.9125
42	48	24	0	23	0.8548	0.0369	0.7642	0.9125
48	54	1	0	1	0.8548	0.0369	0.7642	0.9125

The overall Kaplan-Meier survivor function estimate shows that most deaths had been occurred in the earlier months of ART initiation. Based on the findings, from the total of 25 deaths, 3(12%) of them occurred in the first six months of follow-up and 10(40%) deaths occurred in the first 12 months of follow-up, which became declining through follow up time and continues steadily at later months of follow up (Figure 7). Some graphs compared to other covariates have shown relatively larger gaps between categories, such as INH prophylaxis and Hemoglobin (Hgb) level.

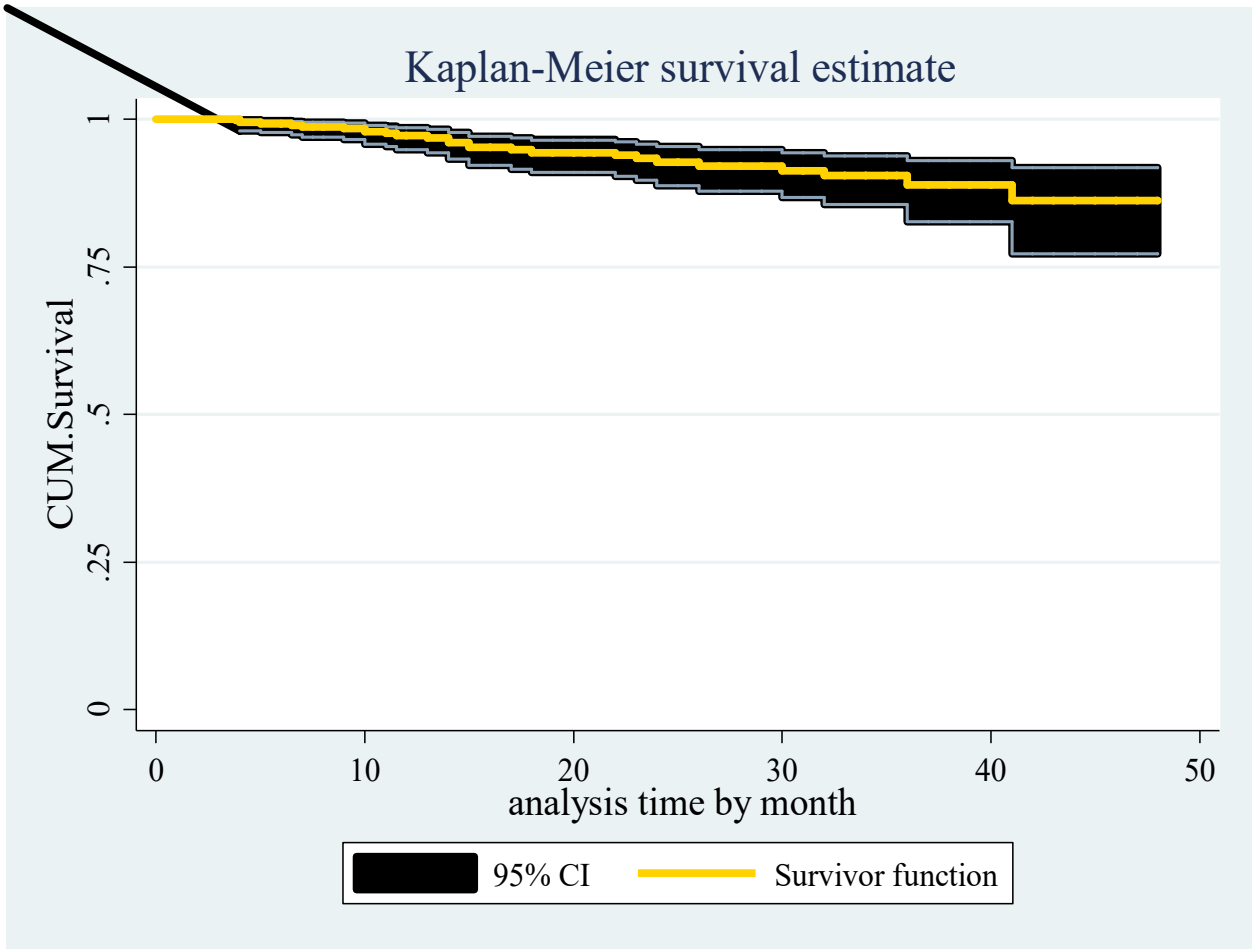


Figure 7 the overall Kaplan Meier survival curve with 95% confidence intervals of HIV infected under five children receiving ART in West Amhara Referral Hospitals between January 2010 and December 2019

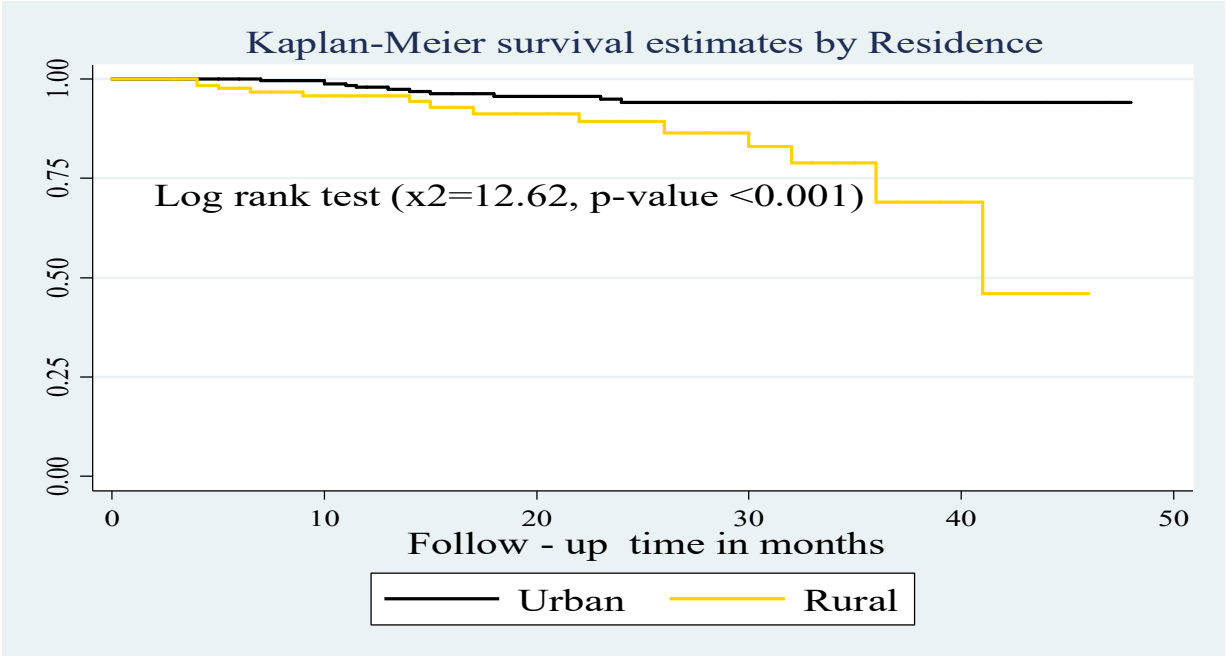


Figure 8 Kaplan-Meier survival estimates based on their residence during the follow up time among under- five children on ART in West Amhara Referral Hospitals between January 2010 and December 2019

