ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF NURSING AND MIDWIFERY

POST GRADUATE PROGRAM

Survival and predictors of mortality among adult HIV/AIDS patients initiating Highly Active Antiretroviral Therapy in Debre-Berhan Referral Hospital, North Showa Zone, Amhara National Regional State: A retrospective study, 2019.

Fetene Nigussie (BSc)

A Thesis Submitted to the School of Nursing and Midwifery, College of Health Sciences, Addis Ababa University in partial fulfillment of the requirements for the Degree of Master of Science in Advanced Adult Health Nursing.

Addis Ababa, Ethiopia

June, 2019

ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF NURSING AND MIDWIFERY

POST GRADUATE PROGRAM

***Survival and predictors of mortality among adult HIV/AIDS patients initiating Highly Active Antiretroviral Therapy in Debre-Berhan Referral Hospital, North Showa Zone, Amhara National Regional State: A retrospective study*, 2019.**

Submitted by: Fetene Nigussie

Submitted by: Fetene Nigussie _____ _____

Principal Investigator Signature Date

Approved for submittal to thesis assessment committee

1. Dr. Erdaw Tachbele (Ph.D.) _____ _____

   Advisor Signature Date

2. Sr. Zuriash Mengistu (M.Sc., Ph.D. Fellow) _____ _____

   Advisor Signature Date

3. _____ _____ _____

   Department chairperson Signature Date

ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF NURSING AND MIDWIFERY

POST GRADUATE PROGRAM

As members of the Examining Board of the final thesis open defense, we certify that we have read and evaluated the thesis prepared by Fetene Nigussie: ***Survival and predictors of mortality among adult HIV/AIDS patients initiating Highly Active Antiretroviral Therapy in Debre-Berhan Referral Hospital, North Showa Zone, Amhara National Regional State: A retrospective study,*** and recommend to be accepted as partially fulfilling thesis requirements for the degree of Master of Science in Advanced Adult Health Nursing

Chairperson (title and name)	Signature	Date
Internal Examiner (title and name)	Signature	Date

Final approval and acceptance of the thesis is contingent upon the submission of its corrected copy to the School Graduate Committee (SGC) through the concerned departmental graduate committee (DGC).

I hereby certify that I have read the revised version of this thesis prepared under my direction and recommend to be accepted as fulfilling the thesis requirement.

Thesis advisor (title and name)	Signature	Date
Thesis advisor (title and name)	Signature	Date
Department chair (title and name)	Signature	Date

STATEMENT OF DECLARATION

By my signature below, I declare and affirm that this thesis is my own work. I have followed all ethical principles of scholarship in the preparation, data collection, data analysis and completion of this thesis. All scholarly matter that is 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.

This thesis is submitted in partial fulfillment of the requirement for a graduate degree from Addis Ababa University at College of Health Sciences, School of Nursing and Midwifery. The thesis is deposited in the Addis Ababa University Digital Library and is made available to local, national and international scientific community. I solemnly declare that this thesis has not been submitted to any other institution anywhere for the award of any academic degree, diploma or certificate.

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

Name of Principal Investigator: Fetene Nigussie

Signature: _____

Date: _____

ABSTRACT

Survival and predictors of mortality among adult patients started highly active antiretroviral therapy in Debre Berhan Referral Hospital, North Showa Zone, Amhara National Regional State, 2019.

Fetene Nigussie

Addis Ababa, 2019

Background: Although different studies on survival and predictors of mortality among HIV/AIDS patients after initiation of antiretroviral therapy, there are inconsistencies in the findings of those studies. Furthermore, no research was done in the study area. **Objective:** The main objective of this study was to assess the survival and predictors of mortality among adult patients started highly active antiretroviral therapy at Debre Berhan Referral Hospital, North Showa Zone, Amhara National Regional State, 2019. **Methodology:** This institution based retrospective study was conducted among the medical records of 447 study subjects' selected using simple random sampling from January 1st 2013 to December 30th 2018. The data was collected using structured data abstraction checklist. Kaplan-Meier survival curve and log rank test were used to test for the presence of difference in survival among predictor variables. Cox regression was used at 5% level of significance to determine the net effect of each explanatory variable on time to death of patients. **Results:** Among 447 adult patients, 54 patients (12.1%) were died giving a crude death rate of 4.18 per 100 person years (95% CI: 3.20- 5.45). The overall estimated survival rate after initiation of antiretroviral therapy was 81.7 % (95% CI, 75.36- 86.54%) at 72 months of follow up. The independent predictors of mortality were clinical stage IV, (HR=15.6, 95% CI (6.609-36.948), baseline opportunistic infections, (HR=1.86, 95% CI (1.048-3.330)), baseline Hgb<10mg/dl (HR=4.655, 95CI(2.253-9.619)), baseline CD4<200cells/µL) (HR=4.71, 95% CI (2.275-9.751), the presence of comorbidity (HR= 2.56 95% CI(1.391-4.740)), being widowed(HR=3.475, 95% CI(1.412-8.550)), bedridden functional status (HR=3.069, 95% CI(1.111-8.480)). **Conclusion and recommendation:** Patients with opportunistic infections, advanced clinical stage disease, bedridden functional status, baseline Hgb<10mg/dl, baseline CD4<200cells/µL and comorbidity face higher hazard of dying from AIDS earlier than their counterparts. Thus, patients with those predictors of mortality should be given special attention, particularly in the first few months after initiating antiretroviral therapy.

Key words: HAART, HIV/AIDS, predictors, survival, Debre Berhan Referral Hospital

ACKNOWLEDGMENT

First of all, I would like to thank the almighty God for helping me to complete this thesis. Next, I would like to thank Addis Ababa University, College of Health Sciences, School of Nursing and Midwifery for providing me the opportunity to conduct this research. My inner most gratitude goes to Debre Berhan University for sponsoring me to pursue my M.Sc. education.

I am also thank-full to my advisors Erdaw Tachbele (Ph. D.) and Zuriash Mengistu (M.sc, Ph.D. Fellow) for providing me valuable guidance, advice, kind support, constructive comments and inputs that made this work successful.

I am also grateful to Debre Berhan Referral Hospital particularly Anti-retroviral Clinic staff members, data collectors and card extractors.

Last but not least, my special thanks goes to my friends and family for the inspiration and moral support they accorded me throughout the development of this work.

ACRONYMS/ABBREVIATIONS

AAU	Addis Ababa University
AIDS	Acquired immune deficiency syndrome
AMA	American medical association
ART	Antiretroviral therapy
ARV	Antiretroviral
CI	Confidence Interval
CPT	Cotrimoxazole Prophylactic Therapy
DB	Debre Berhan
DBRH	Debre Berhan Referral Hospital
EPHI	Ethiopian Public Health Institute
HAART	Highly Active Antiretroviral Therapy
HGB	Haemoglobin
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IQR	Interquartile Range
Mg/dl	Milli gram per deci liter
OIs	Opportunistic Infections
PLWHA	People Living With HIV/AIDS
UNAIDS	United Nations Program on HIV/AIDS
WHO	World Health Organization

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

1.1. Background

Acquired immune deficiency syndrome (AIDS) is among the most destructive epidemics the world has ever witnessed. United Nations program on HIV/AIDS (UNAIDS) estimated that 36.9 million people were living with HIV (PLWH) in 2017. Among these, 1.8 million people were newly infected and 21.7 million were accessing antiretroviral therapy(1). Low- and middle- income countries accounts for the vast majority of people living with HIV (PLWH) with an estimated 25.5 million living in sub-Saharan Africa. Of those, 19.4 million were living in Eastern and Southern Africa which saw 44% of new HIV infections globally in 2016(2).

The first evidence regarding to HIV epidemic in Ethiopia was identified in 1984(3). According to Ethiopian Public Health Institute, HIV-related estimates and projections for Ethiopia indicates that, there were about 722,248 PLWH in 2017. The estimated number of adults living with HIV/AIDS was 665,116 with the annual death of 12,265 in 2017(4).

According to WHO 2018 tracking of progress on Global action plan on HIV drug resistance 2017-2021 by the end of 2017, 21 million people were receiving life-saving antiretroviral therapy. A further 15.8 million were expected to start treatment in accordance with the WHO "treat all" recommendation, resulting in 36.7 million people who must be successfully maintained on lifelong treatment. Achieving high HIV testing access (at least 90% of all people living with HIV) and treatment coverage (at least 90% of the people who know their HIV-positive status) coupled with high levels of viral load suppression (at least 90% of the people receiving treatment), is expected to lead to eliminating HIV as a public health threat by 2030(5).

Antiretroviral therapy is a long-term treatment strategy for PLWH, which has been shown to reduce HIV-related morbidity and mortality among PLWH and to break onward transmission of the virus(6). Most HIV-infected individuals will eventually develop progressive immunodeficiency marked by CD4 T lymphocyte (CD4) cell depletion and

leading to AIDS-defining illnesses and premature death if they do not access antiretroviral therapy (ART).

The primary goal of antiretroviral therapy was to prevent HIV-associated morbidity and mortality(7). Since, one goal of any antiretroviral therapy program was to increase survival among PLWH, WHO currently recommended treatment for all(6). As countries scale up antiretroviral therapy services, ensuring the availability of antiretroviral medicines for the people who need them and understanding why people drop out of treatment programs and how many do this are important efforts(6, 8).

In 2003, the Government of Ethiopia introduced its antiretroviral therapy program with the goal of reducing HIV-related morbidity and mortality, improving the quality of life of PLWH, and mitigating some of the impacts of the epidemic(9). The country has scaled up its ART program since 2005 and made the service available in 913 Health facilities of which 765 are Health centers(10). The introduction of ART significantly improved the survival of HIV patients and changed HIV infection from a fatal illness to a manageable chronic disease(11).

Despite the success of rapid ART initiation in some settings, starting ART on the day of diagnosis requires coordination between testing and treatment settings and access to resources that may limit treatment uptake(12). Hence, intensive effort is required to increase early diagnosis and ART initiation, and strengthen community Health care systems and continued efforts from governments and international agencies for HIV care to achieve ambitious goal of ending AIDS epidemic by 2030(13, 14).

1.2. Statement of the Problem

The human immunodeficiency virus has created an enormous challenge to human beings worldwide. Since the start of the epidemic, an estimated 77.3 million people have become infected with HIV and 35.4 million people have died of AIDS-related illnesses. In 2017, an estimated 940 000 people died of AIDS-related illnesses globally (1). AIDS has claimed the lives of millions and has left behind hundreds of thousands of orphan(10). In 2016, approximately 20,000 AIDS related deaths occurred in Ethiopia(15).

The majority of people living with or affected by HIV are working age. Thus, HIV and AIDS has consequences on the labor force, productivity and economic growth at individual, household, community, and national levels(16). Therefore, further investment is expected to accelerate the expansion of HIV prevention and treatment programs, which are helpful in reducing the likelihood of rebound of HIV epidemics and its serious effects in the coming years (17).

The mean length of hospital stay for HIV-positive participants that were not on ART and HIV-positive participants that were on ART were 15.0 days and 12.2 days respectively(18). Efforts to scale-up HIV care and treatment have been successful at initiating large numbers of patients onto antiretroviral therapy, although persistent challenges remain to optimize scale-up effectiveness in both resource-rich and resource-limited settings(19).

Though, ART is now recommended worldwide for all PLWH, regardless of their CD4 cell count, sociodemographic factors limiting access to testing, treatment, and retention in care have high potential to jeopardize the UNAIDS aspirational objective to end AIDS by 2030(8, 20). Even though the benefit of ART for people living with HIV/AIDS is well established in terms of improving quality of life and reducing morbidity and mortality, there is a regional variation in the extent of its benefit(11).

A significant number of mortalities in HIV patients were recorded within a few years of starting ART. Various studies have found different factors as contributing for the occurrence of death in patients who already started their ART.

Various studies were conducted in Ethiopia to determine the mortality rate from and determinants of mortality among HIV patients who started ART. The estimated mortality ranged from 4.2% to 43% with majority of deaths occurred within 6 months of initiating ART (21-33). According to these studies, advanced stage of the disease (stage III and stage IV), nonworking functional status (bedridden and ambulatory), low baseline hemoglobin level, lower baseline weight patients, a CD4 count < 200 cells/μL of blood, not taking cotrimoxazole prophylaxis therapy, opportunistic infections, educational status, place of residence, nutrition and poor ART adherence were commonly identified as predictors of death in HIV. However, the effect of comorbidity on survival and mortality of PLWH has not been studied.

Little was also known about survival and predictors of mortality among HIV-infected patients in the study area. Hence, this study was aimed to investigate the outcomes of antiretroviral therapy, focused on adults on antiretroviral therapy in Debre Berhan Referral Hospital, North Showa Zone, Amhara National Regional State, Ethiopia.

2. LITERATURE REVIEW

2.1. Introduction to HIV/AIDS and HAART

Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome are global health burden(34). Global trends in HIV infection show an overall increase in HIV prevalence and substantial declines in AIDS related deaths largely attributable to the survival benefits of antiretroviral treatment(35).

Global HIV incidence reached its peak in 1997 with an incidence of 3.3 million new infections. Annual incidence has stayed relatively constant at about 2.6 million per year since 2005, after a period of fast decline between 1997 and 2005(14).

In 2016, there were an estimated 710,000 people living with HIV among the general population. Among these, 650,000 were adults. In the same year 67% of people living with HIV knew their status(36).

