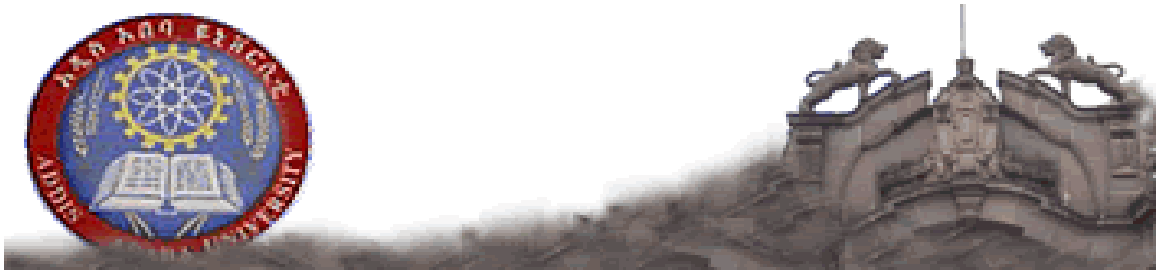

ADDIS ABABA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

DEPARTMENT OF STATISTICS

Survival Time and Immunological Recovery of AIDS Patients under Antiretroviral Treatment: a case study at Felege Hiwot Referal Hospital, Bahir-Dar, Ethiopia.

By

Bezalem Eshetu

A Thesis submitted to the Office of Graduate Programs of Addis Ababa University in Partial fulfillment of the requirements for the Degree of Master Science in Statistics

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This is to certify that the thesis prepared by Bezalem Eshetu , entitled: **Survival Time and Immunological Recovery of AIDS Patients under Antiretroviral Treatment: a case study at Felege Hiwot Referal Hospital, Bahir-Dar, Ethiopia** and submitted in partial fulfillment of the requirements for the Degree of Master of Science in Statistics complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

Signed by the Examining Committee:

Examiner _____ Signature _____Date _____

Examiner _____ Signature _____Date _____

Advisor _____ Signature _____Date _____

Chair of Department or Graduate Program Coordinator

DECLARATION

I, the undersigned, declare that the thesis is my original work, has not been presented for degrees in any other university and all sources of material used for the thesis have been duly acknowledged.

Name: _____

Signature: _____

Date: _____

This thesis has been submitted for examination with my approval as a University Advisor.

Prof. Eshetu Wencheko

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List of abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Treatment
ARVs	Antiretroviral drugs
CDC	Center for disease Control
HAART	Highly Active Anti Retro viral Treatment
HIV	Human Immunodeficiency Virus
PLWHA	People Living With HIV/AIDS
UNAIDS	Joint United Nations Program on HIV/AIDS
WHO	World Health Organization
SPSS	Statistical Package for Social Sciences
FMOH	Federal Ministry of Health
COHERE	Collaboration of Observational HIV Epidemiological Research Europe
FHAPCO	Federal HIV/AIDS Prevention and Control Office

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Abstract

Antiretroviral Treatment (ART), although not a cure, can help people from becoming ill for many years and this has improved the survival and recovery time of HIV patients. In 2011 a number of 249,174 adults were on ART in Ethiopia. Although ART treatment has decreased HIV associated mortality and morbidity, a number of patients still die after the start of ART. The purpose of this study was to identify factors affecting the survival time and time to immunological recovery of HIV/AIDS patients under ART treatment. A sample of 387 patients was taken from patients' records at Bahir-Dar Felege-Hiwot Referral Hospital from June 2006 to August 2013. Kaplan-Meier estimation method and Cox proportional hazard model were applied to describe and analyze the data. Females, baseline CD4 count >200cell/µl, TB-negative, total lymphocyte count ≥1200 cell/mm^3 and baseline weight ≥45kg, no regimen change, good adherence to treatment, WHO stage I, working functional status and negative-anemia were identified with longer survival time and shorter recovery time at 5% of significance level. Patients having no risk behaviors lived longer. Based on the Cox regression model results the adjusted HRs were as follows: high CD4 count (aHR=0.99), negative-anemia patients (aHR=0.27), good adherence to treatment (aHR=0.10), fair adherence to treatment (aHR=0.47), male gender (aHR=1.81), TB-positive (aHR=3.58), bedridden functional status (aHR=5.07), ambulatory functional status (aHR=1.30). The adjusted HRs for recovery time were as follows: patients with high CD4 count (aHR=1.02), high weight (≥45kg.) (aHR=1.03), WHO stage I (aHR=1.88), WHO stage II (aHR=1.67) and negative-anemia (aHR=1.34) had shorter time to immunological recovery at 5% level of significance. Male gender (aHR =0.73), old age (aHR=0.98), total lymphocyte count <1200 (aHR=0.77) and regimen change (aHR=0.688) were significantly associated with extended time to immunological recovery at 5% level.

1. INTRODUCTION

1.1 Background of the Study

Acquired Immune Deficiency Syndrome (AIDS) which is believed to be caused by the Human Immunodeficiency Virus (HIV) has been a major health problem worldwide. The rate of spread of the HIV/AIDS epidemic has reached a shocking level. The expansion of the epidemic has now become a burning issue globally and this is particularly so more important in developing countries. The disease being one without any cure is still accountable for economic, social and health crises in many developing countries. Its high prevalence and distribution among the youth made things even more complicated.