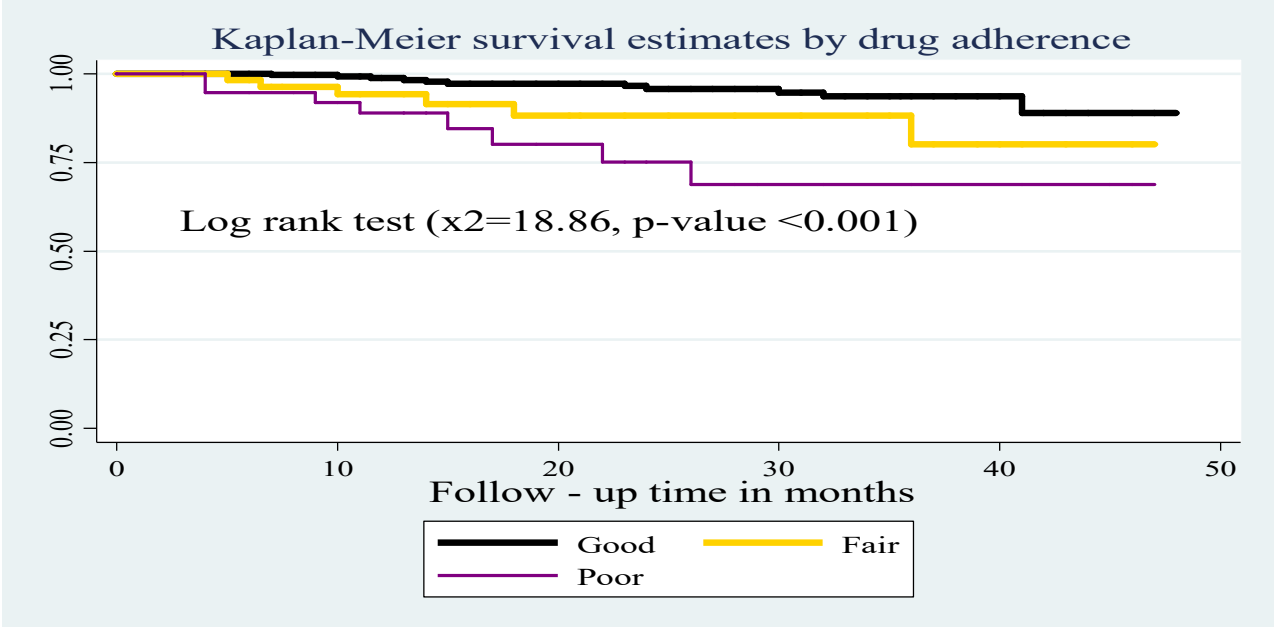


Figure 9 Kaplan-Meier survival estimates based on their drug adherence during the follow up time among under- five children on ART in West Amhara Referral Hospitals between January 2010 and December 2019

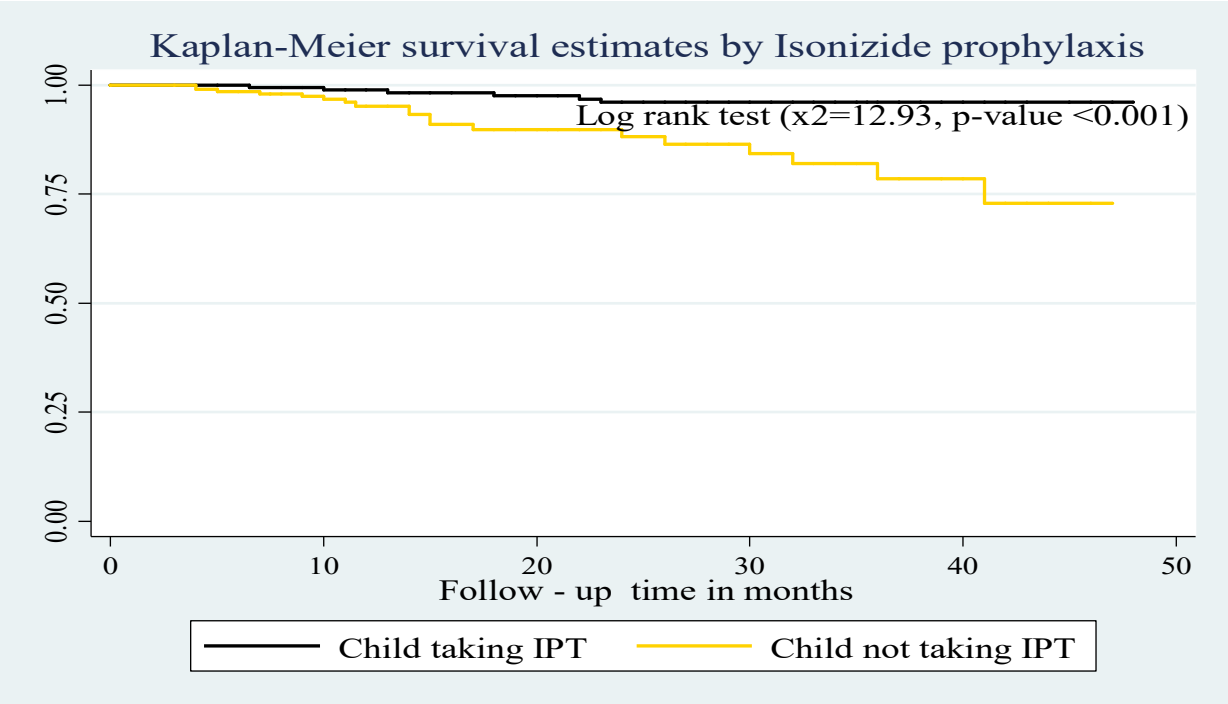


Figure 10 Kaplan-Meier survival estimates based on their Isoniazide Preventive Therapy (IPT) during the follow up time among under- five children on ART in West Amhara Referral Hospitals between January 2010 and December 2019