Antiretroviral therapy is defined as the use of a combination of three or more ARV drugs for treating HIV infection(37). The advent of potent combination therapy has dramatically reduced HIV-associated morbidity and mortality and has transformed HIV infection into a manageable chronic condition (38). Therefore, rapid ART initiation should be offered to all PLWH on the same day to people who are ready to start following confirmation of HIV diagnosis and clinical assessment(37). However, Because of concerns about transmitted drug resistance (e.g., K103N mutation), immediate ART should not be non-nucleoside reverse transcriptase inhibitor (NNRTI) based. Dolutegravir/tenofovir, alafenamide (TAF) (or tenofovir disoproxil fumarate [TDF])/ emtricitabine (or lamivudine) or bictegravir/TAF/emtricitabine or boosted darunavir TAF (or TDF)/emtricitabine (or lamivudine) are recommended for rapid initiation. Patients requiring abacavir should not begin until the result of testing for the HLA-B*5701 allele is available(39).

2.2. The survival and mortality of patients living with HIV/AIDS

A systematic review on mortality and its predictors among HIV infected patients taking antiretroviral treatment in Ethiopia indicated, 5%–40.8% of HIV patients in Ethiopia die in 2–5 years of initiating antiretroviral treatment. Most of the deaths in HIV patients occur early in the course of treatment(11).

Facility and community based Observational, analytical, retrospective non-concurrent cohort study conducted in Khartoum State showed that, the mortality rate was 9.9%(40). Which was a bit higher than a Retrospective study conducted on 520 records of patients in Aksum Hospital, Northern Ethiopia which was 8.85%(22). On the other hand, a retrospective study conducted in the ART center of MKCG Medical College, Berhampur, Ganjam, and Odisha showed that among a total of 956 patients who were under HAART, 204 (21.33 %) died(41). The discrepancy between studies might be due to the difference in sample size and the duration of follow up.

A retrospective cohort study conducted in Debre-Markos Referral Hospital showed that, the survival of patients were 57.0% with the incidence rate of 1.9 per 100 person years at 72 months(33). A study conducted in Somali Region, Eastern Ethiopia showed that among 784 patients, a total of 87 (11.1%) patients died during the five year follow-up period, with majority of deaths 49(56.3%) occurring in the first 3 months. The median survival time for death was 20.7 months and the estimated mortality was 8.4%, 9.8%, 11.3%, 12.7% and 14.1% at 6, 12, 24, 36 and 48 months respectively (26).

According to a Retrospective Study conducted in Dilla University Hospital a cohort contributed a total of 7151 person-years of follow up with 532 person-years for pre-ART and 6619 person-years for ART groups, a total of 243 patients (9.4%) died giving a crude death rate of 3.4 per 100 person-years, 1562 (60.6%) were censored alive, while total of 774 (30%) were lost to follow up. Of these, the majority 443 (57.2%) were those who started ART. For ART groups, 196 deaths (9.0%) were reported, giving an overall mortality rate of 3.0 per 100 person-years, while in a pre-ART group 47 (11.7%) deaths were reported giving a mortality rate of 8.8 per 100 person-years(24).

A retrospective cohort study conducted in Jinka Hospital showed that, among 350 study participants 35 (10.0%) were died providing the mortality rate of 1.75 per 100 person years. Twenty-two (62.9%) of the deaths occurred during the first year of treatment, while eight (22.9%) deaths occurred in the second year of follow-up(32).

A prospective Cohort Study in Seven University Teaching Hospitals also revealed that, among 976 patients, 101 deaths were recorded during follow-up period, all-cause mortality rate 10.3%; 5.4 deaths/100 person years of observation. Seventy percent of the deaths occurred within six months of starting ART(25).

A retrospective analysis of 5299 patient records dating from June 2003-March 2015 in South-West Ethiopia showed that, a total of 326 patients died in the 12 years follow-up period contributing to 6.2% cumulative incidence and 21.7 deaths per 1000 person-year observations incidence rate.(42)

A five year retrospective study conducted in Pawi General Hospital showed that, among six hundred two HIV infected adults were included in the final analysis 4.2% were died.(21)

2.3. Predictors of Survival and Mortality

2.3.1. Socio-demographic Predictors

Despite, the coverage of treatment and HIV care was equal among both genders, the study which was aimed to assess trends in gender disparity in HIV/AIDS in Ethiopia showed, HIV was 1.62 times more prevalent among adult women than men(43). Whereas, The overall mortality rate was 5.3/100 PYAR: 6.5/100 PYAR for males and 4.8/100 PYAR for females in a study conducted in South-Western Ethiopia(28). Another study conducted in Fiche hospital also showed that the proportion of mortality was higher among males than females (19 vs. 17%). The proportion of mortality was higher among the age group of 50+ years followed by 40–49 years (20.5 vs. 19%). With regard to educational status, 36 (26.1%) of the participants who had no education died after initiation of ART(29).

A 12 years follow-up period study in south-West Ethiopia showed early HIV mortality rates among adults were 50% less in separated, divorced or widowed patients compared with never married patients(42).

A cross-sectional study conducted in Vietnam indicated that, the majority attained less than high school (66.0%), lived in urban areas (70.6%), and lived with spouse/ partners (66.5%). Nearly 40% perceived barriers in traveling to ART clinics(44).

From a total of 6268 deaths among persons reported with HIV or AIDS that occurred from 1996 to 2013 in San Francisco, California,, 499 (8%) were women, 5588 (89%) were men, and 181 (3%) were transgender women(45).

A study conducted in Khartoum State showed that, Being literate was significantly associated with longer survival time compared to illiteracy, the hazard ratio HR was 0.338(46).

A retrospective cohort study at a large HIV clinic in South-Western Uganda showed that, older age at ART initiation (> = 50 years) was associated with a higher risk of mortality with adjusted relative risk (RR) at 1.63, (95% CI 1.26–2.11) compared to younger age. Male gender was also significantly associated with higher risk for mortality(47).

2.3.2. Base line Clinical, Laboratory and Treatment Related Predictors

A retrospective study conducted in Karamara general hospital, Jigjiga town, Eastern Ethiopia, revealed that among the 1439 patients, who had their baseline CD4 cell count documented, 935 (65%) had CD4 count ≤200 cell/µl while 113 (7.9%) of them had a CD4 count > 350 cell/µl, 670 (46.6%) of patients were stage III followed by 328 (22.8%) stage I patients, 367(25.5%) patients had a history of tuberculosis treatment and 811 (56.4%)(48).

A study on 5299 HIV/AIDS patients on ART in South-West Ethiopia showed that, early HIV mortality rates among adults were 1.6 times higher in patients with baseline CD4 count<200 cells/µl compared to baseline CD4 count ≥200 cells/µl(42). Another retrospective study conducted in Fiche Hospital in North Shoa, Oromia region, Ethiopia showed that patients with baseline CD4 count less than 200 cells/µl had 2.95 times higher

hazard to die than those had a CD4 ≥200 cells/μl(29). This could be due to the fact that depleted CD4 count can predispose PLWH for opportunistic infection and deficiency of micronutrients. Moreover, a prospective observational study done in Gandhi Hospital, Secunderabad also indicated, Patients whose CD4 count improved after initiation of ART, also had increase in serum albumin, weight gain, less mortality(49).

A retrospective study conducted in Selected Public Hospitals in Harar, Eastern Ethiopia showed that, early HIV mortality rates among adults were 2.134 times high hazard in patients with baseline WHO clinical stage III or IV compared to baseline WHO clinical stage I or II(50). Another retrospective study conducted in South-West Ethiopia also indicated that, early HIV mortality rate among adults were 1.5 times high hazard in patients with baseline WHO clinical stage III or IV compared to baseline WHO clinical stage I or II(42). These studies were also supported by a study conducted in Debre-Markos Referral Hospital, North West Ethiopia which revealed, patients who were on WHO clinical stage III and IV had1.63 times high hazard to die than patients who were WHO clinical stage I and II(33). This can happen because of the late presentation of the disease can pose a risk to the patient to develop immune reconstitution syndrome and in patients as soon as the treatment is initiated.

According to a study conducted in South-West Ethiopia, retrospective study conducted in Ethiopia patients with bedridden functional status had 2.9 times high hazard to die compared to working functional status(42). A retrospective study conducted in Khartoum State also indicted that, patients who were on bedridden and ambulatory functional status had 4.765 times high hazard to die than patients who were on working functional status(46).

A study conducted on a total of 600 HIV patients in Ethiopia, the risk of death for patients who lived with tuberculosis was about 2.872-fold times higher than those patients who were negative. Most of the HIV/AIDS patients on antiretroviral therapy were died in a short period due to tuberculosis comorbidity, began with lower amount of CD4, being underweight, and being on WHO clinical stage IV(30).

National level cross sectional study in Ethiopia showed that, among 7826 study participants a total of 1665 cases of opportunistic diseases were recorded with an overall prevalence estimated at 21.3% (95% confidence interval (CI): 20.36, 22.18%)(51). A retrospective

cohort study conducted in Debre Markos referral hospital showed that, fifty two per cent of the clients had three or more opportunistic illness(33).

A retrospective study conducted in Selected Public Hospitals in Harar, Eastern Ethiopia showed that patients those who had baseline opportunistic infection had 2.34 times high hazard to die than those who did not have(50). Another study conducted in Fiche Hospital, North Shoa, Oromia region, Ethiopia revealed that, those who had at least one and 2 and more baseline opportunistic infections had 1.31 and 2.30 times high hazard to die than those who had not baseline opportunistic infections respectively(29). A Hospital Based Retrospective Cohort Study conducted in India also showed that, patients who had a baseline opportunistic infection were 2.25 times more likely to die compared to those had not baseline opportunistic infections(52). Perhaps, opportunistic infections could increase the fatality of the HIV/AIDS due to paradoxical immune reconstitution syndrome.

A meta-analysis on Survival rate of AIDS disease and mortality in HIV-infected patients revealed that the 2, 4, 6, 8, and 10 years survival probabilities of progression from AIDS onset to AIDS-related death in patients who received HAART were estimated to be 87%, 86%, 78%, 78%, and 61%, respectively, whereas the 2-, 4- and 6-year survival probabilities of progression from AIDS onset to AIDS-related death in patients who did not receive HAART were estimated to be 48%, 26% and 18%, respectively(53).

A retrospective study conducted in Private Health Facilities in Addis Ababa, Ethiopia showed that, 44.2% of the study subjects were on TDF/3TC/EFV at baseline. The next most widely used baseline regimens were AZT/3TC/NVP (21.3%) and AZT/3TC/EFV (13%)(54)

A study conducted in Andhra Pradesh state of India showed, patients on Zidovudine-based ART regimen had a lower hazard for mortality than those on the Stavudine-based ART regimen(55).

A Hospital based retrospective cohort study conducted in India showed that, patients with history of alcohol usage after starting ART was 1.348 times more likely to die compared to those who did not use(52).

According to a study conducted in Jinka Hospital, South Omo, Ethiopia, the retention rate on ART were 79% at 72 months of follow-up(32). The finding of this study was in line with a study conducted in Addis Ababa showed where the retention rate were 80%(56). Another studies conducted in Myanmar(57), Mozambique(58), Zambia(59), Tanzania(60) and Iran(61) reported that the retention rate on ART was, 84%, 91.8%, 65%,53.5%,and 6.3% respectively.

2.4. Conceptual Framework

The conceptual framework used to guide the study explains the interaction between the independent and the dependent/outcome of interest in this study (**Figure 1**). The independent variable comprises of dimensions that include the socio demographic characteristics of the study population, the clinical and laboratory characteristics, treatment related characteristics and risky behaviors(24, 28, 33, 42, 43, 48, 54). Sociodemographic characteristics have direct effect on clinical and laboratory characteristics and risky behavior, which also have both direct and indirect effect on the outcome variable. Hence, the outcome variable is the cumulative effect of independent variables.