On a global scale, the HIV epidemic has stabilized, although with unacceptably high levels of new HIV infections and AIDS deaths. An estimated 34 million people worldwide were living with HIV in 2011 among which 23,500,000 people were living in sub-Saharan Africa (UNAIDS, 2013). According to this report, the adult HIV infection was about 30.7 million and the rest 3.3 million is under the age of 15. Specifically, an estimated 2.5 million became newly infected with HIV and overall 1.7 million people died due to AIDS in 2011. In the same year, an estimated 1.8 million people were newly infected with HIV in sub-Saharan Africa. The report also indicated that the epidemic in sub-Saharan Africa is highly diverse and especially more severe in southern Africa.

Ethiopia is one of the countries hardest hit by HIV/AIDS epidemic. The country is the second most populous nation in sub-Saharan Africa with a population of over 79 million and it has a very large number of HIV/AIDS infected people. The regional prevalence estimates for urban

areas in 2005 range from 3.8% in Somali to 14.1% in Afar (MOH, 2006). According to this report, due to the relatively large population sizes and high HIV prevalence rates in their respective urban areas, 84.6% of PLWHA for urban Ethiopia live in only four of the regions (30.2% in Addis Ababa, 22.7% in Amhara, 22.2% in Oromia and 9.5% in SNNPR) in 2005. In addition, an estimated of 790,000 people were living with HIV in 2011(UNAIDS, 2013). This report added that a total of 59,000 people died due to AIDS in 2011.

HIV infection has changed from a fatal condition to a manageable chronic illness mainly due to the development of antiretroviral therapy (ART). The goal this therapy is to improve survival; to reduce HIV associated morbidity and mortality, to increase the quality of life, to restore immune function and to achieve maximal and sustained suppression of viral replication (OARAC, 2008). By 2010 WHO has planned to put 9.8 million people on ART with the goal of providing universal access to HIV care and ART (UNAIDS, 2013).

To reduce the mortality and morbidity rate caused by the HIV/AIDS epidemic different initiatives were made by international organizations and donors. One of the imitative was the launch of WHO's '3 by 5' initiative in 2003 it was estimated that three million HIV patients in the world would have access to ART by 2005. The initiative enabled many Sub-Saharan African countries to establish national antiretroviral treatment (ART) programs. By the end of 2005 an estimated 1.3 million people in low and middle income countries had access to treatment which is about 20% of those estimated to be in need (WHO and UNAIDS, 2006). The WHO target of providing access to ART for 3 million people by 2005 was not achieved. But in mid-2005, the WHO target had already been overtaken by an even more motivated aim. In July 2005, the G8 group of industrialized countries committed to the goal of achieving "as close as possible to universal access to treatment for all those who need it by 2010" (UNAIDS, 2006). This program

is called UNIVERSAL access 2010. Ethiopia is one of the countries which benefited from this program. To address the problem of provision of a fair access to ART implementation program the government of Ethiopia launched the free ART program in January 2005. In 2011 an estimated number of 249,174 adults (of which 86% were eligible) were on ART treatment in Ethiopia (FHAPCO, 2012).

Although ART was introduced in 2011 in Ethiopia, there is dearth of literature about the impact of ART on changes in CD4 lymphocyte count and weight among patients on treatment. CD4 T lymphocytes remain the surrogate measure for monitoring HIV progress in resource-limited settings. The absolute CD4 cell counts form the basis for ART initiation and monitoring among HIV-infected adults. However, the rate of CD4 cell change differs among patients, and the factors responsible are inadequately documented.

However, most of the studies in Ethiopia focused on the prevention and about factors that increase the chance of contracting the disease. For example Alemtsehai and Eshetu (2006) dealt with prevention before a person is HIV positive, Nuredin and Eshetu (2007) studied factors that influence patient survival, and Habtamu and Eshetu (2012) studied about survival time of HIV infected children.

In the study area of this work, namely Bahir Dar, ART has been started at Bahir Dar Referral Hospitals 9 years ago. In spite of the initiation of ART at the hospital, little research work has been undertaken to study the survival time and immunological recovery of AIDS patients on ART. The current study has the objective to accomplish this task. This study attempts to identify factors that have strong associations with the survival experience and time taken to an increase of 100 CD4 cell count over the baseline CD4 cell count of AIDS patients who started ART in one

of the government hospitals in the regional state of Amhara at Bahir Dar in Felege-Hiwot Hospital.

1.2 Statement of the Problem

Although the current HIV/AIDS surveillance estimates indicate some encouraging signs in that the epidemic is stabilizing, the observed changes are not sufficient enough compared to the desired goals of the response against the epidemic. It is believed that, in resource poor countries like Ethiopia the survival time of patients on ART depends on a variety of factors, which may also vary greatly with economic, demographic, behavioral risk and health factors. In other words, even if ARV treatment has shown significant clinical importance by meeting the goal of therapy, we are still facing a number of deaths that can otherwise be avoided by appropriate interventions on certain socio-economic, demographic, behavioral risk and health factors.

The performance of ART programs can be improved if we can bring behavioral change among HIV patients under ART follow up, take appropriate clinical and non-clinical measures like providing medicine and support to patients. Therefore, this study is motivated to (i) identify the major factors that affect survival time, and (ii) estimate the duration of time taken to observe an increase of 100 CD4 cells over the baseline after initiation of ART.

1.3 Objectives of the Study

This study has two main general objectives.

- The first objective is to identify the determinants of survival time of AIDS patients under antiretroviral treatment (which will attempt to estimate and compare survival time of AIDS patient under antiretroviral treatment) at Bahir-Dar Felege-Hiwot Referral Hospital, Ethiopia.