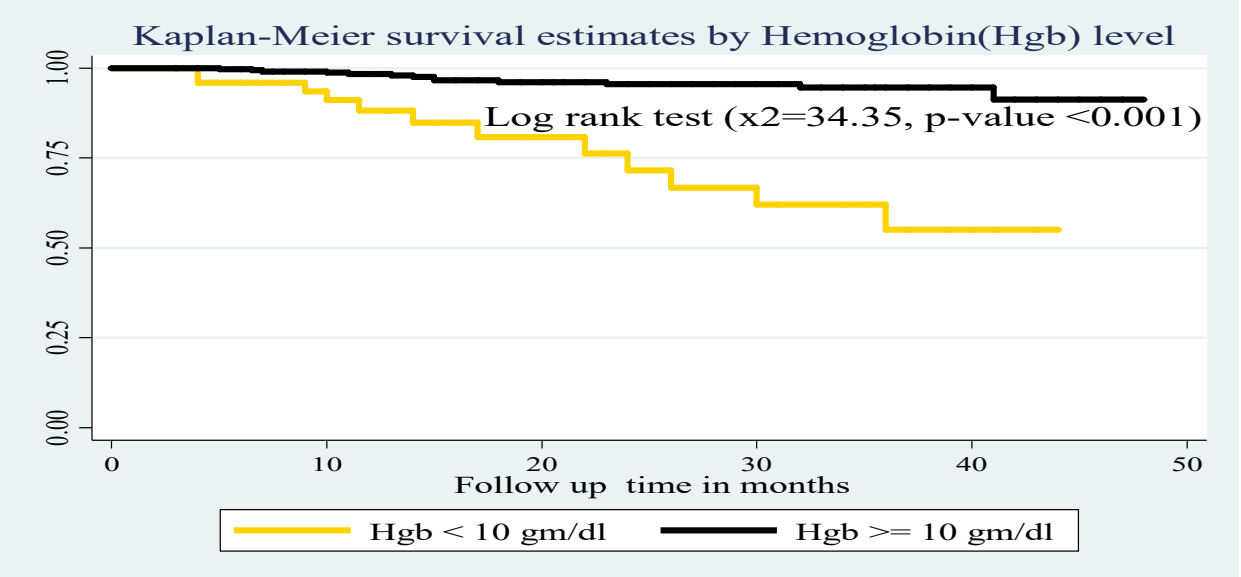


Figure 11 Kaplan-Meier survival estimates based on their level of Hemoglobin (Hgb) during the follow up time among under- five children on ART in West Amhara Referral Hospitals between January 2010 and December 2019

5.4 Predictors of HIV infected under - five child Death (mortality)

In bi-variable Cox proportional regression analysis, age of the child, age of caregiver, status of parents, residence, OI at baseline, CD4 count or percent, underweight, wasting, ART adherence status, CPT prophylaxis status, INH prophylaxis status, OI's during follow up period, Baseline Hemoglobin (Hgb) level, and Baseline WHO Clinical stages were found to havep – value of < 0.25 which were candidate variables for multivariable Cox –proportional hazard analysis. From final multivariable Cox proportional regression analysis residence; ART adherence status, INH prophylaxis, and Hemoglobin (Hgb) level were found to be predictors of death at 5% of the level of significance. The hazard of death among HIV-positive under five children who live in rural areas was 3.3 times higher (AHR 3.32:-95% CI 1.17- 9.39) as compared to those who live in urban areas. The hazard of death among under-five children with poor adherence to ART medications was 3.4 fold higher than those children with good adherence (AHR= 3.36; CI: 1.06, 10.69). Furthermore, the hazard of death in under-five children without history of INH prophylaxis during their under five age was 3.2 fold (AHR=3.15; CI: 1.11, 8.94) higher than those children with INH prophylaxis. Lastly, the hazard of death among anemic under five children was three-fold (AHR: 3.05, 95% CI: 1.16, 8.03) higher as compared to non-anemic under five children (Table 6).

Table 6 Bivariable and Multivariable Cox regression analysis of predictors of Death among HIV infected under five children receiving ART in West Amhara Referral Hospitals between January 2010 and December 2019

Variable	Category of Variables	Outcome status		CHR [95%CI]	AHR[95%CI]	P-value
		Death	Censored			
Age of the child	< 12 months	3	28	2.40(0.71, 8.08)	2.17(0.47, 10.02)	0.321
	12 -59 months	22	362	1	1	
Age of caregiver	18-30 years	9	179	1	1	
	31-40 years	9	150	1.22(0.48, 3.08)	0.58(0.18, 1.82)	0.347
	41-50 years	3	41	2.28(0.61, 8.56)	1.20(0.24, 6.05)	0.824
	> 50 years	4	20	7.88(2.35, 26.48)*	0.76(0.14, 4.19)	0.754
Status of parents	Both alive	17	304	1	1	
	mother alive but father dead	2	29	1.31(0.30, 5.67)	0.86(0.16, 4.63)	0.859
	Mother dead, but father alive	3	13	4.16(1.2, 14.25)*	1.72(0.37, 8.13)	0.491
	Both dead	3	44	2.34(0.68, 8.11)	0.75(0.16, 3.46)	0.715
Residence	Urban	11	274	1	1	
	Rural	14	116	3.85(1.73, 8.58)*	**3.32(1.17, 9.39)**	**0.024****
OI at baseline	Yes	22	239	4.52(1.35, 15.12)*	1.79(0.35, 9.11)	0.483
	No	3	151	1	1	
CD4 count or percent	Above the threshold	5	179	1	1	
	Below the threshold	20	211	2.28(0.91, 5.73)*	0.96(0.32, 2.91)	0.942
Underweight	Normal	10	249	1	1	
	Moderate(WAZ<−2)	6	75	1.74(0.63, 4.79)	0.79(0.20, 3.05)	0.728
	Severe (WAZ < −3)	9	66	2.85(1.15, 7.03)*	1.18(0.29, 4.78)	0.816
Wasting	Normal	10	264	1	1	
	Moderate(WHZ<−2)	5	61	2.07(0.71, 6.07)	2.00(0.56, 7.14)	0.285
	Severe (WHZ < −3)	10	65	4.54(1.89,10.92)*	2.04(0.59, 8.70)	0.237
ART adherence status	Good	11	308	1	1	
	Fair	6	51	3.04 (1.12, 8.22)	1.88(0.53,6.73)	0.329
	Poor	8	31	6.00(2.40, 15.01)*	**3.36(1.06, 10.69)**	**0.040****
CPT	Yes	20	352	1	1	
	No	5	38	4.50(1.66, 12.19)*	1.81(0.50,6.58)	0.366
IPT	Yes	6	192	1	1	
	No	19	198	4.67(1.86, 11.75)*	**3.15(1.11, 8.94)**	**0.031****

OI's during follow up	Yes	19	159	2.79(1.11, 7.049)*	1.51(0.52, 4.34)*	0.446
	No	6	231	1	1	
Baseline hemoglobin(Hgb)	Anemic(< 10 g/dl)	12	39	7.40(3.37, 16.23)*	**3.05 (1.16, 8.03)**	**0.024****
	Nonanemic(≥10g/dl)	13	351	1	1	
Baseline WHO Clinical Stages	Mild (stage I & II)	5	218	1	1	
	Advanced (stage III&IV)	20	172	5.00(1.88, 13.36)*	1.15(0.27, 4.86)	0.845

1- Reference category, * statistically significant at bi-variable with 5% level of significance,

** Statistically significant at multivariable with 5% level of significance, CI- confidence interval

The goodness of fit cox proportional hazard regression model was checked by Cox-Snell residual plot. Based on the finding of cox-Snell residuals, the Nelson Aelon hazard line follows the 45-degree alignment with the reference line which indicates as the model is good to fit **(Appendix 4**). In addition, the proportional hazard assumption of the model was verified by both graphically and through statistical tests using Log-Log survival probability plot, Schoenfeld residuals plot, and Schoenfeld residuals proportional hazard (PH) test respectively. Since the P-value of all variables in the final multivariable Cox-regression model was greater than 0.05, the proportional hazard assumption for such variable is satisfied **(Appendix 5)**. Additionally, the yields of graphical tests (Log –Log survival probability plot and Schoenfeld residuals plot) illustrate as the effect of each predictor on the outcome was constant throughout time (**Appendix 6, 7**)

6. DISCUSSION

This institution-based retrospective follow up study was conducted in West Amhara Referral Hospitals, Northwest Ethiopia to assess the survival time and predictors of death. In this study, the overall incidence rate of death was 2.87 deaths per 1000 child-months (95% CI: 1.94 - 4.25) during the follow-up period. This finding is lower when compared with a study conducted in Oromia Liyu Zone, Amhara Region, Ethiopia (IR: 5.9 deaths per 100 child-months) (17) and in Karonga district of northern Malawi, in which HIV infected under five Child incidence rate was 16.6/1000 PYO(11).The variations might be due to the differences in clinical characteristics of the study Participants and study settings as my study included only referral hospitals. The above disparity could possibly be attributable to differences in ART enrollment periods, as a prior study in northern Malawi's Karonga district looked at children who started ART earlier (before 2012) and had different treatment eligibility criteria. Since 2013, the WHO has made significant adjustments to the recommended pediatric age for ART initiation, regardless of clinical or immunologic state, based on data indicating early ART initiation reduces HIV-related morbidity and mortality in children (41).