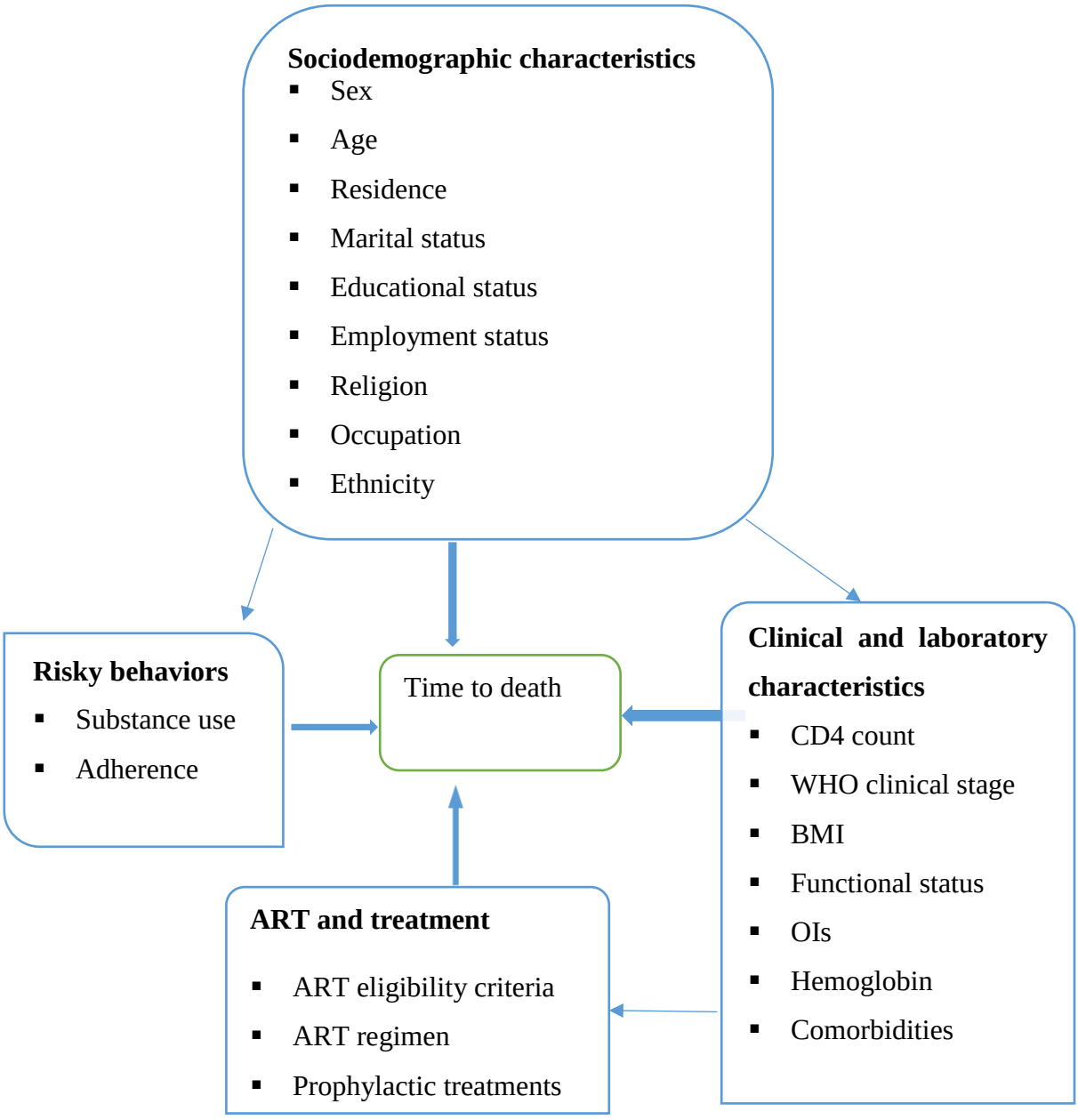

Figure 1: Conceptual frame work on survival and predictors of mortality among adult HIV/AIDS patients on

3. SIGNIFICANCE OF THE STUDY

The findings of this study will provide empirical evidence for program planner, decision makers to design a new and/or strengthen the existing intervention that improves the survival and reduce the high probability of death in HIV patients, for antiretroviral therapy program implementer at the different level by enabling them to access a base line data on predictors of survival of patients on highly active antiretroviral treatment.

4. OBJECTIVES

4.1. General Objective

To assess the survival and predictors of mortality among adult patients started highly active antiretroviral therapy at Debre Berhan Referral Hospital, North Showa Zone, Amhara National Regional State, Ethiopia 2018/2019.

4.2. Specific Objectives

1. To determine the time to death among adults living with HIV/AIDS after initiation of highly active antiretroviral treatment in Debre Berhan Referral Hospital, North Showa Zone, Amhara National Regional State, Ethiopia.

2. To identify predictors of mortality among adults living with HIV/AIDS after initiation of highly active antiretroviral treatment in Debre Berhan Referral Hospital, North Showa Zone, Amhara National Regional State, Ethiopia.

3. To determine the proportion of retention rate of adults living with HIV/AIDS on antiretroviral treatment in Debre Berhan Referral Hospital, North Showa Zone, Amhara National Regional State, Ethiopia.

4. To identify the determinant factors of the retention rate of adults living with HIV/AIDS on antiretroviral treatment in Debre Berhan Referral Hospital, North Showa Zone, Amhara National Regional State, Ethiopia.

5 .METHODOLOGY

5.1. Study Area and Period

The study was conducted at DBRH, which is found 130km North-East of Addis Ababa. The hospital is found in Debre Berhan town, North Showa Zone, Amhara National Regional State, Ethiopia. The foundation of the town was traced back to the regime of Atse Zereyakob.

Regarding health services in the city, there are one government and one private hospital, three government health centers, five health posts, and 18 private clinics.

Debre Berhan Referral Hospital is the only government hospital in the city and it is zonal referral hospital serving the population of the zone as a referral center. It has a total of 150-bed facility with a catchment population of 2.8 million people. The services delivered at DBRH include ear, nose and throat, surgery, outpatients department, emergency, tuberculosis and HIV, gynecology and obstetrics, pediatrics and neonatal intensive care unit (NICU), maternal and child health, physiotherapy, dental, radiology, psychiatry, and internal medicine. The hospital has a total of 334 healthcare employees: 38 physicians, 180 nurses, 26 midwives, 7 anesthetists, 31 laboratory technicians, 2 physiotherapists, 4 dentists, 6 radiographers, 4 optometrists and 36 pharmacists.

Debre Berhan was the only hospital in the North Showa area providing ART in 2007 with core ART team at that time consisted of three physicians, three nurses, three lab personnel, and 11 case managers. Since, the start of expanded Partnership activities like twinning with American International Health Alliance over the years to include collaborations between Debre Berhan Referral Hospital, Mehal Meda Hospital and Enat Hospital, and Debre Berhan University ART uptake in the region has increased from 1,789 patients at one facility to 5,282 patients at Debre Berhan, four rural hospitals, and 86 area health centers(62). Now a days, Debre Berhan hospital provides a care for a total of 2005 HIV/AIDS patients.

The study was conducted from March to April, 2019 based on medical record review of HIV/AIDS patients on HAART enrolled from January 1st, 2013 to December 30th, 2017 time periods will be followed up to December 30th, 2018.

5.2. Study Design

Institutional based retrospective cohort study design was employed for this study.

5.3. Source Population

All adult persons living with HIV/AIDS and that have started antiretroviral therapy in DBRH.

5.4. Study Population

The study population contained adult patients fulfilling the inclusion criteria at DBRH ART center.

5.5. Inclusion and Exclusion Criteria

5.5.1. Inclusion Criteria

- HIV-positive adults aged 15 years or older who started ART since January1st 2013 to December 30th 2018
- HIV patients with complete intake form, registers, and follow up form.

5.5.1. Exclusion Criteria

- Transfer in (patients who initiated treatment outside Debre Berhan Referral Hospital)
- Patients with competing causes of death (accident, or any non-AIDS malignancies)

5.6. Sample Size Determination

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

P = proportion of mortality among adult on ART is 43%, from study done in Debre Markos Referral Hospital(33).

$Z_{\alpha/2}$ = the corresponding Z score of 95% CI, d= Margin of error (5%) and N= Sample size

$$n = \frac{(Z\frac{\alpha}{2})^2 \times p(1-p)}{(d)^2}$$

$$n = \frac{(1.96)^2 \times 0.43(1-0.43)}{(0.05)^2}$$

$n = 377$, Adding 10 % contingency rate for an incomplete chart makes the final sample size 415.

For the second objective, the sample size was determined using double population proportion formula by considering sex, WHO clinical stage(stage I/II vs stage III/IV), CD4 count(≥ 200 cells/µl vs <200 cells/µl) and functional status(Working/ Ambulatory vs bed ridden) as the major predictor variables based on study done in Jimma university teaching hospital(42) . The sample size was calculated using two sample proportion formulas in Epi-Info version 7 for windows(63). Calculation was based on the assumption that type I error of 5%, power of 80%. CD4 count is considered as independent predictor since it gives the maximum sample size (Table 1).

$$let\ p = \frac{p1 + rp2}{1 + r}$$

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

Where

P1=proportion of death among none exposed.

P2=proportion of death among exposed

α=level of significance, Zα/2=1.96 at 95%CI

Power=80%=1-β, Zβ=1.28

n=the minimum required sample size in each group and r is the ratio of non-exposed to exposed 1:1

Table 1: Sample size calculation to assess Survival status and predictor of mortality among adult HIV/AIDS patients on ART in DBRH ART clinic, North Showa, Amhara National Regional State, Ethiopia, 2019.

Variable	Assumptions	Total sample size	After adding 10%
Sex	P1= 7 P2= 8.8	270	297
WHO staging	P1= 8.5 P2= 9.4	220	242
Base line CD4 count	P1= 4.7 P2= 8.4	406	447
Functional status	P1= 5.2 P2= 18.9	366	403

Then the largest sample size (N= 447) was selected as the final sample size for the study.

5.7. Sampling Technique

Simple random sampling technique was used for selecting study subjects among 1186 patients` card that were obtained from ART clinic.

5.8. Data Collection

A standard data abstraction checklist was used for recording information extracted from electronic and paper based database and patient cards. This form was developed using the standardized ART entry and follow up form employed by the ART clinic. Training was given to data collectors on how to review registration logbooks and medical charts and maintain confidentiality of the data. ART nurses working in the ART clinics were recruited as data collectors.

The collected data was preserved in a secure environment to avoid loss and breach of confidentiality. All collected data was cleaned, validated, coded and stored at the end of each day by the principal investigator**.** Processing and storing was done both electronically by entering data in to epi data version 4.2.

5.9. Study Variables

5.9.1. Dependent Variable

- Time to death (survival status)

5.9.2. Independent Variable

- Socio demographic factors including age, sex, educational status, occupational status, marital status
- Clinical and laboratory factors including CD4 count, WHO clinical staging, functional status, hemoglobin level,
- ART regimens and medications
- Risk behaviors including substance use, adherence

5.10. Operational Definitions

Antiretroviral therapy: the use of a combination of three or more ARV drugs for treating HIV infection(37).

Event: Death in HIV/AIDS related illnesses, which is labeled as "1".

Time: The time from the beginning of an observation period to an event, or end of the study, or loss of contact or withdrawal from the study, which is measured in months.

Time to death: time to death was calculated at the time between the date of unequivocal initiation of ART to the date of death.

Censored: A subject without an event during the observation time, which is labeled as "0"

Survival time: is the time to the occurrence of a given event of interest, in the case of this study the death of a person(64).

Retention: is defined as the ability to adhere to critical aspects of care(59). In the current study retention was determined by a patient attending the last scheduled follow up appointment.

Adherence: Adherence is defined as the correct and timely dosing of prescribed medication by the health care provider.

Comorbidity: According to International Classification of Disease-10, Disease from Charles comorbidity index was used during data collection. The presence of any of these diseases at a time of diagnosis co-occurring with HIV/AIDS labeled as "yes" response(65).

5.11. Data Quality Assurance

The quality of data was assured before, during and after data collection accordingly.

Before data collection: - objective based and standardized questionnaire was prepared, Pretest on 5% of medical record review was done to identify variables which could be added and to reduce unrecorded from the medical chart and electronic records. Training to data collectors on sampling procedures and data collection process was provided for two days.

During data collection: - the principal investigators had insured completeness and consistence of the questionnaires administered each day.

After data collection:-the collected information was rechecked for its completeness and consistence by the principal investigators before transferring to a computer software. Non overlapping code was given for each question and the coded data was entered and cleaned in Epi data version 4.2.

5.12. Data Processing and Analysis

Data was entered using epi data version 4.2 and Statistical analyses was performed using Stata version 15.0. Descriptive statistics such as mean, median, interquartile range (IQR) and standard deviation were used to summarize the characteristics of the cohort. Kaplan-Meier models was used to estimate the patients` survival after ART initiation, and log rank tests was used to compare survival curves. The necessary assumptions for the model was checked by scheonfeld residual test.

Cox proportional hazards regression models was used to identify independent predictors of mortality and calculate hazard ratios. Bi-variable Cox proportional hazards regression was tested first and those independent variables which become fitted on the bi-variable regression at 0.25 level of significance were included in the multivariable analysis(66). Multiple Cox

proportional hazards regression was done at 0.05 level of significance to determine the net effect of each explanatory variable on time to death after initiation of ART. The results of these models were expressed as hazard ratios (HRs) with 95% CI.

5.13. Ethical Consideration

Ethical clearance had been obtained from the Institutional Review Board (IRB) of Addis Ababa University, College of Health Science before conducting the study. After securing ethical clearance from IRB of Addis Ababa University, Debre Berhan Referral Hospital had been informed about the objective of the study through a support letter from Addis Ababa University, School of nursing and midwifery.

Informed consent was not needed. Since, the study was conducted through review of medical records, the individual patients had not been exposed to any harm as far as the confidentiality were kept. To keep the confidentiality of the patients, data collectors were recruited from ART clinic and personal identifiers had not been included in the data collection format.

5.14. Dissemination of the study

After completion of research, the result of the study will be presented and submitted to School of Nursing and Midwifery College of Health Science, Addis Ababa University in partial fulfillment of the requirements for the degree of Masters of Science in Adult Health Nursing. The result will also be submitted to DBRH. In addition, the final result document will be presented to responsible bodies working in the area and the findings of the study will be published through peer reviewed journals.

6. RESULT

6.1. Socio-demographic characteristics of the study participants

Among 1186 HIV positive adults (≥15 years), who were enrolled from January 1st, 2013 to December 30st, 2018, 447 patients on ART were followed. Among 447 patients, about two-third 299 (66.89%) of study participants were females, 358 (80.1%) were from urban area. The mean and median age of the cohort at ART initiation was 37 years and 36 years (IQR, 30 to 44 years), with SD ± 10.818years respectively. The majority of study participants 414(92.6%) were Orthodox Christians, 146(28.2%) completed primary school. The socio-demographic characteristics of the study participants are shown below (Table 2).