- The second objective is to identify the determinant of time to immunological recovery of AIDS patients under antiretroviral treatment (which will attempt to estimate and compare time to immunological recovery of AIDS patients) at Bahir-Dar Felege-Hiwot Referral Hospital, Ethiopia.

1.4 Significance of the Study

Ethiopia is one of the few African countries that undertakes survey about HIV prevalence with a good vital registration system. However, the data cannot provide planners with a direct measure of the demographic impact of HIV/AIDS. For this purpose appropriate statistical models are needed to analyze the data. These models, if appropriately constructed, can also be used to assess the likely effect of different prevention and treatment programs could serve in policy formulation.

The outcome of the research may help healthcare workers to anticipate and inform patients about the possible causes of death they might encounter. Moreover, clinicians can decrease mortality among HIV positives by early diagnosis and appropriate intervention. On top of this, the result of the study may enable clinicians and policy makers to enhance the awareness of the society about factors which increase the probability of death among HIV patients. The result of this study could also be used as source of information to other researches in the future.

Therefore, the rationale behind such a research undertaking is to find ways in which health institutions of the country can minimize HIV related mortality, and also serve as an input for policy makers and health specialists. This study may also contribute to achieving of WHO and Ethiopian FMOH HIV/AIDS treatment goals.

1.5 Limitations of the study

- The study was conducted based on secondary data which might have incomplete and biased information.
- The study was restricted to adults, and results might not be applicable to infants and children.
- Lack of literature on our country related to the subject under study.
- Since the data were secondary it is inevitable to confront the problem of missing data. There were some missing values in some of the variables: marital status (3), educational level (6), functional status (1), knowledge of ART(75), VCT (42), risk factor (79), TB status (5), baseline CD4 count(14), baseline weight (6), regimen type (1) and adherence (15).

2. LITERATURE REVIEW

2.1 Antiretroviral Treatment

Antiretroviral therapy (ART) has been proved to improve lives of HIV infected persons by reducing HIV/AIDS-related mortality and morbidity (WHO,2011; UNAIDS,2012). The introduction of antiretroviral treatment has altered the course of the HIV/AIDS epidemic (Yamashita et al.,2001 and Resino , et al., 2002). Antiretroviral drugs reduce viral replication which in most cases is measured by increases in CD4 lymphocyte count (Jacobson et al., 2004). This has led to drastic reductions in morbidity and mortality from AIDS, and improvement in the quality of life of patients (Siegel et al., 2002, Palella et al., 1998 and Murphy et al., 2001). The clinical benefit of ART for AIDS patients, in terms of mortality reduction and improved quality of life, is well established but shows regional variations, with higher case fatality rates in poor countries (Braitstein *et al.*, 2006). Effective ART has significantly increased the life expectancy of HIV-infected patients (Egger et al., 2002, Seyler et al., 2003, Laurent et al., 2005, Braitstein et al., 2006 and Ivers et al., 2005) in developed and resource-limited countries. An estimated 2.5 million deaths were averted in low and medium income countries (LMIC) between 1995 and 2010 when ART was introduced (WHO, 2011). Of these averted deaths, 1.8 million were in sub Saharan Africa, a region with over 69% of the estimated 34 million people living with HIV (WHO, 2011 and UNAIDS, 2012).

There was an estimated 25% reduction in new infections in sub-Saharan Africa in 2011 (total 1.8 million new infections) compared to 2001 (2.4 million new infections) (WHO, 2011) and 27% fewer infections in 2010 compared to 1996 after introduction of ART (UNAIDS, 2012). In 2012, 9.7 million of the 34 million people living with HIV (PLWH) were estimated to be on ART in low-and medium-income countries (WHO, 2013), which is a six-fold increase from 2005 when only 1.3

million people were receiving ART (WHO, 2011). Between 2003 and 2010 there was an increase in ART coverage from 20% to 47% for low and mid income countries (WHO, 2011). The HIV treatment coverage in low-and middle-income countries represented only 34% (32-37%) of the 28.6 million people eligible in 2013 (WHO, 2013).

In Ethiopia the percentage of adults and children receiving ART in 2011 was 86% (WHO, 2012). The ARV drugs approved by FMOH for use in Ethiopia as first line drugs are NRTI and NNRTIs (d4T, 3TC, AZT, EFV and NVP). These drugs are combined to form the following four first line regimens taken by more than 95 % of adult HIV/AIDS patients in the Felege-Hiwot Referral Hospital: (d4T/3TC/NVP(1a), d4T/3TC/EFV(1b), AZT/3TC/NVP(1c) and AZT/3TC/EFV(1d).

2.2 Studies on the Survival of HIV/AIDS Patients

The notion that all demographic, socioeconomic, health and risky behavioral factors may have significant relationship is supported by many researchers (Zahang, 2007; Holmes *et al*., 2003; Merito-logo and patrifio, 2006). The impact of HIV on an individual's chance of dying is complex and depends on many factors including the prevalent types of AIDS defining diagnoses, diagnostic routines, general standard of healthcare and access to healthcare at the cohort site, degree to which treatment was available to the cohort, the treatment policies, mode of infection, number of infections, age at infection(s), immune competence, overall health, and treatment (Zahang, 2007).

Zahang (2007) and Merito-logo and Patrifio (2006) examined the survival probability of AIDS patients using socio-demographic factors. According to their report the survival of AIDS patient decreased as age increased. Sieleunou et *al.* (2009) and Mee-Kyung *et al*. (2009) indicate that

age and sex for HIV/AIDS are important determinants of disease progression. According to their report younger patients have the advantage of surviving longer than older patients, and male sex was a predictor of mortality with a risk almost doubles that of female sex. Nguyen N et al., (2008) show an association between survival time of HIV/AIDS patients and age of the patients. Furthermore, there appears to be an association between rapid progress to AIDS and shorter survival time in older HIV-infected patients (Nguyen and Holodniy , 2008). In another study, patients whose age 50 years and older had shorter survival time as compared to younger age groups, (Youmans et al., 2011).