In this study, high number of deaths 10 (40%) occurred within the first one year after starting ART. This finding is similar to the studies conducted in Oromia Liyu Zone, Amhara Region, Ethiopia(17)Gonder(30), Ngeria(42), Cameroon(43) and study in Sub-Saharan Africa(12), reporting that the death rate was high in early times of ART initiation. This could be due to undetected (undiagnosed) Immune Reconstitution Inflammatory Syndrome (IRIS), a common consequence in individuals initiating ART, particularly in patients with advanced disease stages and low CD4 cell counts. According to a study conducted in South Africa, IRIS affected 21% of children starting ART, and IRIS was responsible for one-quarter of mortality in the first six months (44). Additionally, based on a study conducted in Japan, 50% of ART-associated IRIS occurred within the first month of ART initiation and this might cause higher early mortality(45).

Higher premature mortality in this study also might be associated with INH prphylaxisis of included participants as more than half (52.7%) of the study participants had not received IPT. The reason for not taking IPT might be due to the presence of OIs (attacked by different types of OIs) which are the most common causes of premature death.

The cumulative probability of survival of children on ART in this study was 85% at the end of the follow up period (95%CI; 76.42 - 91.25).This was comparable with the report of a study conducted in Oromia Liyu Zone, Amhara Region, Ethiopia in which the cumulative probability of survival was 87% (17). The possible elucidation may be due to almost similar follow up periods (follow up times) for children after started ART.

In this study residence of children is one of the predictor of reducing survival of children on ART. Living in rural area is 3.3 times higher for the hazard of death than living in urban area children. This is similar to the study conducted in Wolaita zone health facilities, Ethiopia and Tanzania (22, 29). This similarity shows Mortality rates in urban areas are consistently lower than in rural areas in child mortality. This could be due to poor hygiene and sanitation, malnutrition is prevalent in rural, poor knowledge of on care of HIV and others (46).

Additionally, the study found that ART drug adherence was another important predictor of mortality. Individuals who had poor ART adherence levels were more at risk of being died than individuals who had good adherence levels. Adherence status of the child to medications throughout the follow-up time is important predictor in agreement with majority of studies. This finding is in line with a study conducted at Oromia Liyu Zone, Amhara Region, Ethiopia,Gamo Gofa Zone, Southern Ethiopia, Wolaita zone health facilities (4, 17, 22). The possible elucidation may be because the relationship between adherence and mortality directly forwarding. Those factors which may contribute to poor adherence will indirectly cause death of patients from their regular follow -up. Furthermore, poor adherence of ART leads to virologic, immunologic and clinical failure that is mediated mainly by two potentially reinforcing mechanisms. 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 and also 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. Based on the findings of a qualitative study conducted in Uganda, the principal factors for poor adherence were poverty, presence of drug side effects, depression, poor peer support and counseling, stigma and discrimination which indirectly contribute to the increased incidence of treatment failure and death(47).

INH prophylaxis status of under-five children during their age was among one of significant determinants of death. Children with no history of INH prophylaxis were associated with reduced survival. This finding was consistent with findings in a study done in Oromia Liyu Zone, Amhara Region, Ethiopia (17), Gamo-Gofa (Ethiopia) (4). The possible reason for such higher level of death on these under-five children without INH prophylaxis during ART enrolment could be due occurrence of some OIs like pneumocystis pneumonia, toxoplasmosis, tuberculosis and recurrent diarrheal diseases. If there were OIs present for the child INH prophylaxis could not be given.

This study also found that the risk of mortality among anemic HIV-positive under five children was three-fold higher as compared to their non-anemic counterparts. Previous Ethiopian studies also documented that anemia had a significant impact on the survival of HIV-infected children (13, 22, 30). Additionally, studies from other sub Saharan African countries also demonstrated that low hemoglobin was a predictor of mortality (20, 29, 32) . The most common cause of anemia among people living with HIV is the side effects of zidovudine, in which 53.5% of this study participants were taking a combination of 4c (AZT-3TC-EFV) or 4d (AZT-3TC-NVP) during the follow-up time. One of the most common causes of anemia (megaloblastic anemia) among HIV - infected patients is AZT (48, 49).

7. LIMITATION OF THE STUDY

This study did not incorporate important predictors, like viral load, income, immunization status of the children, micronutrient deficiency due to incomplete recording system and provider and system-related factors with mortality. Furthermore, early mortality might be under estimated since the study excluded children's who had ART follow-up was less than 3 month.

8. CONCLUSION

The incidence rate of death is 2.87 deaths per 1000 child-months and the cumulative incidence of death is 6.02%.The cumulative survival probability of under-five children on ART after last month of follow-up was 85%. Death of HIV-infected under-five children on ART is high within the first one year after enrolment.The risk of death was higher for those who are rural resident, had poor ART adherence, lack isoniazide prophylaxis and present with anemia.

9. RECOMMENDATION

For Health care providers

- ❖ Health care providers shall give special emphasis and close follow-up for HIV positive Under five children is important especially within the first year of enrolment to the chronic HIV care and a careful monitoring and follow up of patients with who came from rural areas.
- ❖ The health care providers shall strengthen their collaborative work with adherence counsels to address barriers of poor adherence and patients with poor adherence shall have frequent follow-up schedules.
- ❖ Additionally, clinicians shall give more emphasis to anemia in HIV-infected children.
- ❖ All eligible HIV-positive patients shall be received IPT if no contraindications because it has numerous advantages which indirectly improves patient survival.

To West Amhara Referral Hospitals ((UoGCSH , FHCSRH, DTCRH and DMCRH)

- ✓ Additional follow-up visits and close monitoring shall be facilitated and provided on the first 01 year after ART initiation since the highest incidence of death occurs in this time.
- ✓ Special consideration shall be given to improve the ART adherence levels of patients through integrating different case teams, strengthen the adherence counseling strategies, and providing continuous monitoring and supervision for adherence supporting teams

Regional health bearou (RHB), Amhara Public Health institute (APHI) and Federal Ministry of Health (FMOH)

- ❖ All of the above stakeholders shall strengthen close monitoring and supportive supervisions for ART sites in such areas.
- ❖ Integrating the HIV care to ART adherence with other developmental organizations like NGOs and community supporters.

Non-Governmental Organizations (NGOs)

- ❖ NGOs shall provide continuous supportive supervision on sustaining regular follow up by giving special attention to those high-risk individuals

For Research community

- ❖ It is recommend future researchers undertake prospective studies by including different Variables (viral load, liver and kidney function tests, behavioral factors, mental Status, provider and system-related factors and pill burden).