Table 2: Socio-demographic characteristics of adult HIV/AIDS patients on ART in DBRH ART clinic, North Showa, Amhara National Regional State, Ethiopia, 2019 (n=447)

Variable	Category	Vital status at last contact		Total No. (%)
		Censored No. (%)	Death No. (%)	
Age of patient	15-24	41(95.35)	2(4.65)	43(9.62)
	25-34	131(89.12)	16(10.88)	147(32.89)
	35-44	122(83.56)	24(16.44)	146(32.66)
	≥45	99(89.19)	12(10.81)	111(24.83)
Sex	Male	129(87.16)	19(12.84)	148(33.11)
	Female	264(88.29)	35(11.71)	299(66.89)
Family size	≤2	107(88.43)	14(11.57)	121(27.1)
	3-4	165(85.05)	29(14.95)	194(43.4)
	>4	121(91.67)	11(8.33)	132(29.5)
Region	Amhara	364(87.9)	50(12.1)	414(92.6)
	Oromia	22(84.6)	4(15.4)	26(5.8)
	Others	7		7(1.6)
Residence of patients	Urban	312(87.15)	46(12.85)	358(80.1)
	Rural	81(91.01)	8(8.99)	89(19.9)
Marital status of women	Single	82(91.1)	8(8.9)	90(20.13)
	Married	224(89.6)	26(10.4)	250(55.92)
	Divorced	43(76.8)	13(23.2)	56(12.53)
	Widowed	44(86.27)	7(13.73)	51(11.42)
Educational status	Illiterate	90(87.4)	13(12.6)	103(23)
	Can read and write	83(89.25)	10(10.75)	93(20.8)
	Primary	113(89.7)	13(10.3)	126(28.2)
	Secondary	69(86.25)	11(13.75)	80(17.9)
	Tertiary	38(84.4)	7(15.6)	45(10.1)
Occupational status	Farmer	39(86.7)	6(13.3)	45(10.1)
	Merchant	44(91.7)	4(8.3)	48(10.7)
	Governmental employee	59(86.76)	9(13.24)	68(15.2)
	Non-governmental employee	48(87.27)	7(12.73)	55(12.3)
	Day laborer	42(84)	8(16)	50(11.2)
	Jobless	52(89.66)	6(10.34)	58(13)
	Driver	4(100)	0	4(0.9)
	House-wife	105(88.24)	14(11.76)	119(26.6)
Disclosure status	Disclosed	328(89.37)	39(10.63)	367(82.1)
	Not disclosed	65(81.25)	15(18.75)	80(17.9)

6.2. Baseline clinical, laboratory and ART information of adults on ART

A large proportion of the study participant, that is 169(37.7%) of the study participant were on WHO clinical stage II at the baseline. More than two-third, 340(76%) of the cohort had at least one opportunistic infections. The median CD4 count was 329 (IQR, 187-578) cells/µl. The median hemoglobin value was 14 (IQR, 12.1-15.2) g/dl. The vast majority (about 85%) of patients received cotrimoxazole prophylaxis; and 16.5% were on anti-tuberculosis treatment. The overwhelming majority, that is 412(92.2%), of the study participant had good adherence as shown in Table 3.

Table 3: Clinical, laboratory and treatment related characteristics of adult HIV/AIDS patients on ART in DBRH ART clinic, North Showa, Amhara National Regional State, Ethiopia, 2019 (n=447)

Variable	Category	Vital status at last contact		Total No. (%)
		Censored No. (%)	Death No. (%)	
WHO staging	Stage I	149(94.3)	9(5.7)	158(35.3)
	Stage II	153(90.5)	16(9.5)	169(37.8)
	Stage III	76(85.4)	13(14.5)	89(19.9)
	Stage IV	15(48.4)	16(51.6)	31(7)
Opportunistic infections	No	83(77.57)	24(22.43)	107(24)
	Yes	310(91.2)	30(8.8)	340(76)
TB treatment during follow up	Yes	57(77)	17(23)	74(16.5)
	No	336(90.1)	37(9.9)	373(83.5)
CD4 count	≥200 cells/μL	304(96.2)	12(3.8)	316(70.7)
	<200 cells/μL	89(67.9)	42(32.1)	131(29.3)
Body mass index	≤18.5	82(67.8)	29(32.2)	121(27.1)
	18.5-25	239(91.6)	22(8.4)	261(58.4)
	≥25	62(95.4)	3(4.6)	65(14.5)
functional status at base line	working	325(92.9)	25(7.1)	350(78.3)
	Ambulatory	67(77.9)	19(22.1)	86(19.2)
	bedridden	1(9.1)	10(90.9)	11(2.5)
Hgb at base line	≥10 gm/dl	365(93.8)	24(6.2)	389(87)
	<10 gm/dl	28(48.3)	30(51.7)	58(13)
ART eligibility criteria	CD4 below 200	205(87.6)	29(12.4)	234(52.4)
	WHO stage I, II, and III with TLC <1200	85(98.8)	1(1.2)	86(19.2)
	WHO stage IV	32(68.1)	15(31.9)	47(10.5)
	Residence of catchment area	28(93.3)	2(6.7)	30(6.7)
	No identified barriers for adherence	43(86)	7(14)	50(11.2)
CPT	Yes	341(89.3)	39(10.7)	380(85)
	No	52(77.6)	15(22.4)	67(15)
Comorbidity	Yes	59(65.6)	31(34.4)	90(20.1)
	No	334(93.6)	23(6.4)	357(79.9)
Substance use	Yes	96(82.8)	20(17.2)	116(26)
	No	297(89.7)	34(10.3)	331(74)
Adherence	Good	373(90.5)	39(9.5)	412(92.2)
	Fair	17(65.4)	9(34.6)	26(5.8)
	Poor	3(33.3)	6(66.7)	9(2)

6.3. Survival status of patients on ART

The mean survival time of patients was 63.7months (95%CI; 61.66- 65.79) at 72 months of follow up. The overall mortality rate in the cohort during the 1,291 person-years of observation (PYO) was 4.18 per 100 (95% CI: 3.20- 5.45) person-years follow up. The cumulative incidence of death for this study was 54(12.1%) with the confidence interval (95%CI, 8.9-15.2%) of patients were died over six years. Whereas, 393 (87.9%) of the study participant were censored, including 298 (66.7%) on ART, 4(0.9%) stopped ART, 25 (5.6%) were lost to follow-up, and 66(14.8%) were transferred out. More than half, 30 (55.6%) of the deaths occurred during the first year of treatment initiation, while 12 (22.2%) of the deaths occurred in the second year of follow-up.

6.4. Overall survival of patients on ART

In the present study, 447 patients on ART were followed up for a total of 72 months. The Kaplan-Meier survival estimation showed that overall estimated survival rate after the initiation of HAART was 81.7 % (95% CI, 75.36-86.54%) at 72 months of follow up. The estimated cumulative survival was 92.4%, 89.6%, 88.1%, 86.6%, 85.3% and 81.7% at 12, 24, 36, 48, 60 and 72 months respectively as shown in **figure2**. The study revealed that the highest rate of mortality occurred during the first year of initiation of highly active anti-retroviral therapy.

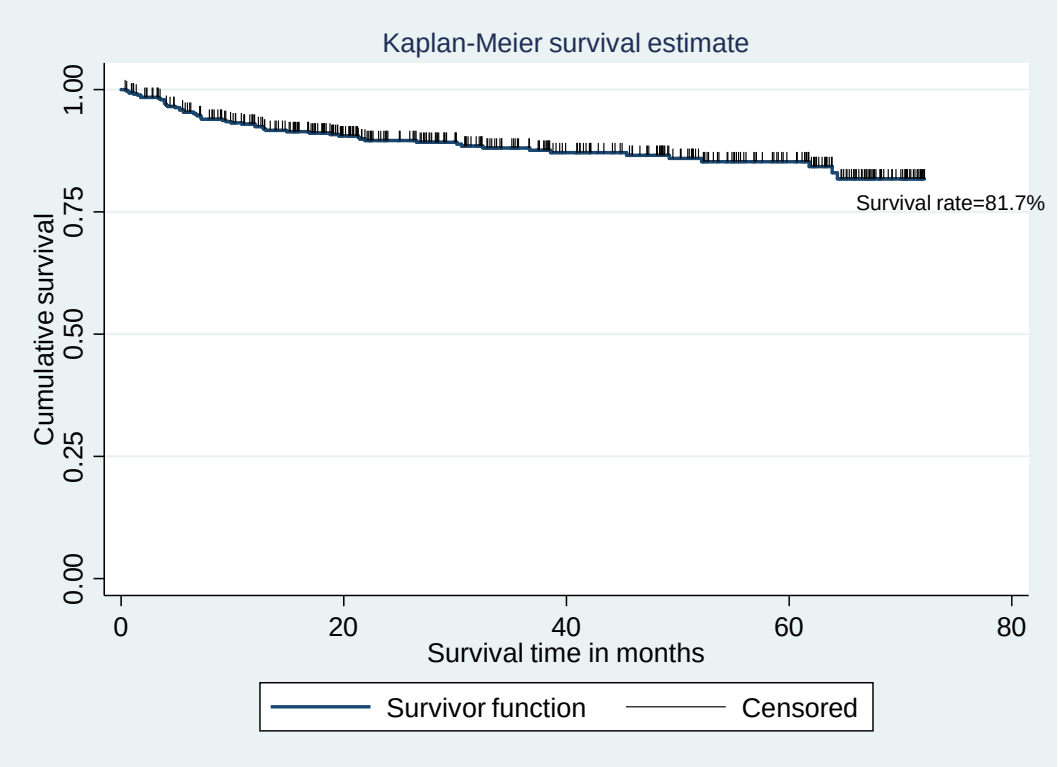

Figure 2: Overall Kaplan-Meier estimates of patients starting ART in DBRH from January 1st 2013 to December 30th 2018

6.5. Survival function among different groups of patients on ART

The log-rank test was conducted to check for the existence of any significant differences in survival among the various levels of categorical variables considered in the study. The test statistics in this study showed that a significant association in survival function for different categorical variables. Accordingly, the Kaplan-Meier analysis indicated significant evidence of differences in baseline opportunistic infections, functional status, comorbidity, WHO clinical staging, baseline hemoglobin and baseline CD4 count. The Kaplan-Meier survival function indicated that, those who had WHO clinical stage I, II and III at baseline had a longer survival time than those with WHO clinical stage IV (34.3 months, 95% CI; 23.03-45.6). This difference was statistically significant at P-value=0.000. The mean survival time for those who had comorbidity and past opportunistic infection was (49.13 months, 95% CI; 42.70-55.56) and (57.1 months, 95% CI; 51.8-62.4) respectively. The survival time of patients with bedridden functional status was shorter than those with working and

ambulatory functional status (7.26 months, 95% CI; 3.75-10.76). This difference was statistically significant at P-value=0.000.

The lowest survival probabilities were observed for patients with a bed ridden functional status (0%), a baseline haemoglobin <10(36.74%), a baseline CD4 count <200 cells/μL (55.25%) and WHO stage IV disease (45.77%) as shown in table 4.

Table 4: Survival time, cumulative survival probability, significance and log rank test for the study population according to different characteristics of patients during six-year of follow-up (Kaplan-Meier method) of HIV/AIDS patients on ART in DBRH, North Showa, Amhara National Regional State, Ethiopia, 2019 (n=447)

Variable	Category	Mean Survival time in month (95% CI)	Overall 6- year survival (%)	Log rank test (p-value)
Age of patient	15-24	68.64 (64.131- 73.2)	93.8	0.1301
	25-34	64.68 (61.4- 67.98)	79.79	
	35-44	60.6 (56.46- 64.74)	75.4	
	≥45	64.27(60.29- 68.24)	87.2	
Sex	Male	63.05 (59.31- 66.79)	84.92	0.8217
	Female	63.9 (61.4-66.4)	78.81	
Residence	Urban	63.3 (60.9-65.6)	79.78	0.3909
	Rural	65.54 (61.28-69.80)	90.09	
Religion	Orthodox	63.7 (61.49-65.92)	82.12	0.6106
	Muslim	65.478(60.00-70.95)	80.19	
	Protestant	59.35 (45.6-73.09)	81.82	
	Others	46.92(12.2-81.58)	50	
Educational status	Illiterate	63.88 (59.88-67.89)	76.15	1.70 (0.7899)
	Can read and write	64.48 (60.09-68.87)	85.83	
	Primary	64.6 (60.9-68.42)	86.78	
	Secondary	62.64 (57.6-67.67)	82.11	
	Tertiary	59.33(51.86-66.79)	71.67	
Occupational statues	Farmer	61.10 (54.18-68.03)	85.08	2.31 (0.9409)
	Merchant	65.80 (60.04-71.57)	89.09	
	Governmental employee	62.13 (56.3-68.02)	84.46	
	Non-governmental employee	62.58 (56.16-69.00)	80.36	
	Day laborer	61.40 (54.70-68.11)	79.39	
	Jobless	65.65(61.03-70.27)	72.28	
	House-wife	64.19 (60.40-67.97)	81.76	
Family size	≤2	64.33 (60.52-68.13)	78.64	2.65 (0.2662)
	3-4	61.89 (58.52-65.26)	79.56	
	≥4	65.91 (62.64-69.20)	89.95	
Marital status	Married	65.76 (61.67-69.86)	88.26	8.62 (0.0348)
	Single	64.82 (62.24-67.40)	85.32	