Clinical psychiatry news of September 2003 (Robert, 2003) reported a longitudinal study which included highly diverse participant by ethnicity, gender, and socioeconomic status . The group was 25% white, 43% African American, 28% Hispanic, and 5% others. Males made up 65% of the group; 62% of the group earned less than $10,000 annually; 20% earned between $10,000 and $20,000, and the rest earned more than $20,000. Socioeconomic status was defined as a weighted composite of education, income, and job status. This longitudinal study of 186 HIV-positive patients revealed a significant connection between socioeconomic status and disease progression markers, including morbidity, mortality, and CD4 cell count.

A retrospective cohort study was conducted in eastern Ethiopia with the objective of identifying factors that influence time to death and survival over time in HIV-infected patients starting ART. The study used Kaplan-Meier curves to estimate survival time and Cox proportional hazards models to investigate factors that influence time to death. It was found that previous history of weight loss, bedridden functional status at baseline, low CD4 cell count and advanced WHO status patients had a higher risk of death (Sibhatu et al.,2012).

Laxmi et al., (2013) conducted a retrospective cohort study on 1024 Nepal patients who were on ART between May 15th 2006 and May 15th 2011 in five ART sites in the far-western region, Nepal. Kaplan-Meier curves and Cox proportional hazards regression model were used in the analysis. This study showed that the determinants of mortality were male sex (hazard ratio (HR) 4.55, 95% CI 2.43-8.51), poor baseline performance scale bedridden <50% of the day during the past month (HR 2.05, 95% CI 1.19-3.52), bedridden for half a day during the past month (HR 3.41, 95% CI 1.67-6.98) compared to normal activity; low WHO clinical stages (stage III, HR 2.96, 95% CI 1.31-6.69; stage IV, HR 3.28, 95% CI 1.30-8.29) compared to WHO clinical stage I or II.

According to Sandra et al. (2009) the rate of morbidity and mortality was very high among HIV-patients without stable housing, more referral hospitalizations, less use of ART, and worse medication adherence than HIV infected persons in the USA. The study showed that bad housing is associated with poor survival. Kim *et al.* (2006) also show AIDS patient with bad housing had lower survival.

Patient's educational status is a major predictor of survival (Monge et al.,2011) in Thailand. HIV individuals with lower education had a higher risk of death and increased risk for HIV disease progression. Monge et al. (2011) also show that HIV educated patients were more likely to live longer compared to those who were farmers. Guerreiroa *et al*. (2011) observed that the risk of dying for HIV patients who did not have university education was much higher than that for those who had university education.

Mortality rates among drug users (i.e., cocaine, alcohol, and/or benzodiazepines) have been historically high and are still significantly higher than the rates for the general population.

Frequent causes of death among drug users include bacterial infection, overdose, accidents, and AIDS (Galai *et al*., 2003; Wang *et al*., 2005; Ana and guimaraes, 2005). Nonetheless, cohort studies from Western Europe have revealed decreased mortality rates among HIV infected individuals (including drug users) in the decade before the introduction of ART and the intensification of clinical care (Detels *et al*., 2010). Even though HIV-infected drug users are less likely to start taking ART, their response to therapy (in terms of survival) is similar to that for other exposure groups, as long as adherence to treatment is satisfactory (Mocroft *et al*., 2007; Johnson, 2010).

Opportunistic infections (OIs) are common causes of death among HIV-infected patients. ART has reduced the incidence of opportunistic infections for certain patients with access to care. However, opportunistic infections may continue to cause substantial morbidity and mortality in patients with HIV infection (Holmes *et al*., 2003). Another explanation could be that, as an opportunistic infection, pulmonary tuberculosis affects 30.9% of the diagnosed cases, and it is characterized as an AIDS-defining disease. Disseminated tuberculosis associated with pulmonary tuberculosis occurs in 6.4% of the cases. To treat these patients, there is a need to modify the antiretroviral therapeutic regimen and delay its start to avoid drug interactions between the two courses of therapy, which could compromise their clinical progress due to a delay in introducing protease inhibitors. Thus, extensive diagnostic procedures and treatment delay, and the often concomitant occurrence of tuberculosis could explain the greater impact on survival from the second year onwards (Begovac *et al*., 2006; Dias *et al*., 2007).

Tuberculosis remains one of the major causes of death in patients infected with HIV in resource-limited settings (Harries AD et al., 2010). Tuberculosis continues to be a leading cause of illness and death among people with HIV/AIDS in resource-poor areas of the world (Ngo AT et al.,

2007). It is possible that up to 50% of HIV/AIDS patients died from opportunistic infections such as tuberculosis (Cain et al, 2009).

Merito-logo *et al*.(2006); Sieleunou *et al.* (2009) and Brian *et al*.(2009) shows that baseline CD4 count, baseline lymphocyte and WHO clinical stage are factors associated with survival of AIDS patients. According to Sieleunou *et al.*(2009) patients with a low baseline CD4 count were exposed to mortality risk twice as high as those with larger CD4 count and patients in WHO stage III and IV were two to four times more likely to die than patients in stages I and II. Merito-logo and Patrizio (2006) and Zhang (2007) show the survival probability of AIDS patients would improve with increased CD4+ count. Brian *et al*.(2009) also indicated that determinants that favored a good immunological recovery process after ART initiation were baseline CD4 count (> 200 *cells* / μl) and baseline total lymphocytes count (≥ 1200 cells/mm^3). Decline in CD4 lymphocyte count and weight loss among patients on anti-retroviral treatment are associated with increased mortality and morbidity manifesting in the form of deterioration of clinical conditions and decreased functional status in adults (Grinspoon et al., 2003). The increment of CD4 count and weight gain were found to be important factors predicting patient survival (Biadgilign et al., 2012).