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11. APPENDIXES

Appendix 1: Information sheet

The title of the Research Project: Survival time and predictors of death among HIV-infected under five children after initiation of Anti-Retroviral Therapy in West Amhara Referral Hospitals Northwest Ethiopia: A Retrospective follow up study

Name of principal Investigator: Gebrie Getu (BSc)

Phone number: +251918663516

E-mail: gebryegetu27@gmail.com

Name of the Organization: Bahir Dar University, collage of medicine and health science, school of public health, Department of Epidemiology and Biostatistics.

Purpose of the Research Project: -To assess the Survival time and predictors of death among HIV-infected under five children after initiation of Anti-Retroviral Therapy

Procedure: In order to achieve the above objective, information which is necessary for the study was taken from HIV care medical record follow-up forms, ART intake forms, and medical history sheet.

Risk and /or Discomfort: The study will not harm patients and retrieved information will be used for only the study purpose since the information for the study is collected from patient charts. The name of the patient isn't recorded during data extraction and all information that taken from patient charts was kept confidential. The information extracted was kept secured by locked into locker by key. After the data was entered into the computer, it was secured by password. The information retrieved was only used for the study purpose.

Benefits: The research had no direct benefit for those 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 for the children with HIV infection. Of all, the research work has a paramount direct benefit for health

care planners and managers, especially for those on HIV/AIDS collaborative program planning and management.

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

Appendix 2: Data abstraction tool

This tool is prepared for the collection of socio-demographic, clinical, laboratory, treatment and outcome related information that were important for the assessment. This is data collection checklist intended Survival time and predictors of death among under five children receiving ART in West Amhara Referral Hospitals, Northwest Ethiopia. All these variables will be retrieved from the individual patient chart without mentioning name.

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 characteristics	Possible answers	Skip
101	Age of the child at enrollment	(…….)Years or (…….) months	
102	Sex of the child	1. Male 2. Female	
103	Age of care giver	.....years	
104	Sex of care giver	1. Male 2. Female	
105	Residence	1. Urban 2. Rural 3. Not recorded	
106	Status of parents	1. Both alive 2. mother alive but father dead 3. Mother dead, but father alive 4. Both dead	

107	Relationship of caregiver for the child	1.parent 2. Sister/brother 3. Uncle/aunt 4. Grandparent 5. Others specify……	
Part II	**Baseline clinical, laboratory and ART information**		
201	Baseline opportunistic infection	1. No 2. Herpes zoster 3. Candidiasis 4. Wasting syndrome 5. Pneumonia 6. TB 7. Diarrhea 8. Others specify.....	
202	CD4 count or CD4% at baseline	..... /.....%	
203	Hgb level at base line	.....g/dl	
204	Developmental status at baseline	1. Appropriate 2. Delayed 3. Regressed	
205	WHO clinical staging at baseline	1. Stage I 2 Stage II 3. Stage III 4. Stage IV	
206	Past TB test	1. Not determined 2. Positive 3. Negative	
207	Past TB treatment	0. No 1. Yes	
208	Weight at baseline	(.....) kg	
209	Height/length at baseline	(.....) cm	

Part III	**ART treatment and other medication**		
301	ART eligibility criteria	1. Immunologic/CD4 2. WHO stage 3. Both WHO and Immunologic 4. No criteria	
302	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. 4g=ABC-3TC-LPN/r 6. 1e=TDF-3TC-EFV 7. 2nd line regimens 8. Others specify (……...)	
303	Did the child had treatment failure?	0. No 1. Yes	If 0→ 305
304	If Yes for question No 303 type of failure	1.Immunologic 2.Virologic 3.Clinical	
305	Adherence within 3 month of ART initiation	1.Good 2.Fair 3.Poor	
Part-IV	**Patient follow up information (filled from ART follow up form) recent results**		
401	Date of HIV positive confirmed	(……/……/……)DD/MM/YY	
402	Starting date of ART	(……/……/……)DD/MM/YY	
403	Last follow up date	(……/……/……)DD/MM/YY	
404	Duration since initiation of ART	(……)Month/s	

405	Opportunistic infections during follow up	1. No 2. Herpes zoster 3. Pneumonia 4. TB 5. Oral thrush 6. Diarrhea 7. Wasting syndrome 8. Others specify.....	
406	Does the regimen change	0. No 1. Yes	If 0→408
407	If the regimen is changed reason for regimen change	1. Toxicity/Side effect 2. New drug available 3. Drug out of stoke 4. Clinical failure 5. Immunologic failure 6. Virologic failure 7. New TB 8. Other specify----------	
408	Cotrimoxazole preventive therapy	1. Given 2. Not given	
409	Isonized preventive therapy	1. Given 2. Not given	

- ✓ Status 1. Alive 2.Dead 3.Lost to follow up 4.Transfer out
- ✓ If dead when, after initiation of ART (----------) months
- ✓ If lost to follow up when after initiation of ART (----------) months
- ✓ If transfer to another health facility when after initiation of ART (----------) months