Table 4 cont`d

	Widowed	62.16 (55.45-68.87)	80.52	
	Divorced	56.25 (49.12-63.4)	50.89	
Disclosure status	Disclosed	64.6(62.4-66.78)	84.55	3.88
	Not disclosed	59.68 (54.05-65.33)	69.59	(0.0488)
WHO staging	Stage I	68.14 (65.70-70.59)	92.89	88.49
	Stage II	66.08 (63.32-68.84)	80.29	(0.0000)
	Stage III	59.75 (53.99- 65.5)	77.20	
	Stage IV	34.3 (23.03-45.6)	45.77	
Opportunistic infections	Yes	57.1 (51.8-62.4)	71.86	12.90
	No	65.84 (63.75-67.93)	85.02	(0.0003)
TB treatment during follow up	Yes	56.11 (49.5-62.71)	74.11	10.18
	No	65.19 (63.12-67.26)	82.87	(0.0014)
Comorbidity	Yes	49.13 (42.70-55.56)	58.42	54.53
	No	67.62 (65.89-69.35)	87.90	(0.0000)
CD4 count	≥200 cells/µl	69.38(67.93-70.83)	92.80	77.23
	<200 cells/µl	50.14 (44.79-55.50)	55.25	(0.0000)
Body mass index	≤18.5	54.90 (49.58-60.22)	67.16	26.95
	18.5-25	66.27 (63.98-68.56)	84.24	(0.0000)
	≥25	68.87 (65.49-72.25)	94.86	
functional status at base line	working	67.25 (65.46-69.05)	86.94	201.57
	Ambulatory	56.41 (50.37-62.45)	71.42	(0.0000)
	bedridden	7.26(3.75-10.76)	0.000	
Hgb at base line	≥10 gm/dl	67.81 (66.19-69.43)	88.91	128.58
	<10 gm/dl	36.74 (28.33-45.15)	34.90	(0.0000)
CPT	Yes	64.96 (62.87-67.04)	84.14	8.13
	No	56.55 (49.83-63.27)	67.58	(0.0043)
Substance use	Yes	60.39(55.78 64.9)	71.16	4.03
	No	64.8 (62.63 67.14)	85.47	(0.0447)
Adherence	Good	65.49 (63.5-67.4)	85.38	49.03
	Fair	45.20(34.79-55.61)	34.33	(0.0000)
	Poor	29.73 (13.95-45.52)	25.40	

The graph below shows that those who had no baseline opportunistic infections had better mean survival time which was (65.84 months, 95% CI: 63.75-67.93) than those who had opportunistic infections at the baseline (57.1 months, 95% CI: 51.8-62.4), this difference was statistically significant with p-value=0.0003. Figure 3

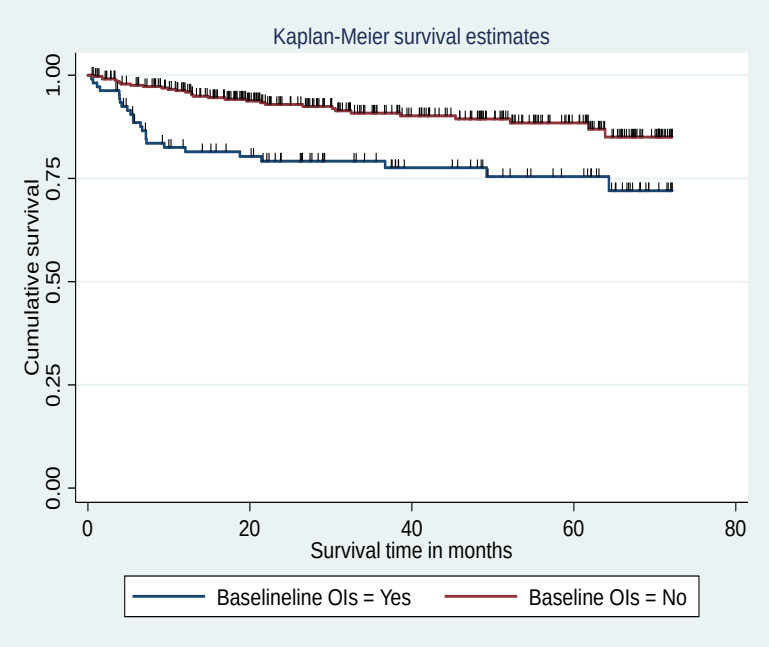

Figure 3: The Kaplan-Meier survival curves compare survival time of patients starting ART by baseline OIs in DBRH, North Showa, Amhara National Regional State, Ethiopia from January 1st 2013 to December 30th 2018.

The mean survival time for those who had clinical stage I, II or III at baseline had a longer survival time than those in advance clinical stage (IV) (34.3 months, 95% CI; 23.03-45.6) this difference was statistically significant with p-value = 0.000 **figure 4.**

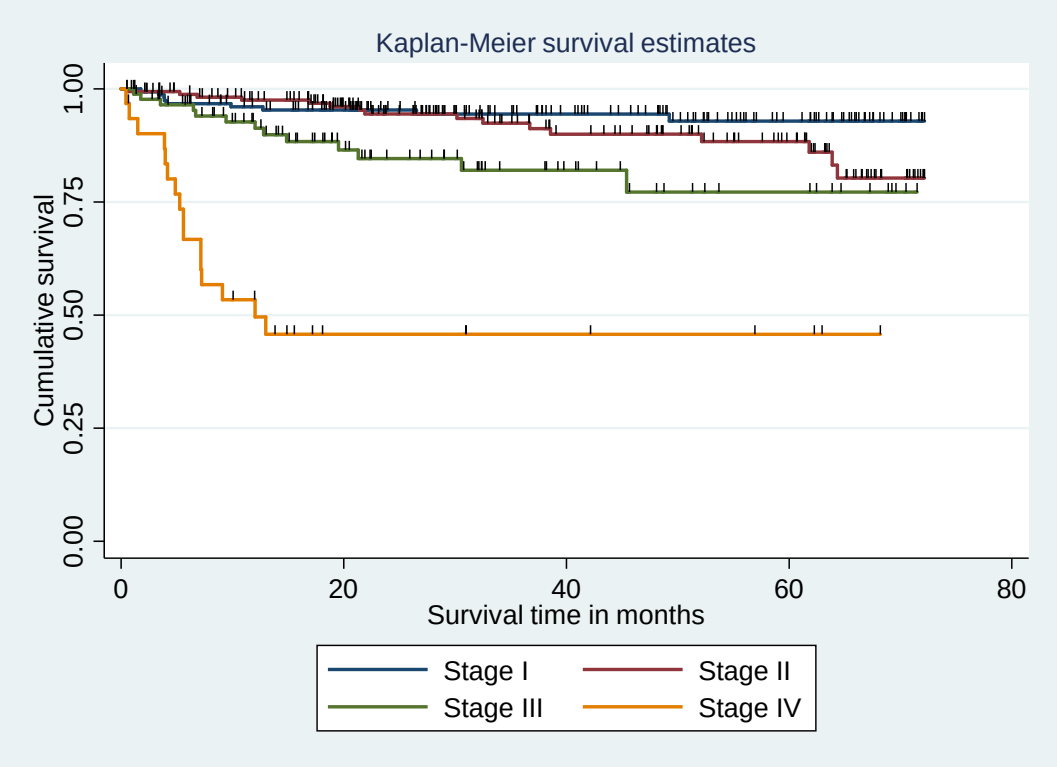

Figure 4: The Kaplan-Meier survival curves compare survival time of patients starting ART by baseline WHO clinical stage in DBRH, North Showa, Amhara National Regional State, Ethiopia from January1st 2013 to December 30th 2018.

The Kaplan-Meier graph shows that mean survival time for those who had working and ambulatory functional status was ((67.25months, 95%CI; 65.46-69.05 for working and 56.41months, 95%CI; 50.37-62.45 for ambulatory), which was higher than the mean survival time of individuals who were bedridden (7.26months, 95% CI: 3.75-10.76). This difference was statistically significant with p-value = 0.000(Figure 5).

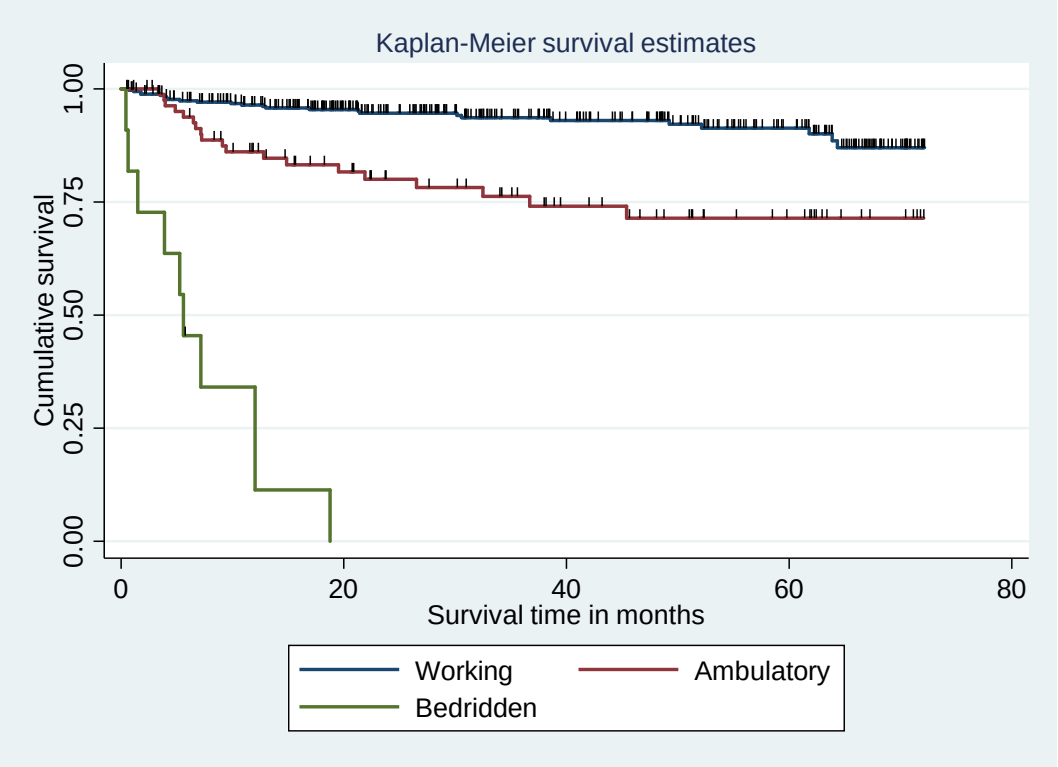

Figure 5: The Kaplan-Meier survival curves compare survival time of patients starting ART by functional status in DBRH, North Showa, Amhara National Regional State, Ethiopia from January 1st 2013 to December 30th 2018.

The Kaplan-Meier graph shows that mean survival time for those who had haemoglobin level ≥10 mg/dl was (67.81 months, 95%CI; 66.19-69.43), which was higher than the mean survival time of individuals who had a hemoglobin level Below 10 mg/dl (36.74 months, 95% CI: 28.334-45.15). This difference was statistically significant with p-value = 0.0043 (Figure 6).

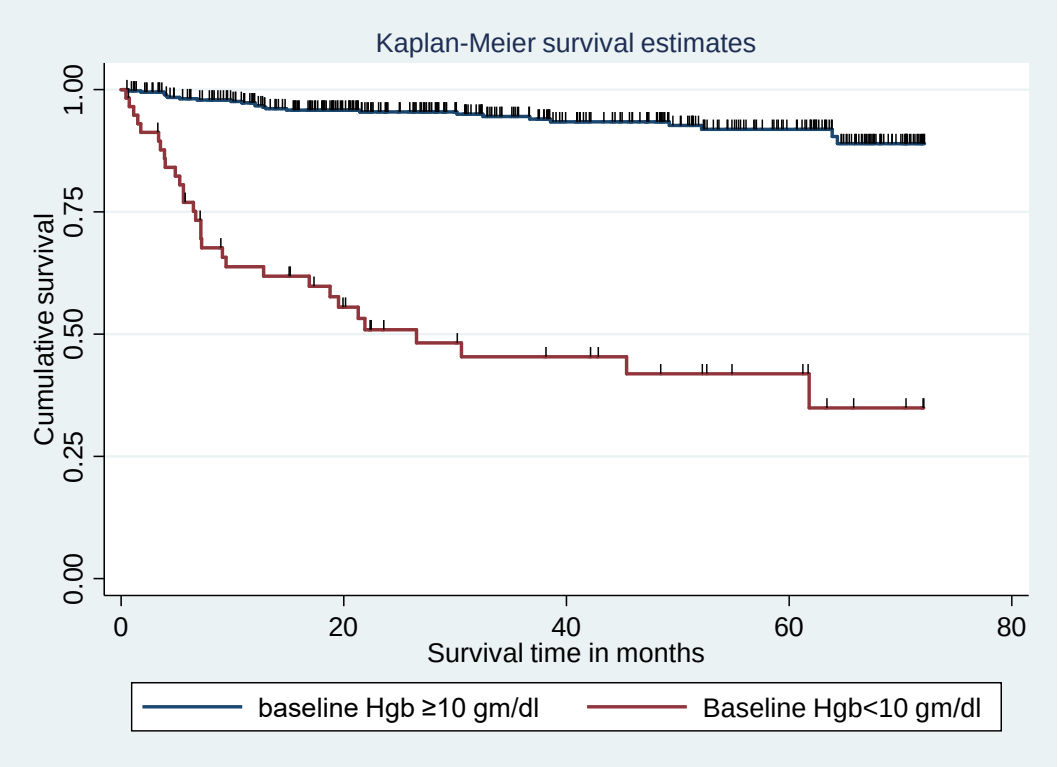

Figure 6: The Kaplan-Meier survival curves compare survival time of patients starting ART by base line Haemoglobin in DBRH, North Showa, Amhara National Regional State, Ethiopia from January1st 2013 to December 30th 2018.