Mariz and colleagues reported that older age among patients on ART was associated not only with increased weight gain but also with becoming overweight among patients in Brazil (Mariz et al., 2011). They reported that patients older than 40 years of age were at risk of overweight or even obesity. Among patients on ART in Tanzania, slightly higher weight loss was observed among patients between 15 and 29 years of age, and patients above the age of 50 three months after initiation of ART (Li et al.,2012). Starting ART at low CD4 count has also been associated with increased toxicity of antiretroviral (ARV). Data from the HIV Outpatient Study (HOPS)

cohort in the US revealed that initiating therapy at progressively higher CD4 count cuts the risk of three major nucleoside toxicities, namely neuropathy, anemia, and renal insufficiency (Lichtenstein et al., 2007). Low CD4 count (CD4 < 200 cells/μL) independently increased the risk of peripheral neuropathy 1.54 times, while the risk of anemia increased 1.58 times and renal insufficiency increased 2.22 times (Lichtenstein et al., 2007).

2.3 Studies on time to immunological recovery of HIV/AIDS Patient

Chronic HIV infection is characterized by progressive loss of CD4+ T cells, suppression of viral replication with antiretroviral agents among most subjects in rapid CD4 recovery (Azzoni et al,2007), and decreased T cell activation. According to Allison (2008), as untreated HIV progresses, CD4 count decreases by about approximately 4% every year. With successful ART the CD4 count might increase by greater than 50cells per micro litre within weeks after viral suppression. Additionally, it may increase by 50-100 cells per micro litre per year thereafter, until a threshold is reached (Allison, 2006). Most patients exhibit a rapid increase in the peripheral CD4+ cell count during the first 8–12 weeks of therapy. This is often followed by a more gradual increase until a normal CD4+ cell count is achieved (Pakker et al.,1998; Bucy et al.,1999). Several studies have focused on rates of CD4+cell count increases and have found that patient CD4+ cell count continues to increase as long as CD4+ cell count remains <500, although the rate decreases after several years (Mocroft et al.,2007). A study based on 358 patients on ART from southern Ethiopia found that longer duration on treatment was significantly associated with improvements in CD4 count and weight (Tafese et al., 2012). In a multi-country study among sub-Saharan African patients, median CD4 cell counts increased from a baseline of 97 cells/ml to 261 cells/ml at 48 weeks; whereas the proportion of patients

with a CD4 cell count ,100 cells/ml came down from 50% at baseline to 4% at 48 weeks (Lawn et al.,2006)

Monitoring clinical and diagnostic progression of patients on ART is important to examine responses to the treatment and for clinical decision-making. Patient responses and clinical diagnostic measures to ART show differences based on individual and population characteristics, and the type of setting where treatment is delivered (Yamashita et al., 2001 and Oyomopito et al., 2010). These include drug resistance levels, adherence to treatment, age, source of infection and substance use among others (Jacobson et al., 2004, Yamashita et al., 2001, Hirschel et al., 1999 and Modjarrad et al., 2010). Defective early recovery has been demonstrated to be associated with increased morbidity (Baker et al., 2008). However, the extent of this recovery over time is difficult to predict, as it likely depends on multiple factors. ART outcomes including mortality, immunological and virological response may potentially be influenced by age (Nguyen et al., 2008; Gebo et al., 2008). Hence it is important to understand treatment outcomes to inform on appropriate HIV management in older adults. Previous studies from Europe and North America ((COHERE, 2008; Grabar et al., 2004; Greenbaum et al., 2008; Silverberg, 2007) have also reported poorer immunological but better virological responses among older paients compared to younger adults but have not explored how these may relate to mortality rates in older age groups receiving ART. Younger adults had superior immunological responses and inferior virological suppression, a finding that supports previous observations (COHERE, 2008, Grabar et al. 2004; Greenbaum et al., 2008; Silverberg et al., 2007).

Eric et al., (2012) show Among HIV-infected adults in West Africa that the immunological response after 12 months of ART was significantly poorer in elderly patients. As the population of treated patients gets older, the impact of this age effect on immunological response to ART

may increase over time. Data from Europe and the USA reported a lower immune response to ART in older patients (Nogueras et al., 2006, Gandhi e al., 2006 and COHERE, 2008). Other studies, with smaller sample size, did not find any effect of age on the immune response to ART (Tumbarello et al., 2004 and Orlando et al., 2006). The effect of age on the response to ART in sub-Saharan Africa has not been well documented so far. And yet, due to several immunological and demographic specificities of sub-Saharan Africa, the effect of age on immune restoration may differ from that observed in high-income countries. On one hand, HIV-infected patients in Africa are presenting at a higher level of T-cell activation compared to those in high-income countries (Rizzardini et al., 1998), whereas an increased T-cell activation is found to be related to a lower CD4 gain after ART initiation (Hunt et al., 2003). Data on the effect of age in Africa are very scarce but always showed a poorer ART response in older patients (Seyler et al., 2003, Laurent et al., 2005).