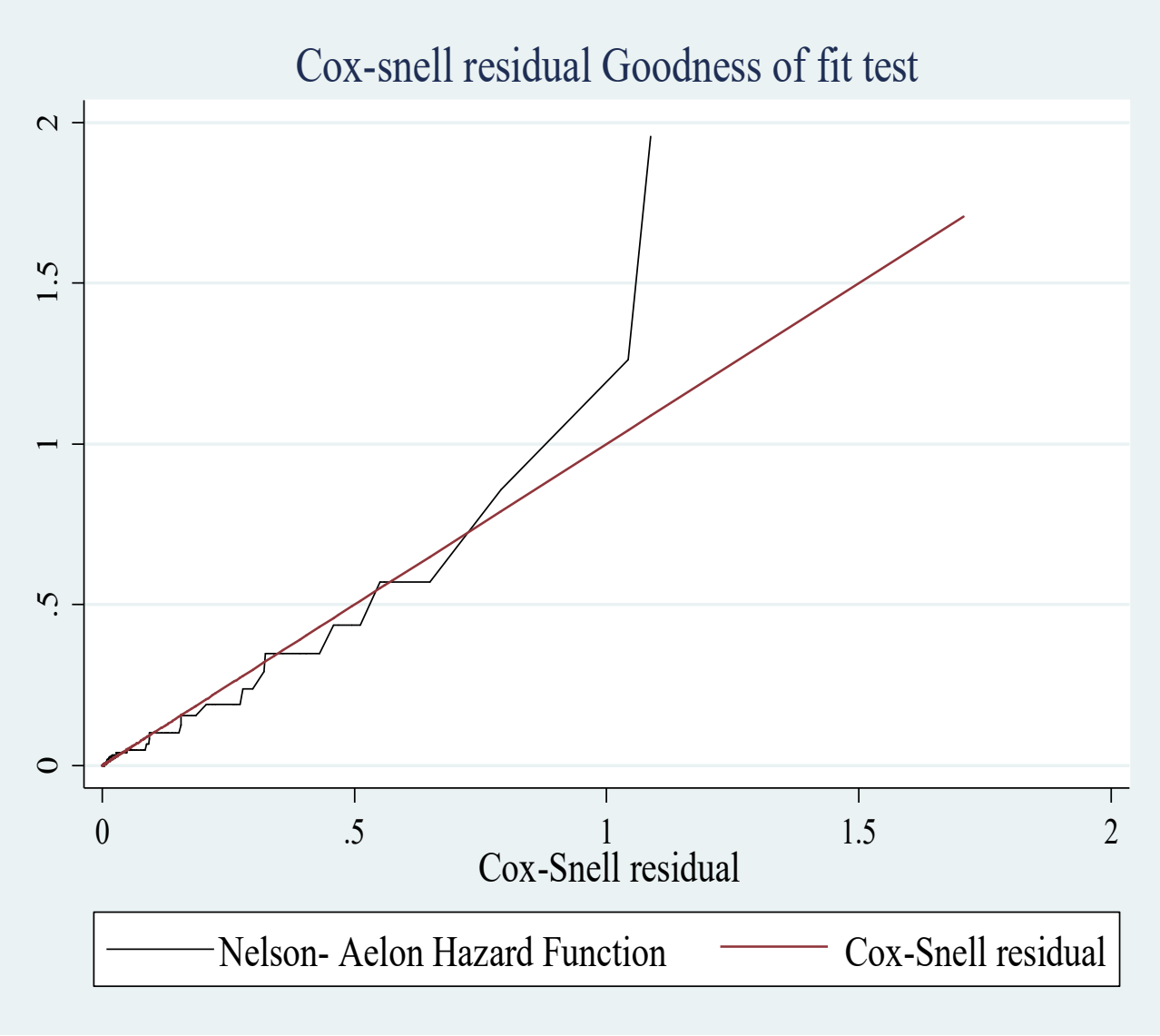
Appendix 3: Output of multivariable Cox- regression analysis

```
. stcox ib(first).i.RESIDENC i.OIBASELI  ib(2)i.TRESHODC i.UNDERWEI i.WASTING i.ADHERENC i.INH i.CPT i.FOLOWUP
> O  i.AGEOFCARcat ib(2)i.agecat ib(2)i.HGBcate i.WHOstagecat i.STATUSPA

        failure _d:  Event == 1
  analysis time _t:  Survivtime

Iteration 0:   log likelihood = -134.48831
Iteration 1:   log likelihood = -112.00516
Iteration 2:   log likelihood =   -106.976
Iteration 3:   log likelihood = -106.53789
Iteration 4:   log likelihood = -106.53294
Iteration 5:   log likelihood = -106.53294
Refining estimates:
Iteration 0:   log likelihood = -106.53294

Cox regression -- Breslow method for ties

No. of subjects =          415                 Number of obs    =         415
No. of failures =           25
Time at risk    =       8700.5
                                                LR chi2(21)      =       55.91
Log likelihood  =   -106.53294                  Prob > chi2      =      0.0001
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
RESIDENC						
Rural	3.318293	1.761263	2.26	0.024	1.172517	9.390965
OIBASELI						
Yes	1.790622	1.485771	0.70	0.483	.3521422	9.105203
TRESHODC						
Below the threshold	.9598896	.5429524	-0.07	0.942	.3167724	2.908676
UNDERWEI						
Moderate	.7863556	.5441545	-0.35	0.728	.2025776	3.052436
Severe	1.180019	.8416354	0.23	0.816	.2915946	4.775281
WASTING						
Moderate	2.001841	1.298954	1.07	0.285	.5611801	7.140965
Severe	2.256947	1.553898	1.18	0.237	.5854271	8.701013

ADHERENC						
Fair	1.884492	1.223502	0.98	0.329	.5279026	6.727206
Poor	3.358753	1.983948	2.05	0.040	1.055335	10.68971
INH						
Not given	3.148202	1.67597	2.15	0.031	1.108968	8.937301
CPT						
Not given	1.812495	1.192685	0.90	0.366	.4990642	6.582593
FOLOWUPO						
Yes	1.507902	.812724	0.76	0.446	.524319	4.336615
AGEOFCARcat						
31-40	.5755169	.3382086	-0.94	0.347	.1819032	1.820856
41-50	1.20199	.9915186	0.22	0.824	.2386418	6.054176
>50	.7608682	.6625352	-0.31	0.754	.1380751	4.192794
agecat						
less than12months	2.170512	1.694465	0.99	0.321	.4699485	10.02476
HGBcate						
anemic	3.05172	1.50588	2.26	0.024	1.160157	8.027354
WHOstagecat						
sever	1.154016	.8467355	0.20	0.845	.2739433	4.861422
STATUSPA						
mother alive but father dead	.8579949	.7383643	-0.18	0.859	.1588424	4.634499
Mother dead, but father alive	1.723937	1.363883	0.69	0.491	.3656775	8.127266
Both dead	.7521258	.5857661	-0.37	0.715	.1634417	3.461132

Appendix 4: Cox- Snell residual overall goodness of fit test result among under five children receiving ART in West Amhara Referral Hospitals, Northwest Ethiopia, from 2010 to 2019



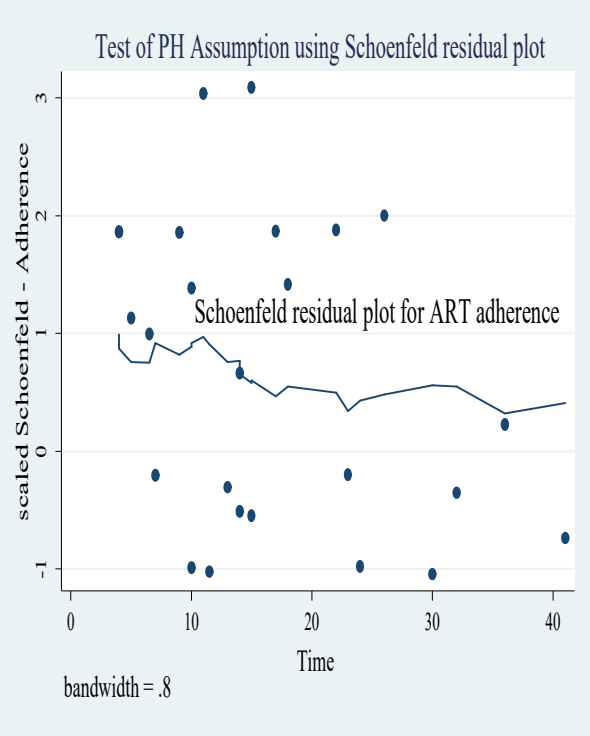