Regarding with the CD4 count, the mean survival time for those who had a CD4 count ≥200 cells/µL had a longer survival time than those with a CD4 count <200 cells/µL(50.14months, 95%CI; 44.79-55.50),which was statistically significant at P-value=0.000 figure 7.

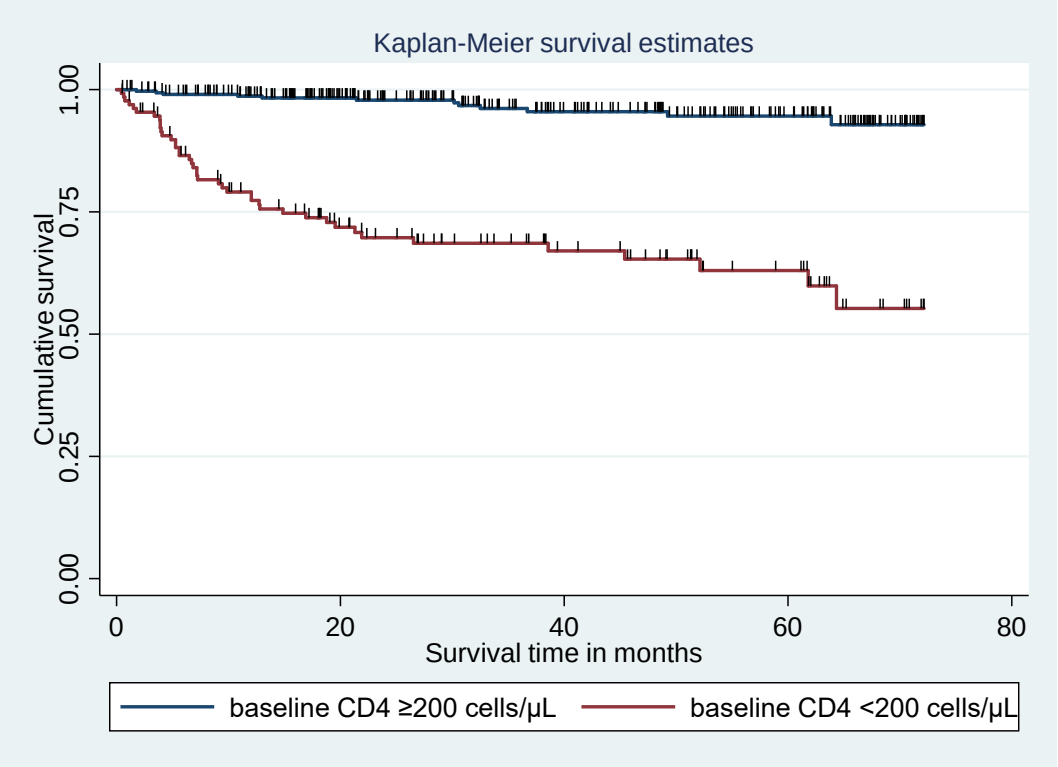

Figure 7: The Kaplan-Meier survival curves compare survival time of patients starting ART by base line CD4 in DBRH, North Showa, Amhara National Regional State, Ethiopia from January1st 2013 to December 30th 2018

The Kaplan–Meier graph along with log rank test revealed that the mean survival time for those who had no comorbidity had a longer survival time (67.62months, 95% CI: 65.89-69.35) than who had comorbidity (49.13 months, 95% CI: 42.70-55.56).This difference was statistically significant with p-value = 0.000

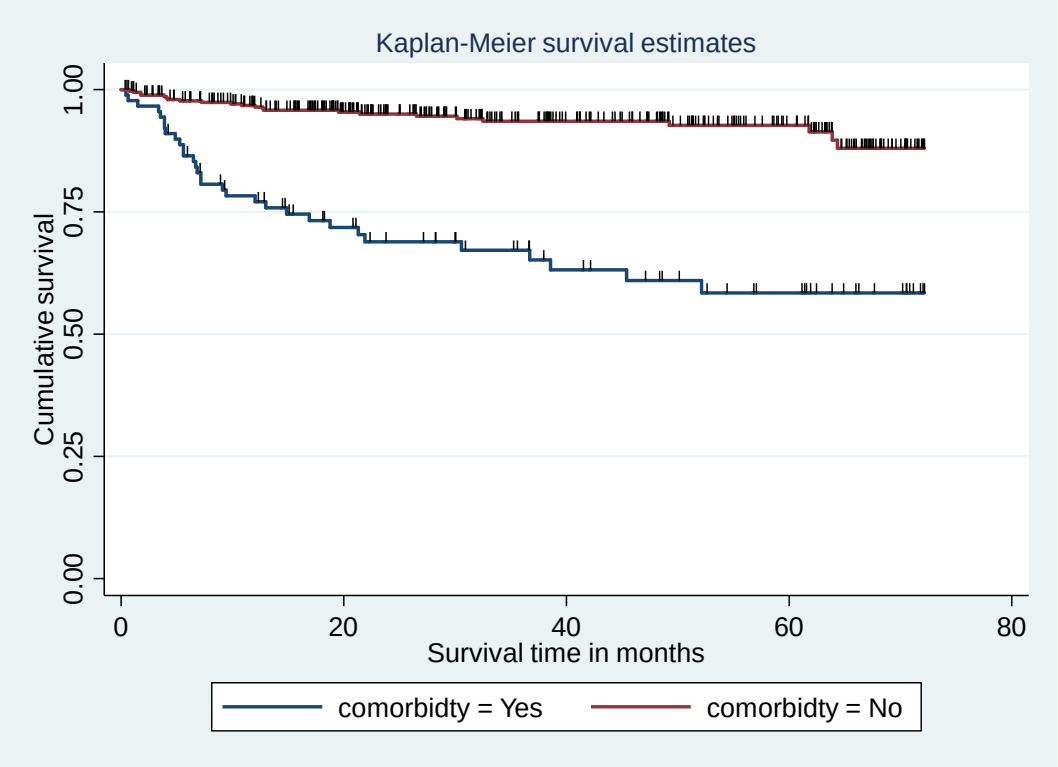

Figure 8: The Kaplan-Meier survival curves compare survival time of patients starting ART by comorbidity in DBRH, North Showa, Amhara National Regional State, Ethiopia from January1st 2013 to December 30th 2018

6.6. Predictors of mortality

In bivariable cox proportional Hazard regression model, marital status, disclosure status, substance use, baseline opportunistic infections, WHO clinical stage, functional status, baseline haemoglobin level, baseline CD4 count, body mass index, cotrimoxazole prophylactic therapy adherence and comorbidity were all associated with survival status (P <0.25).

In multivariable Cox regression analysis those variables with p-value <0.25 in the bivariable analysis were included. In multivariable cox proportional hazards model, seven variables were associated with mortality of patients on ART.

The result of multivariable analysis revealed that those who had opportunistic infection had 1.86 times high hazard to die compared to those who had not (aHR: 1.86, 95%CI: 1.048-3.330). Patients who had comorbidity had 2.56 times high hazard to die than those who had

not comorbidity (aHR: 2.56, 95% CI: 1.391-4.740). Regarding to WHO clinical staging, Patients with stage III had 2.88 times high hazard to die than who had stage I (aHR: 2.88, 95% CI; 1.204-6.899) and those who had stage IV had 15.6times high hazard to die than those with stage I (AHR: 15.6, 95%CI; 6.609-36.948) **see table 5**.

6.7. The Retention Rate and Factors Affecting the Retention of Patients on ART

The ART retention rate 66.7% (95%CI, 62.4-70.7) after 72 months of follow-up. The ART retention rate was significantly associated with being divorced (aOR, 2.8; 95%CI, 1.19-6.34) and widowed (aOR, 3.7; 95% CI, 1.49-9.41) in marital status, baseline Hgb ≥10mg/dl (aOR, 3.4; 95% CI, 1.76-6.52), baseline CD4≥200 cells/μl (aOR, 1.7; 95% CI, 1.075-2.83). Patients with these predictors were more likely to continue ART than their counterparts **see table 5**.

Table 5: Results of the bi-variable and multivariable Cox regression analysis of HIV patients receiving ART in DBRH, North Showa, Amhara National Regional State, Ethiopia in 2019 (n=447)

Covariates	Bivariate cHR(95%CI)	p-value	Multi-variate aHR (95%)	p-value
Marital status				
single	1		1	
Married	1.180(0.534-2.606)	0.682	1.513(0.660-3.469)	0.328
Divorced	2.826(1.171-6.822)	0.021	3.475(1.412-8.550)	0.007
Widowed	1.669(0.605-4.605)	0.322	1.500(0.543-4.147)	0.435
Substance use				
Yes	1.748(1.006-3.037)	0.048	1.586(0.844-2.982)	0.152
No	1		1	
Disclosure				
Yes	1		1	
No	1.804(0.994-3.274	0049	1.237(0.609-2.511)	0.556
Past OIs				
Yes	2.584(1.509-4.425)	0.000	1.86 (1.048-3.330)	0.034
No	1		1	
TB treatment				
Yes	2.474(1.391-4.400)	0.002	1.646(0.848-3.194)	0.141
No	1		1	
CPT				
Yes	1		1	
No	2.320(1.279-4.209)	0.006	1.128(0.495-2.570)	0.773
Comorbidity				
Yes	5.969(3.479-10.241)	0.000	2.56 (1.391-4.740)	0.003
No	1		1	
Base line Hgb				
≥10mg/dL	1		1	
<10mg/dL	11.746(6.847-20.149)	0.000	4.7(2.253-9.619)	0.000
Baseline CD4				
≥200 cells/µl	1		1	
<200 cells/µl	10.224(5.379-19.436)	0.000	4.710(2.275-9.751)	0.000
Functional status				
Working	1		1	
Ambulatory	3.545(1.950-6.443)	0.000	1.027(0.467-2.259	0.947
Bed ridden	42.804(94.318)	0.000	3.069(1.111-8.480)	0.031
WHO clinical staging				
Stage I	1		1	
Stage II	1.690(0.747-3.824)	0.208	1.659(0.718-3.831)	0.236
Stage III	3.334(1.420-7.827)	0.006	2.88 (1.204-6.899)	0.017
Stage IV	16.312(7.140-37.265)	0.000	15.6 (6.609-36.948)	0.000
ARV adherence				
Good	1		1	
Fair	4.419(2.134-9.151)	0.000	0.972(0.342-2.763)	0.957
Poor	9.260(3.906-21.953)	0.000	2.366(0.759-7.377)	0.138
BMI				
≤18.5	6.764(2.058-22.232)	0.002	1.777(0.500-6.322)	0.374
18.5-25	2.074(0.621-6.932)	0.236	1.449(0.423-4.969)	0.555
≥25	1		1	

Table 6: Factors affecting ART retention rate of patients receiving ART in DBRH, North Showa, Amhara National Regional State,, Ethiopia, 2019 (n=447)

Covariate	Category	Adverse outcome	retention	cOR (95% CI)	P-value	aOR (95% CI)	P-value
Marital status	Single	24(26.7)	66(73.3)	1		1	
	Married	84(33.6)	166(66.4)	1.97(1.52-2.57)	0.000	1.89(0.98-3.67)	0.058
	Divorced	28(50)	28(50)	2.75(1.72-4.38)	0.000	2.8(1.19-6.34)	0.017
	Widowed	13(25.5)	38(74.5)	2.9(1.56-5.48)	0.001	3.7(1.49-9.41)	0.005
Baseline Hgb	≥10mg/dl	111(28.5)	278(71.5)	2.5(2.01-3.12)	0.000	3.4(1.76-6.52)	0.000
	<10mg/dl	38(66.5)	20(33.5)	1		1	
Baseline CD4(cells/µl	≥200	83(26.3)	233(73.7)	2.8(2.18-3.60	0.00	1.7(1.075-2.83)	0.024
	<200	66(50.4)	65(49.6)	1		1	
Baseline BMI	≤18.5	53(43.8)	68(56.2)	1.28(0.89-1.84)	0.174	0.35(0.16-0.75)	0.008
	18.5-25	83(31.8)	178(68.2)	2.14(1.65-2.78)	0.000	0.45(0.22-0.93)	0.031
	≥25	13(19.7)	53(80.3)	1		1	

6.8. Testing proportional hazard assumption

A Cox regression model was used to examine the effects of sociodemographic, clinical and treatment characteristics of patients on time to death. The following variables were included in the model as predictors: age group, sex, place of residence, family size, educational status, occupational status, marital status, disclosure status, substance use, WHO clinical stage at initiation of ART, baseline opportunistic infections, functional status, cotrimoxazole prophylaxis therapy, baseline haemoglobin, baseline CD4 count, body mass index, adherence and comorbidity. A goodness-of-fit (GOF) test was conducted to assess the proportional hazard (PH) assumptions of the Cox model for given predictor variables (Table 6). The findings indicated that all variable included in the model satisfy PH assumptions (p-value>0.05).

Table 7: Goodness-of-fit test assessing proportional hazards Assumption

Predictors	rho*	chi^2	df **	p-value
Age	-0.21093	2.02	1	0.1554
Sex	0.07791	0.33	1	0.5638
Residence	-0.14362	1.01	1	0.3151
Marital status	0.16773	1.61	1	0.2046
Educational status	-0.18497	1.83	1	0.1762
Occupational status	0.08496	0.29	1	0.5873
Disclosure status	-0.01890	0.02	1	0.8826
Substance use	-0.19532	1.92	1	0.1660
Opportunistic infections	0.07398	0.34	1	0.5579
Staging	-0.03825	0.12	1	0.7251
Functional status	-0.04094	0.12	1	0.7273
Past TB treatment	0.25181	3.79	1	0.0516
CPT	0.08569	0.43	1	0.5132
Adherence	0.26219	5.15	1	0.0232
Comorbidity	-0.03682	0.07	1	0.7843
Baseline Hgb	0.07189	0.35	1	0.5547
Baseline CD4	-0.12846	0.93	1	0.3340
BMI	-0.12100	0.78	1	0.3772
Family size	-0.00772	0.00	1	0.9657
Global test		22.65	19	0.2532

*The correlation coefficient between the residuals and time.