Studies based on alcohol use among HIV-1 infected patients provide conflicting and limited information regarding prevalence, as well as impact on HIV replication, disease progression and response to antiretroviral therapy. F Guerreirioa et al., (2002) showed that heavy alcohol users receiving antiretroviral therapy were twice as likely to have CD4 counts below 500 than light or non-drinkers. Alcohol consumption is prevalent in HIV-1 infected drug user cohort and significantly impacts the immunological response to ART treatment. Fieldman et al. (2006) show that tobacco smoking is associated with poorer response to antiretroviral therapy and worse disease progression in HIV/AIDS patients especially women according to a report published in the June 2006 American Journal of Public Health.

Immune activation of the T cell compartment alterations of memory T cell subsets and depletion of innate immune subsets are associated with advanced HIV infection (Appay et al.,2008).

However, while most of these cell subsets are at least partially recovered by ART, although with different kinetics, their potential association with early CD4 recovery has not been explored. In a reported multivariate analysis, age, baseline CD4 count and initial viral load were found to be inversely associated with early CD4 response to suppressive ART (Florence et.al., 2003). Reports from an HIV/ART Swiss cohort showed that over one-third of patients failed to attain an absolute CD4 count of 500 cells/µl during a follow-up period of 4 years (Kaufmann et al., 2005 and Cairns et al., 2005), and baseline CD4 status was a predictor of immunological recovery. Poor survival among patients who started ART at low CD4 counts has been observed in some studies (Zachariah et al., 2006, Egger et al., 2002, May et al., 2007, Severe et al., 2011, Hawkins et al., 2007 and Manosuthi et al., 2007). Based on data from some of these studies, immunological and virological recovery was low among patients who started ART at low baseline CD4 counts, with the greatest risk among patients with CD4 count <50 cells/µl.

Patients who start ART early gain roughly equal numbers of CD4 cells regardless of their initial count, except for those starting with extremely low or extremely high counts. Patients starting treatment at low count will probably never reach CD4 count anywhere near normal. It is recommended to start ART before CD4 cell count fall below 350 cell/µl (Huges *et al.,* 2007).

The UK CHIC cohort study of over 17,000 UK HIV patients enrolled clients who started ART between the beginning of 1998 and the end of 2005 and who had maintained undetectable viral loads from six months after the start of treatment to the end of the study. The patients had at least one pre-treatment CD4 count and another one at least six months after the start of therapy (in practice, the average number of CD4 counts done per patient was 13). Annual viral load measurements were made. Over 4,100 patients met the testing criteria of which 2,780 (67.6%) maintained undetectable viral loads through to the end of 2005. The study found that the pre-

treatment (baseline) CD4 count varied according to the type of patient. For instance, gay men comprised only 38% of those who started with the lowest CD4 counts (below 25 cells/mm3), 75% of the 91 patients started ART with CD4 counts over 500 cells/mm3. Heterosexuals formed 56% of those who started ART with counts under 25 cells/mm3 but only 18% had more than 500 cells/mm3, according to Huges *et al* (2007). In general, a higher proportion of those starting treatment with CD4 counts below 200 cells/mm3 were females, African and heterosexual.

3. DATA AND METHODOLOGY

3.1 Description of the Study Area and Population

The study is based on data obtained from Felege-Hiwot Referral Hospital, in Bahir-Dar city of the Amhara Region. The city is located approximately 578 kms northwest of Addis Ababa at latitude and longitude of 11° 36'N, 37° 23'E with elevation of 1,840 above sea level.

The Hospital is run by the Amhara Regional Government Health Bureau. Currently it is giving service to more than 16,000,000 people living in northwest Ethiopia. In addition, it is a training center for health science students. In 2003 the ART clinic of the Hospital started its activity after the Ethiopian government launched free ART. In 2005 it started to provide free service to patients. The ART clinic has currently three physicians, three nurses and four data clerks attending HIV/AIDS patients regularly and filling the follow up charts more or less appropriately.

Felege-Hiwot Referral Hospital has sufficient data on a large number of patients on ART as it started treatment follow up earlier than the other similar public health institutions. This study kept the personal integrity of the patients included in the study thereby confidentiality and medical ethical standards were adhered to according to a laws of the country.

3.2 The Data

The target population for this study was patients under the follow up of ART at Felege-Hiwot Referral Hospital from June 2006 to August 2013. The study reviewed patient intake forms and follow up cards of HIV patients taking ART in the ART clinic. The patient charts are prepared by Federal Ministry of Health to be uniformly used by clinicians to early identify and document

clinical and laboratory measurement. Thus, this study used secondary data obtained from intake forms and patient follow up cohort (ART clinic patient record) based on the questionnaire designed to extract only the variables to be considered in this study. The data used in this study satisfy the following criteria:

Inclusion and Exclusion Criteria

The study considered all HIV infected patients under ART who were 15 years and older regardless of their treatment category during the study period in the Hospital. The study excluded patients on ART whose diagnosis year or month was missing, patients who did not have at least two follow-up CD4 measures, and patients whose date of death was missing. All of these were confirmed by looking at the patients' record.

There were a total of 11,040 patients in our sampling frame, which is the list of all patients who received ART from the Referral Hospital from June 2006 to August 2013. Each patient has a chart/record with distinctive identification number which is known as ART unique identification number. A simple random sampling method is adopted for selecting a representative sample of the patients based on their ART unique identification number.

3.3 Sample Size Determination

A simple random sample (SRS) of size n consists of n individuals from the population chosen in such a way that every set of n individuals has an equal chance to be the sample actually selected. A random method of selection is one which gives each of the N (total number of the population) units in the population equal chance of being selected. In this study, patients who started the medication in the Hospital and those who had been transferred from other facilities were given a sequential order number. A simple random sampling procedure is then applied on this list.