Appendix 5: Proportional hazard assumption with global test result of different predictor variables of under five children receiving ART in West Amhara Referral Hospitals, Northwest Ethiopia, from 2010 to 2019

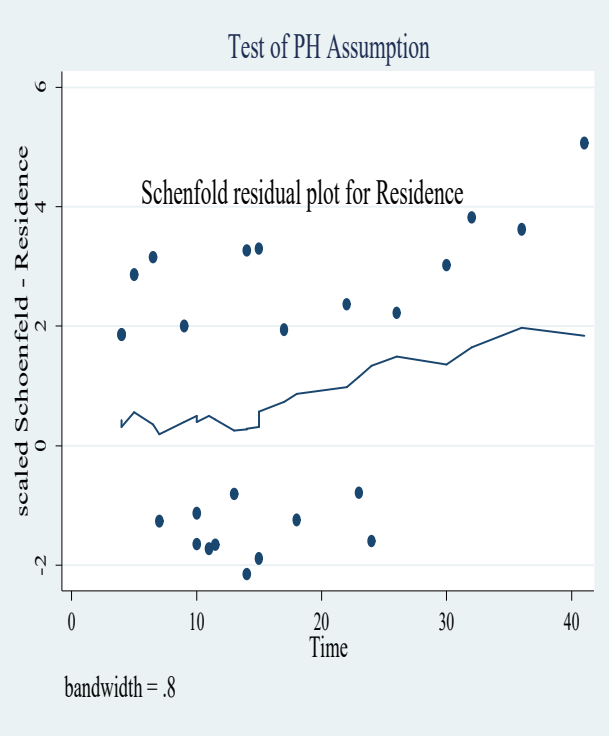
Variables		Rho*	chi2	df **	P-value
Residence(Urban reference)	Rural	0.23135	1.71	1	0.1915
Baseline OI (No is a reference)	Yes	0.20755	1.69	1	0.1930
Threshold level of CD4 (above the threshold as a reference)	Below the Threshold	-0.25026	2.00	1	0.1568
Underweight at baseline (Normal is a reference)	Moderate	0.11283	0.34	1	0.5580
	Severe	-0.11602	0.59	1	0.4413
Wasting at baseline (Normal is a reference)	Moderate	-0.06935	0.14	1	0.7078
	Severe	0.02616	0.02	1	0.8956
Adherence within the 1st 3 months (Normal is a reference category)	Fair	-0.14261	1.16	1	0.2823
	Poor	-0.14974	0.89	1	0.3453
IPT (No is a reference category)	Yes	0.09686	0.30	1	0.5846
CPT (No is a reference category)	Yes	-0.03628	0.03	1	0.8606
OI during follow - up (No is a reference category)	Yes	-0.28727	2.89	1	0.0893
WHO stage at baseline (mild(I and II) is a reference category)	Sever(III &IV)	-0.11830	0.69	1	0.4051
Hgb level at baseline (>= 10g/dl is a reference category)	<10g/dl	0.31577	2.71	1	0.1000
Age of the child at baseline(12 -59 months is a reference category)	< 12 months	0.12002	0.74	1	0.3891
Age of care giver at baseline (18-30 is a reference category)	31-40 years	0.11809	0.45	1	0.5010
	41-50 years	0.19443	2.44	1	0.1186
	>50 years	0.15241	1.07	1	0.3003

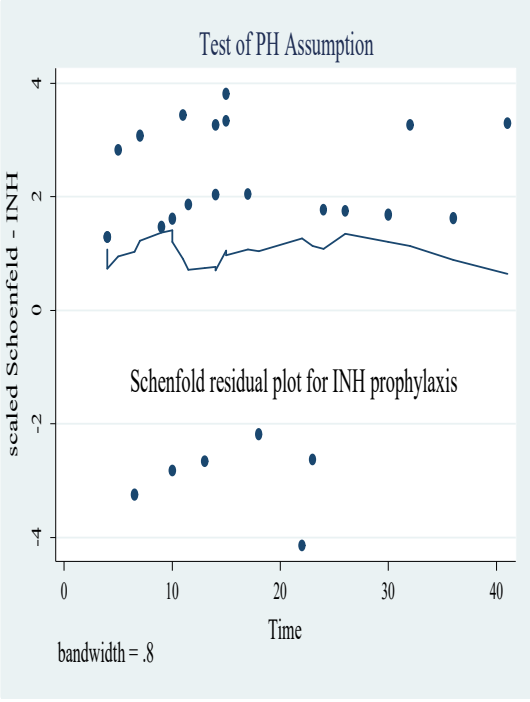
Status of parents (both alive is used as a reference category)	Father dead	-0.14371	0.59	1	0.4432
	Mother dead	0.00326	0.00	1	0.9851
	Both dead	-0.16855	1.38	1	0.2404
Global test			**25.4621**	**21**	**0.2278**

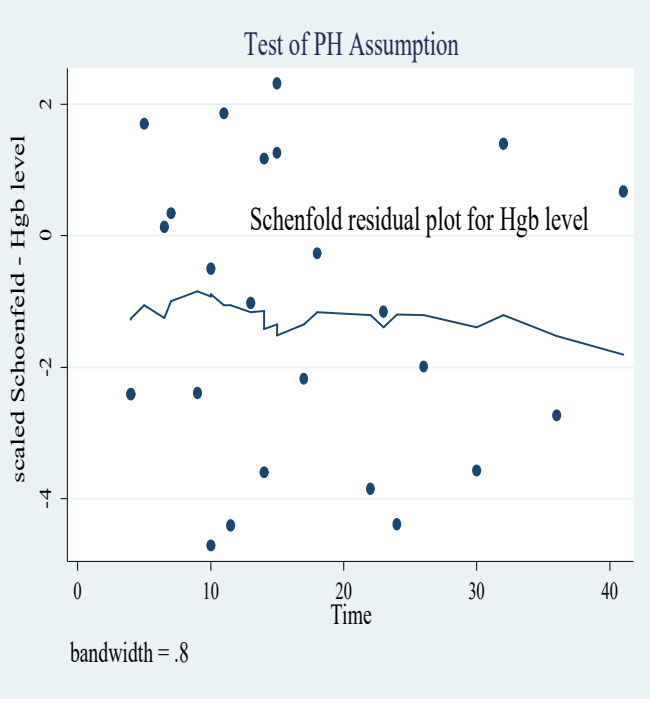
*The correlation coefficient between the residuals and time and **Degree of freedom

Appendix 6: Schoenfeld Residual plot result Among Under –Five children receiving ART in West Amhara Referral Hospitals, Northwest Ethiopia, from 2010 to 2019.

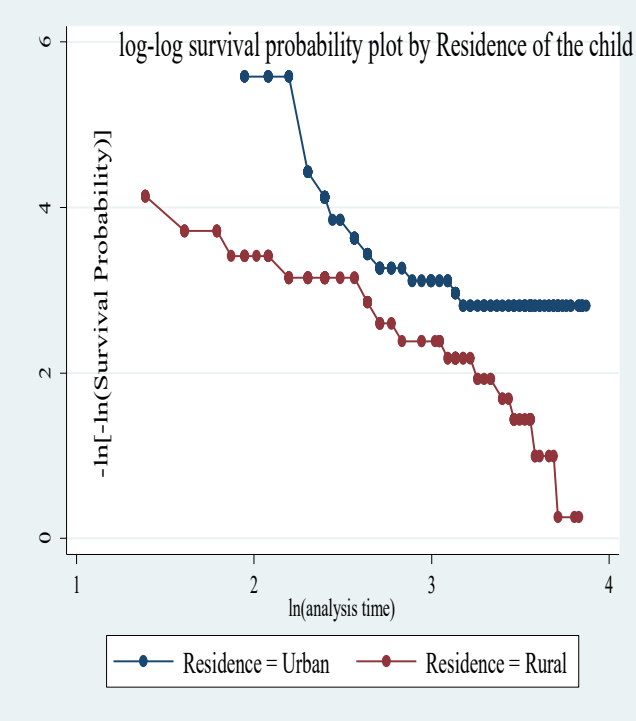


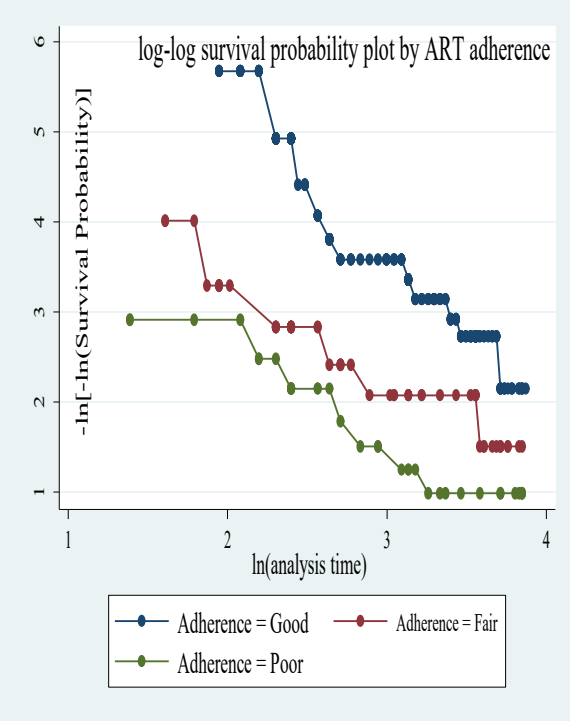


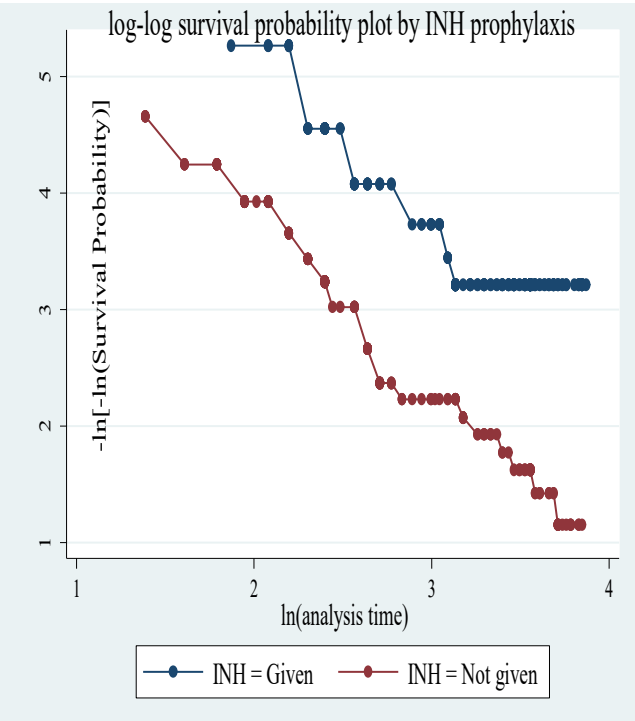


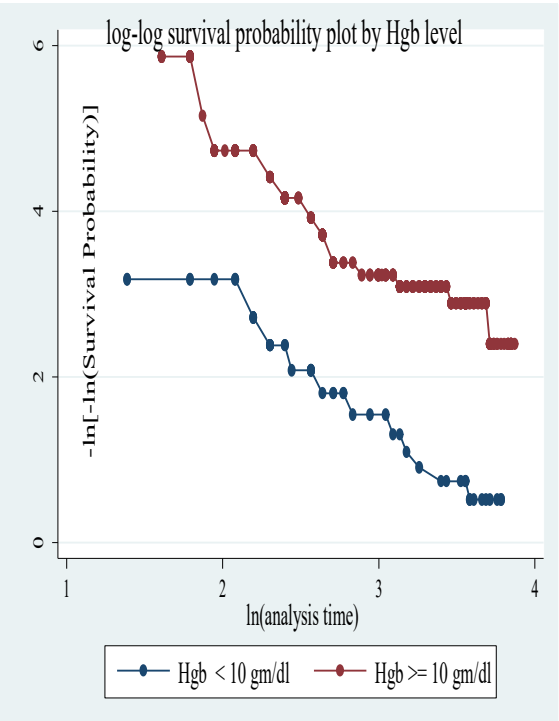


Appendix 7: Log _Log Survival probability plot results of selected variables on under-five children receiving ART in West Amhara Referral Hospitals, Northwest Ethiopia, from 2010 to 2019.









Appendix 8: Declaration Sheet