**Degree of freedom

7. DISCUSSION

This retrospective cohort study was aimed to assess the survival and predictors of mortality among adult HIV/AIDS patients who initiated highly active antiretroviral therapy. At the end of follow up, about 54 patients were dead and 493 patients were censored. That, resulted in a cumulative incidence of deaths 12.1% over six years. This finding is in line with A study conducted in Somali Region, Eastern Ethiopia which is 11.1% (26), South Omo, Ethiopia, which was 10%(32). However, the total number of deaths that occurred in this study was higher than other studies conducted in south west Ethiopia showed 6.4%(42), North west Ethiopia 4.2%(21). But, there are studies which reported higher findings compared with this study in the ART Centre of MKCG Medical College, Berhampur, Ganjam, and Odisha (21.33 %) (41), Debre Markos 43%(33). The discrepancy of results among studies might be due to difference in sample, in length the study period and differences in initiation of Anti retro-viral therapy.

The current study revealed, the overall mortality rate of patients on ART during 72 months follow up was 4.18/100 person years- years. This finding is in line with the study conducted Dilla University Hospital(24), at seven university teaching hospitals, Ethiopia(25) where the incidence rate per person year is 3.0 and 5.4 respectively. However, this finding is much higher than the findings reported in Debre-Markos Referral hospital(33), Jinka Hospital, South Omo Zone, Ethiopia(32), Jimma University Teaching Hospital, South-West Ethiopia (42) to which the mortality rate was reported as 1.9 per person years, 1.75 per person years and 2.17 per person years respectively. The observed difference in mortality rates might be due to the difference in sample size, duration of the study period and the time duration each cohort contributed.

The presence of opportunistic infection at the time of ART initiation was found to be an important predictor of survival. Accordingly, patients who have an opportunistic infection at ART initiation are 1.86 times more likely to die as compared to those who did not have an opportunistic infection on ART initiation. The study conducted at Fiche hospital in North Showa, Oromia region Ethiopia, selected public hospital in Harar, eastern Ethiopia and India supported that the presence of opportunistic infection increases the probability of death (29,

50, 52). This might be because opportunistic infections may increase the risk of mortality in the first few months after initiating ART due to immune reconstitution syndrome, a paradoxical worsening or recurrence of opportunistic infection symptoms as a result of rapid immunological recovery.

The current study revealed that Patients with baseline WHO clinical stage III and IV were 2.88 times and 15.6 times more likely to die compared to patients with WHO clinical stage I or II respectively. Different studies had supported this idea (33, 50). This might be due to the fact that patients died mostly because of their late initiation of ART when they had the worst health condition. Early initiation before the advancement of the disease is recommended as soon as the confirmation of HIV diagnosis, which is helpful in decreasing the morbidity and mortality of HIV/AIDS. In addition, People with advanced HIV disease require closer follow-up during the initial period of receiving ART to monitor the response to ART and to identify signs and symptoms of possible immune reconstitution inflammatory syndrome.

This study showed that patients who were bedridden at ART initiation were 3.069 times more likely to die compared to the patients with working functional status at treatment initiation. This finding is supported by the study conducted in Jimma university teaching hospital, Khartoum State, Sudan and Eastern Ethiopia in which bedridden patients were 2.5, 4.765 and 4.09 times more likely to die than those patients with working and ambulatory functional status respectively (42, 46, 67). This could be due to poor immunologic response mainly failure to restore CD4 cells to 500 cells/μL despite being virally suppressed.

This study indicated that the baseline hemoglobin level <10 gm/dl was found a significant predictor of death among HIV positive patients on ART. Accordingly, patients who had a hemoglobin level <10 gm/dl were 4.7 times more likely to die as compared to those who had hemoglobin level greater than or equal to 10 gm/dl. This finding is supported by previous studies which have been conducted in Aksum, Northern Ethiopia(22). These May be because Anemia is one of the markers of advanced disease and can increase mortality of patients.

This study revealed that patients who had CD4 count <200cells/μl were found to be 4.7 times more likely to die than to those who have CD4 count ≥200cells/μl. whereas, a study

conducted in Jimma university teaching hospital indicated that patients who were on ART with CD4 <200cells/µl were 1.3 times more likely to die when compared to those whose CD4 was ≥200cells/µl (42).

This discrepancy might be due to a difference in sample size and the eligible age groups for the study. Above all , reduction of CD4 count decrease the immunity of patients, expose them to opportunistic infections and predispose to micronutrient deficiency like iron which in turn causes the reduction of the amount of haemoglobin, which was an important predictor for mortality of patients initiated ART. Moreover, PLWH who have a CD4 cell count below 200 are at high risk of developing serious illnesses.

The current study showed that on patients who had comorbidity have 2.56 times higher hazard of mortality than those who had not comorbidity. This could be due to the fact that Comorbidities complicate caring infrastructures for HIV-infected patients, because patients with multiple diseases and on complex pharmacological treatments are particularly difficult to manage, both in chronic and acute phases.

This study indicated that the ART retention rate is 66.7% after 72 months of follow-up. This finding is in line with a study conducted in Kabwe district Zambia, where retention rate on ART was reported 65%(59). The studies conducted in Tanzania and Iran showed lower reports compared to this study to which the ART retention was 53.5% and 6.3% respectively(60, 61). The finding of the current study is lower than those findings reported in Mozambique(58), Myanmar(57), Addis Ababa(56) and Jinka Hospital, South Omo, Ethiopia(32) where the ART retention rate is 91.8%, 84%, 80% and 79% respectively. This dissimilarity might be due to the difference in the continuous influx and referral of severely immunocompromised patients to the health facilities for better treatment, number of patients who may have died shortly after starting ART, or simply returned back to their place of residence without a formal transfer-out procedure.

8. STRENGTHS AND LIMITATIONS

8.1. Strength

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

8.2. Limitations

Despite the above strengths, this study was subjected to some limitations. Selection bias was possibly introduced due to the fact that patients with incomplete records of variables or charts which were lost for some patients were excluded. Therefore, those study subjects whose charts were not included in the study and with missing value may undermine the result if it is related with death. The other limitation of the current study is that it assumes all deaths were caused by HIV/AIDS.

9. CONCLUSION AND RECOMMENDATION

9.1. Conclusion

In the current study, a total of 54(12.1%) patients on ART were died during the follow up period. Hence, the overall incidence rate was 4.18 per 100-person years with overall mean survival time of 63.7months. WHO clinical staging, functional status, baseline opportunistic infections, baseline haemoglobin count, baseline CD4 count and comorbidity was significant predictors of mortality of patients who initiated ART.

9.2. Recommendation

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

1. To governmental and nongovernmental organizations

Chronic HIV care clinics need to be strengthened more to develop a way to reduce mortality by providing important clinical laboratory monitoring services like adequate organ function tests and albumin tests which are very important to detect the direct effect ART medications and the immonocompromization effect of the disease by itself .

2. To health care providers working at ART Clinic of Debre Berhan Referral Hospital

Close follow-up and monitoring should be given to patients who have baseline CD4<200cells/ µl, opportunistic infections at baseline, patients with haemoglobin <10gm/dl, functional status of bedridden, and those who have comorbidity.

A special emphasis and close follow up should be given to patients had baseline stage III and IV disease. This patients are prone to opportunistic infections and development of immune reconstitution syndrome. Thus, early identification of OIs will be helpful in identifying patients who need intense follow-up for the treatment of specific OI.

3. To researchers

Further studies on survival status among patients on ART that can address the limitations of this study by use of prospective design.

Further predictors of mortality of patients on ART needs to be studied with another strong (prospective) study design.

10.REFERENCES

1. UNAIDS. 2017 Global HIV statistics. 2018

2. UNAIDS. Global statistics of hiv/aids. 2017.

3. Kloos H. HIV/AIDS in Ethiopia: The Epidemic and Social, Economic, and Demographic Impacts. 2001.

4. EPHI. HIV Related Estimates and Projections for Ethiopia. 2017.

5. WHO. Global action plan on hiv drug resistance 2017–2021: 2018 progress report. 2018.

6. UNAIDS. Global AIDS monitoring 2019 indicators for monitoring the 2016 political declaration on ending AIDS. 2018.

7. WHO. supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2014.

8. Abgrall S, del Amo J. Effect of sociodemographic factors on survival of people living with HIV. Current Opinion in HIV and AIDS. 2016;11(5):501-6.

9. FMOH. Guide for implementation of antiretroviral therapy program in Ethiopia, federal HIV/AIDS prevention and control office. 2007.

10. FMOH. National guidelines for comprehensive hiv prevention, care and treatment 2017.

11. Biset Ayalew M. Mortality and Its Predictors among HIV Infected Patients Taking Antiretroviral Treatment in Ethiopia: A Systematic Review. AIDS research and treatment. 2017;2017.

12. AMA. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults. 2018.

13. Aung ZZ, Oo MM, Tripathy JP, Kyaw NTT, Hone S, Oo HN, et al. Are death and loss to follow-up still high in people living with HIV on ART after national scale-up and earlier treatment initiation? A large cohort study in government hospital-based setting, Myanmar: 2013-2016. PloS one. 2018;13(9):e0204550.

14. Collaborators GH. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2015: the Global Burden of Disease Study 2015. The lancet HIV. 2016;3(8):e361-e87.

15. Deribew A, Biadgilign S, Deribe K, Dejene T, Tessema GA, Melaku YA, et al. The Burden of HIV/AIDS in Ethiopia from 1990 to 2016: Evidence from the Global Burden of Diseases 2016 Study. Ethiopian journal of health sciences. 2019;29(1):859-68.
16. ILO. The impact of HIV and AIDS on the world of work: Global estimates /International Labour Office – Geneva: ILO, 2018. 2018.
17. Bekker L-G, Alleyne G, Baral S, Cepeda J, Daskalakis D, Dowdy D, et al. Advancing global health and strengthening the HIV response in the era of the Sustainable Development Goals: the International AIDS Society—Lancet Commission. The Lancet. 2018;392(10144):312-58.
18. Maheswaran H, Petrou S, Cohen D, MacPherson P, Kumwenda F, Lalloo DG, et al. Economic costs and health-related quality of life outcomes of hospitalised patients with high HIV prevalence: A prospective hospital cohort study in Malawi. PloS one. 2018;13(3):e0192991.
19. Lahuerta M, Ue F, Hoffman S, Elul B, Kulkarni SG, Wu Y, et al. The problem of late ART initiation in Sub-Saharan Africa: a transient aspect of scale-up or a long-term phenomenon? Journal of health care for the poor and underserved. 2013;24(1):359-83.
20. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach: World Health Organization; 2016.
21. Assemie MA, Muchie KF, Ayele TA. Incidence and predictors of loss to follow up among HIV-infected adults at Pawi General Hospital, northwest Ethiopia: competing risk regression model. BMC Research Notes. 2018;11(1):287.
22. Tadesse K, Haile F, Hiruy N. Predictors of mortality among patients enrolled on antiretroviral therapy in Aksum hospital, northern Ethiopia: a retrospective cohort study. PloS one. 2014;9(1):e87392.
23. Mengesha S, Belayihun B, Kumie A. Predictors of survival in HIV-infected patient after Initiation of HAART in Zewditu Memorial Hospital, Addis Ababa, Ethiopia. International scholarly research notices. 2014;2014.
24. Hailemariam S. Determinants of Survival in HIV Patients: A Retrospective Study of Dilla University Hospital HIV Cohort2016.

25. Fekade D, Weldegebreal T, Teklu AM, Damen M, Abdella S, Baraki N, et al. Predictors of survival among adult Ethiopian patients in the national ART program at Seven University Teaching Hospitals: A prospective cohort study. Ethiopian journal of health sciences. 2017;27(1):63-71.
26. Damtew B, Mengistie B, Alemayehu T. Survival and determinants of mortality in adult HIV/Aids patients initiating antiretroviral therapy in Somali Region, Eastern Ethiopia. The Pan African medical journal. 2015;22:138-.
27. Kebebew K, Wencheko E. Survival analysis of HIV-infected patients under antiretroviral treatment at the Armed Forces General Teaching Hospital, Addis Ababa, Ethiopia. Ethiopian Journal of Health Development. 2012;26(3):186-92.
28. Seyoum D, Degryse J-M, Kifle Y, Taye A, Tadesse M, Birlie B, et al. Risk Factors for Mortality among Adult HIV/AIDS Patients Following Antiretroviral Therapy in Southwestern Ethiopia: An Assessment through Survival Models. International Journal of Environmental Research and Public Health. 2017;14(3):296.
29. Tesfamariam K, Baraki N, Kedir H. Pre-ART nutritional status and its association with mortality in adult patients enrolled on ART at Fiche Hospital in North Shoa, Oromia region, Ethiopia: a retrospective cohort study. BMC Research Notes. 2016;9(1):512.
30. Tadege M. Time to death predictors of HIV/AIDS infected patients on antiretroviral therapy in Ethiopia. BMC Research Notes. 2018;11(1):761.
31. Refera H, Wencheko E. Survival of HIV-TB co-infected adult patients under ART in Ambo Referral Hospital, Ethiopia. Ethiopian Journal of Health Development. 2013;27(2):88-93.
32. Tachbele E, Ameni G. Survival and predictors of mortality among human immunodeficiency virus patients on anti-retroviral treatment at Jinka Hospital, South Omo, Ethiopia: a six years retrospective cohort study. Epidemiology and health. 2016;38.
33. Tadele A, Shumey A, Hiruy N. Survival and predictors of mortality among adult patients on highly active antiretroviral therapy at Debre-markos referral hospital, North West Ethiopia; a retrospective cohort study. Journal of AIDS & Clinical Research. 2014.
34. Sweileh WM. Global research output on HIV/AIDS–related medication adherence from 1980 to 2017. BMC Health Services Research. 2018;18(1):765.