The appropriate formula for determination of sample size using simple random sampling is adopted from Cochran (1977) as

$$n = \frac{\frac{Z^2 p(1-p)}{d^2}}{1 + \frac{1}{N}\left(\frac{Z^2 p(1-p)}{d^2} - 1\right)}$$

where Z is the upper $\alpha/2$ point of standard normal distribution with α=0.05 significance level, which is Z=1.96. The degree of precision d is taken to be 0.025. The parameter p represents proportion of death. The value p=0.07 was used in this study relying on a similar previous study at Adama Referral Hospital (Nuredin and Eshetu, 2007). Accordingly, the sample size from population size N=11,040 for the current study is n = 387.

3.4. Variables considered in the research

The response variables are

1. "Time" (Survival time in months) and "Status" (dead=1, Censored=0)
2. "Time" (Time to recovery in months) and "Status" (CD4 cells count where time to an increase of 100 cells over baseline =1, Censored=0)

The independent variables: Several predictors are considered in this study to investigate the major factors associated with of survival and recovery time of AIDS patients. Some of these variables are categorical and others are continuous. They are given in detail below.

1. Gender (male, female)
2. Age of the patients at the start of ART
3. Residence (urban, rural)
4. Marital status (never married, married, separated/divorced/widowed)
5. Level of education (no education, primary, secondary and above)

6. Voluntary counseling and testing (VCT) categorized as (yes, no)
7. Partner's HIV status (positive, negative, unknown)
8. Knowledge of ART (yes, no)
9. CD4 count at the start of ART
10. Weight at the start of ART
11. Total lymphocyte count at the start of ART (<1200, ≥1200)
12. WHO clinical stage at the start of ART (stage I, stage II, stage III, stage IV)
13. Functional status of the patient at the start of ART (bedridden, ambulatory, working)
14. Risk factor (alcohol intake, soft and hard drug use, tobacco use) categorized as (yes, no)
15. Condom use (yes, no)
16. TB status (positive, negative)
17. Anemia status (normal, sever/mild/moderate)
18. ARV regimen (D4T-3TC-NVP, D4T-3TC-EFV, AZT-3TC-NVP, AZT-3TC-EFV, TDF-3TC-EFV,TDF-3TC-NVP, others)
19. Regimen change (yes, no)
20. Adherence to treatment (yes, no)

3.5. Survival Analysis

Survival analysis a statistical analysis that used to describe the analysis of data in the form of a well defined time origin until the occurrence of some particular event or end point. Generally, survival analysis is a collection of statistical procedures for data analysis for which the outcome variable of interest is time until an event occurs. If the end point is the death of a patient, the resulting data are literally survival times. However, data of a similar form can be obtained when

the end point is not fatal, such as the relief of a pain, or the recurrence of symptoms. In this case the observations are often referred to as time-to-event data.

Survival analysis consists of a set of specialized statistical techniques used to study time-to-event data. In analyzing such data, the main objective is to determine the length of time interval for the occurrence of an event. Survival analysis is mainly used for two distinguishing features of time-to-event data. Duration times are non-negative values usually exhibiting highly skewed distribution and therefore the assumption of normality is violated. Secondly, censoring may occur or the true duration is not always observed or known, that is, some subjects are potentially being unobserved for the full time to failure.

The main feature of time-to-event data is the presence of censoring which occurs when the periods of time to event occurrence of some individuals cannot be completely observed. The process of censoring and truncation make these data unsuitable to analyze with traditional regression method and hence, the appropriate technique is survival analysis. Details on various estimation methods developed in survival data analysis that taken censoring and truncation in to account can be obtained in Hosmer and Lemeshow (1998).

In this study the Cox proportional hazard model were used to examine survival time and time taken to an increase of 100 CD4 cells over the baseline after of starting ART. Kaplan-Meier estimators were applied to estimate survival curves and time to immunological recovery and the log rank test was used for the comparison between the variable categories. And with this understanding, we start our method by giving the definition of censoring, Kaplan-Meier and Cox proportional model; we then proceed to model building and assessments.

3.5.1 Censoring

Due to time period confinement, censoring and truncation are common in survival data analysis and need to taken into considerations. A censored observation is one whose value is incomplete due to random factors for each subject. The most common form of censoring for incomplete data is **right censoring** when a subject's follow-up time terminates before the outcome of interest is observed. The second type of censoring is **left censoring** which is observed when an individual had developed the event of interest prior to the beginning of the study. An observation is categorized into an **interval censored** if it is only known that the event of interest occurs within an interval of time without the knowledge of when exactly it occurs. In this study by construction, we can have right censored data but not the others.

3.5.2 Kaplan-Meier Estimation

Kaplan-Meier Estimation is a product limit estimation of the survivorship function which is developed by Kaplan-Meier (1958). Kaplan-Meier (KM) estimator is used by most software packages because of the simplistic step approach. The KM estimator incorporates information from all of the observations available, both censored and uncensored, by considering any point in time as a series of steps defined by the observed survival and censored times. When there is no censoring, the estimator is simply the sample proportion of observations with event times greater than t. The technique becomes more complicated but still manageable when censored times are included. The KM estimator consists of the product of a number of conditional probabilities resulting in an estimated survival function in the form of a step function. It is a nonparametric estimator of the survivor function $S(t)$.

$$\hat{S}(t) = \prod_{t_j<t} (1 - \frac{d_j}{n_j})$$

where d_j is the number of individuals who experienced the event at time t_j, and n_j is the number of individuals who have not yet experienced the event at that time.