Through my signature below, I declared and affirmed that this thesis is my work. I have followed all ethical principles of scholarship in the preparation, data collection, data analysis, and completion of this thesis work. All scholarly matter that was included in the thesis has been given recognition through citation. I affirm that I have cited and referenced all sources used in this document. Every effort has been made to avoid plagiarism in the preparation of this thesis work. This thesis is submitted for partial fulfillment of a master of public health degree in Epidemiology from college of medicine and health sciences, Bahirdar University. The thesis would be deposited in the library of Bahir Dar University and will be made accessible for readers under the rules of the library. I solemnly declared that this thesis has not been submitted to any other institution anywhere for the award of any academic degree, diploma or certificate.

Student Name: Gebrie Getu (BSc Nurse)

Signature: _____

Place of submission: Department of Epidemiology and Biostatistics, school of Public Health, College of Medicine and Health Sciences, Bahir Dar University.

Date of Submission: _____

Appendix 9: Advisor's approval form

BAHIR DAR UNIVERSITYCOLLEGE OF MEDICINE AND HEALTH SCIENCES SCHOOL OF PUBLIC HEALTH DEPARTMENT OF EPIDEMIOLOGY AND BIOSTATISTICS

Approval of research thesis report for submission:

The undersigned examining committee certify that the research thesis report presented by Gebrie Getu entitled: Survival time and predictors of death among HIV-infected under five children after initiation of ART in West Amhara Referral Hospitals Northwest Ethiopia, 2021, submitted to Bahir Dar University, College of Medicine and Health Sciences, School of Public Health , Department of Biostatistics and Epidemiology, in partial fulfillment of the requirements for master of degree in Epidemiology compiles with the regulation of the University and meets the accepted standards with respects to originality and quality. I recommend the research thesis report to be submitted.

Principal investigator: Gebrie Getu Signature _____ Date_____

Advisors:

Name	Signature	Date
1. Mr. Anemaw Asrat (MPH, Associate professor)	_____	_____
2. Mr. Zelalem Mehari (MSc., Assist professor)	_____	_____

FINAL APPROVAL OF RESEARCH THESIS REPORT SHEET

BAHIRDAR UNIVERSITY, COLLEGE OF MEDICINE AND HEALTH SCIENCES,

SCHOOL OF PUBLIC HEALTH, DEPARTMENT OF EPIDEMIOLOGY AND BIOSTATISTICS

I hereby certify that I have examined this thesis report entitled "Survival time and predictors of death among HIV-infected under five children after initiation of ART in West Amhara Referral Hospitals Northwest Ethiopia, 2021". A retrospective follow-up study supported By Gabriela Gan. We recommend and approved the thesis report for a degree of "Master of Public Health in Epidemiology".

Board of Examiners

External examiner

Admit Asmamaw (Ph.D) Signature _____ Date _____

Internal examiner

Dr Getiyow Wudie (Assistant Professor in Epidemiology) Signature _____ Date 15-5-14

Department head

Dr. Getiyow Wudie (Assistant Professor in Epidemiology) Signature _____ date 15-5-14