35. Kharsany ABM, Karim QA. HIV Infection and AIDS in Sub-Saharan Africa: Current Status, Challenges and Opportunities. The open AIDS journal. 2016;10:34-48.
36. Girum T, Wasie A, Worku A. Trend of HIV/AIDS for the last 26 years and predicting achievement of the 90–90-90 HIV prevention targets by 2020 in Ethiopia: a time series analysis. BMC Infectious Diseases. 2018;18(1):320.
37. WHO. Guidelines for managing advanced hiv disease and rapid initiation of antiretroviral therapy. HIV treatment. 2017.
38. Health UDo, Services H. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2018.
39. S. Saag M, Benson C, T. Gandhi R, F. Hoy J, Landovitz R, J. Mugavero M, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the international antiviral society–USA Panel2018. 379 p.
40. Hassan RHA, Abdelaal AA, Mohammed HA, Elbashir MA, Khalid KB. Survival and Mortality Analysis for HIV Patients in Khartoum State, Sudan 2017. World. 2018;3(4):118-24.
41. Benu P, Rao SHB, Ramachandra M, Simanchal P, Prasanna K. Predictors of Mortality among HIV Patients on HAART in an ART Centre–A Retrospective Study. International Journal of Medicine and Public Health. 2016;6(4).
42. Gesesew HA, Ward P, Woldemichael K, Mwanri L. Early mortality among children and adults in antiretroviral therapy programs in Southwest Ethiopia, 2003–15. PloS one. 2018;13(6):e0198815.
43. Girum T, Wasie A, Lentiro K, Muktar E, Shumbej T, Difer M, et al. Gender disparity in epidemiological trend of HIV/AIDS infection and treatment in Ethiopia. Archives of Public Health. 2018;76(1):51.
44. Mai HT, Le GM, Tran BX, Do HN, Latkin CA, Nguyen LT, et al. Adherence to antiretroviral therapy among HIV/ AIDS patients in the context of early treatment initiation in Vietnam. Patient preference and adherence. 2018;12:2131-7.
45. Hessol NA, Schwarcz SK, Hsu LC, Shumway M, Machtinger EL. Gender differences in causes of death among persons with HIV/AIDS in San Francisco, California, 1996–2013. International Journal of STD & AIDS. 2017;29(2):135-46.

46. Sato S, Masui K, Nishina N, Kawaguchi Y, Kawakami A, Tamura M, et al. Initial predictors of poor survival in myositis-associated interstitial lung disease: a multicentre cohort of 497 patients. Rheumatology. 2018;57(7):1212-21.
47. Ssebutinde P, Kyamwanga IT, Turyakira E, Asiimwe S, Bajunirwe F. Effect of age at initiation of antiretroviral therapy on treatment outcomes; A retrospective cohort study at a large HIV clinic in southwestern Uganda. PloS one. 2018;13(8):e0201898.
48. Seifu W, Ali W, Meresa B. Predictors of loss to follow up among adult clients attending antiretroviral treatment at Karamara general hospital, Jigjiga town, Eastern Ethiopia, 2015: a retrospective cohort study. BMC Infectious Diseases. 2018;18(1):280.
49. Deepak P, Manjula B, Mallikarjun P. Role of serum albumin in pre treatment assessment, monitoring of therapy and disease progression in HIV/AIDS patients. International Journal of Scientific Research. 2018;6(7).
50. Digaffe T, Seyoum B, Oljirra L. Survival and Predictors of Mortality among Adults on Antiretroviral Therapy in Selected Public Hospitals in Harar, Eastern Ethiopia. J Trop Dis. 2014;2(148):2.
51. Weldegebreal T, Ahmed I, Muhiye A, Belete S, Bekele A, Kaba M. Magnitude of opportunistic diseases and their predictors among adult people living with HIV enrolled in care: national level cross sectional study, Ethiopia. BMC Public Health. 2018;18(1):820.
52. Joseph N, Sinha U, Tiwari N, Ghosh P, Sindhu P. Prognostic Factors of Mortality among Adult Patients on Antiretroviral Therapy in India: A Hospital Based Retrospective Cohort Study. BioMed research international. 2019;2019.
53. Poorolajal J, Hooshmand E, Mahjub H, Esmailnasab N, Jenabi E. Survival rate of AIDS disease and mortality in HIV-infected patients: a meta-analysis. Public Health. 2016;139:3-12.
54. Yimer YT, Yalew AW. Magnitude and predictors of anti-retroviral treatment failure in private health facilities in Addis Ababa, Ethiopia. PLoS One. 2015;10(5):e0126026.
55. Dandona R, Rewari BB, Kumar GA, Tanwar S, Kumar SGP, Vishnumolakala VS, et al. Survival outcomes for first-line antiretroviral therapy in India's ART program. BMC Infectious Diseases. 2016;16(1):555.

56. Mekuria LA, Prins JM, Yalew AW, Sprangers MA, Nieuwkerk PT. Retention in HIV care and predictors of attrition from care among HIV-infected adults receiving combination anti-retroviral therapy in Addis Ababa. PloS one. 2015;10(6):e0130649.
57. Thida A, Tun STT, Zaw SKK, A Lover A, Cavailler P, Chunn J, et al. Retention and Risk Factors for Attrition in a Large Public Health ART Program in Myanmar: A Retrospective Cohort Analysis2014. e108615 p.
58. Decroo T, Koole O, Remartinez D, dos Santos N, Dezembro S, Jofrisse M, et al. Four - year retention and risk factors for attrition among members of community ART groups in T ete, M ozambique. Tropical Medicine & International Health. 2014;19(5):514-21.
59. Mwale JC. Factors affecting retention in care of patients on antiretroviral treatment in the Kabwe district, Zambia. 2016.
60. Mee P, Rice B, Lemsalu L, Hargreaves J, Sambu V, Harklerode R, et al. Changes in patterns of retention in HIV care and antiretroviral treatment in Tanzania between 2008 and 2016: an analysis of routinely collected national programme data. Journal of global health. 2019;9(1).
61. Limaki AK, Farhoudi B, Rasoolinejad M, Safari S. Patient Retention in Antiretroviral Therapy Programs; A Retrospective Cohort Study in a Triangular HIV Clinic. Galen Medical Journal. 2017;6(2):110-7.
62. AIHA. How Twinning Helped Transform Debre Berhan Referral Hospital into a National Model for Quality Care and Effective Management. The Debre Berhan / Elmhurst Hospital Center Partnership: A Successful Model for Global Health and Development 2014 24 p.
63. CDC. Epi Info™ version 7.1.2.0. 2013.
64. Awor AC. Determinants of long term survival of patients initiated on HAART at the AIDS support organization, Uganda. 2017.
65. Diseases ICo. Comorbidity scores. Charlson comorbidity score. 2012 Last updated on April 17, 2019. Report No.
66. Zhang Z. Model building strategy for logistic regression: purposeful selection. Annals of translational medicine. 2016;4(6).
67. Biadgilign S, Reda AA, Digaffe T. Predictors of mortality among HIV infected patients taking antiretroviral treatment in Ethiopia: a retrospective cohort study. AIDS Research and Therapy. 2012;9(1):15.

ANNEXES

Annex I: Information Sheet

Title of the Research Project: survival and predictors of mortality among adult HIV/AIDS patients initiating highly active antiretroviral therapy at Debre-Berhan referral hospital, North Showa zone, Amhara region; a retrospective study, 2019

Name of Investigator: Fetene Nigussie (BSc)

Name of the Organization: AAU

Name of the Sponsor: AAU

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

Purpose of the Research Project: To assess the survival and predictors of mortality among adult patients started highly active antiretroviral therapy at Debre Berhan Referral Hospital, North Showa Zone, Amhara National regional State, Ethiopia.

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

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

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

especially for those on HIV prevention, treatment and support program planning and management.

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

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

1. Fetene Nigussie, AAU University ,College of Medicine and Health Science, Department of Adult health Nursing: principal investigator.

Cell phone: +251-932274797

E-mail: fetenenigussie27@gmail.com

2. Erdaw Tachbele(PhD), AAU University, College of Medicine and Health Science, School of Nursing and midwifery: Main-Advisor.

E-mail: erdawt@yahoo.com

3. Zuriash Mengistu (MSc, PhD fellow), AAU University, College of Medicine and Health sciences, School of Nursing and midwifery: Co- Advisor.

E-mail:zuriashaau@yahoo.com

Annex II: Data Extraction Form

INTRODUCTION:

This patient information collection sheet is intended to assess Survival and Predictors of Mortality among Adult HIV/AIDS patients initiating Highly Active Antiretroviral Therapy at Debre-Berhan Referral Hospital, North Showa zone, Amhara region, Ethiopia. The study will be conducted through reviewing secondary data. The study is aimed to fill the information gap and provide empirical evidence for program planner, decision makers and ART program implementer at the different level by enabling them to access a base line data on predictors of survival. Moreover it will be a paramount important to curb the horizon of the disease. And it assists in the development of a system for improving the survival of PLWHA.

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

Name and signature of reviewer----------

Time Started_____ Time ended_____

Name and signature of the supervisor……

Date……

Total no of records reviewed----------

Reviewed Patient's card No from _____to_____

Result:

A) Completed ---------- B) Incomplete ----------C) excluded----------

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

PART I. STUDY SUBJECT'S BASELINE INFORMATION (TO BE FILLED FROM ART CLINIC INTAKE FORM)

SECTION I: SOCIO-DEMIOGRAPHIC CHACTERSTICES

ART unique number _____

1.1 Date of diagnosis…. /…../……..

1.2 Age at diagnosis……

1.3 Date of initiation into HAART …. /…../……

1.4 Age at initiation of HAART……

NO	QUESTINAIRE/ VARIABLE S	Coding categories
1	Age of the patient's	_____ years
2	Sex	1. Male 2. Female
3	Ethnicity	1. Amhara 2. Oromo 3. Afar 4. Other(specify) _____
4	Religion	1. Orthodox 2. Muslim 3. Protestant 4. Others(specify) -----
5	Educational status	Illiterate Read and write Primary Secondary Tertiary
6	Occupational statues	Farmer Merchant Governmental employee Non-governmental employee Day laborer Jobless Driver Others(specify) _____
7	Marital status	Single Married Divorced Widowed
8	Family size	_____

9	Disclosure status	1. Disclosed 2. Not disclosed
10	Residence	Urban Rural
11	Distance from DBRH	……..in kilometers

SECTION II: BASE LINE CLINICAL AND LABORATORY CHARACTERISTICS

NO	QUESTINAIRE/ VARIABLE S	Coding categories
1	WHO staging	Stage I Stage II Stage III Stage IV
2	Opportunistic infections	No Yes(specify)----------
3	TB treatment during follow up	1. Yes 2. No If Yes, Date of Dx:
5	Past TB treatment	No Yes (specify) _____ Rx outcome
6	CD4 count	_____
7	Height at base line	_____ (cm)
8	weight at base line	_____ (kg)
9	functional status at base line	**W**. working **A**. Ambulatory **B**. bedridden
10	Hgb at base line	_____
11	WBC base line	
12	TLC base line	
13	Comorbidity	1. Yes 2. No

SECTION III: ART AND TREATMENT

NO	QUESTINAIRE/ VARIABLE S	Coding categories
1	ARV eligibility criteria used	1. CD4 below 200 2. WHO stage I, II, and III with TLC <1200 3. WHO stage IV 4. Residence of catchment area

		5. No identified barriers for adherence
2	Initial regimen	_____
3	Regimen change during follow up	Yes (_____) No
4	Reason for switch the first regimen	Side effect Pregnancy Tuberculosis Stock out Not recorded
5	OI prophylaxis at base line	not given Cotrimoxazole INH Fluconazole Others----------
6	TB treatment during follow up	1. Yes 2. No
7	7 If yes, date of diagnosis	_____/_____/_____

SECTION IV: RISKY BEHAVIORS

1	Has the client ever smoked cigarettes?	Yes No
2	Is the client currently smoking cigarettes?	Yes No
3	Does the client drink alcohol?	Yes No
4	Does the client chew chat?	Yes No

Survey result

1 = On ART

2 = Stopped ART

3 = Dead

4 = Transferred out

5 = Lost to follow up

Annex III: Charles Comorbidity Index

Based on the International Classification of Diseases code 10, each condition is assigned with a score of 1, 2, 3 or 6 associated with risk of dying.

Conditions

Acute Myocardial Infarction

Congestive Heart Failure

Peripheral Vascular Disease

Cerebrovascular Disease

Dementia

Chronic Obstructive Pulmonary Disease or other Respiratory diseases

Rheumatic-like Diseases

Ulcers of the Digestive System

Liver Disease – Mild

Diabetes - No Chronic Complications

Diabetes with Chronic Complications

Hemiplegia or Paraplegia

Renal (Kidney) Disease

Any malignancy including lymphoma and leukemia

Moderate to Severe Liver Disease

Cancer (Metastatic - secondary)