Having the description of the overall survival experience in the study, attention is given to a comparison of the survivorship experience in key subjects in the data. The simplest way of comparing the survival times obtained from two or more groups is to plot the Kaplan-Meier curves for these groups on the same graph. In general, the pattern of one survivorship function lying above another means, the group defined by the upper curve lived longer or had a more favorable survival experience than the group defined by the lower curve. However, this graph does not allow us to say, with any confidence, whether or not there is a real difference between the groups. The observed difference may be due to a true difference or may be due to chance. Assessing whether or not there is a real difference between groups can be done using statistical test procedures. These tests, which have the same generalized form or algebraic presentation, include the Log Rank test, Generalized Wilcoxon test, Tarone and Ware test, Peto-Peto-Prentice test and Harrington-Fleming test. The calculation of each test is based on a contingency table of groups by status at each observed survival time. The general form of these test statistics for the comparison of survival functions between two groups can be defined as follows.

$$Q = \frac{\left[\sum_{i=1}^{m} w_i \left(d_{1i} \_ \widehat{e}_{1i}\right)\right]^2}{\sum_{i=1}^{m} w_i^2 \widehat{v}_{1i}}$$

where:

d_{1i} is the observed number of failure (death) in group 1 at failure time t_i

$\hat{e}_{1i} = \frac{n_{1i} * d_i}{n_i}$ is the expected number of failures corresponding in group 1 at time t_i

$\hat{V}_{1i} = \frac{n_{1i} n_{2i} d_i (n_i \_ d_i)}{n_i^2 (n_i \_ 1)}$ is the variance of the number of failures in group 1 at time t_i

m is the number of rank-ordered failure (death) times.

n_{1i} is the number of individuals at risk in group 1 just prior to failure time t_i

n_{2i} is the number of individuals at risk in group 2 just prior to failure time t_i

n_i is the number of individuals at risk in both groups 1 and 2 just prior to failure time.

The test statistic Q has X^2 distribution with 1 degree of freedom under the null hypothesis that the two survivorship functions are the same when the total number of observed events and sum of expected number of events are large and assuming that the censoring experience is independent of group **(**Hosmer and Lemeshow, 1999**)**. The statistic Q can be extended for comparing more than two groups of survival experience(Hosmer and Lemeshow, 1999 and Collett, 2003).

The most frequently used tests, the log rank test and the generalized Wilcoxon test, use weight $w_i = 1$ and $w_i = n_i$ respectively. Of the two tests, the log-rank test is the more suitable(powerful) when there is no difference between the survival times of the two groups is tested against the alternative that the hazard of death in any given time for an individual in one group is proportional to the hazard at that time for a similar individual in the other group.

3.5.3 Proportional Hazards Model

The basic model for survival data to be considered in this study is the proportional hazard model. This model was proposed by David Cox (1972) and has also come to be known as the Cox regression model. The model is also referred to as a semi-parametric model. Semi-parametric models are models that parametrically specify the functional relationship between the lifetime of an individual and his characteristics but leave the actual distribution of lifetimes arbitrary.

David Cox's (1972) paper took a different approach to standard parametric survival analysis and extended the methods of the non-parametric Kaplan-Meier estimates to regression type arguments for life-table analyses. Cox advanced to prediction of survival time in individual subjects by only utilizing variables covering with survival and ignoring the baseline hazard of individuals. Cox assumed only that the hazard functions of different individuals remained proportional and constant over time and he made no assumptions about the baseline hazard of individuals.

Many researchers favor Cox's proportional hazards modeling because of the robust semi-parametric method of calculating the probabilities of survival while simultaneously adjusting for other possibly influential variables. Other attractive features of Cox modeling include: the relative risk type measure of association, no parametric assumptions, the use of the partial likelihood function, and the creation of survival function estimates and it does not choose the density function of a parametric distribution.

Cox's semi-parametric modeling allows for no assumptions to be made about the parametric distribution of the survival times, making the method considerably more robust. Instead, a researcher must only validate the assumption that the hazards are proportional over time. The

proportional hazards assumption refers to the fact that the hazard functions are multiplicatively related. That is, for any two individuals with covariates $\mathbf{X_i}$ and $\mathbf{X_j}$ the ratio $h(t|\mathbf{X_i})/\mathbf{h}(t|\mathbf{X_j})$ is assumed to be constant over survival time.

The Hazard Function

Cox proportional hazard model is usually written in terms of the hazard model formula. This model gives an expression for the hazard at time *t* for an individual with a given specification of a set of explanatory variables denoted by **X** and it is generally given by:

$$h(t, \mathbf{X_i}, \boldsymbol{\beta}) = h_o(t)\exp(\boldsymbol{\beta}' \mathbf{X_i})$$

where $h_o(t)$ is the baseline hazard function which is obtained when all **X**'s are set to zero, $\mathbf{X_i}$ is the vector of values of the explanatory variables for the i^{th} individual at time *t* and $\boldsymbol{\beta}$ is the vector of unknown regression parameters that are assumed to be the same for all individuals in the study, which measures the influence of the covariate on the survival experience.

An attractive property of the Cox model is that, even though the baseline hazard part of the model is unspecified, it is still possible to estimate the $\boldsymbol{\beta}$'s in the exponential part of the model. So, it can equally be regarded as linear model, as a linear combination of the covariates for the logarithm transformation of the hazard ratio given by:

$$\log\left\{\frac{h(t, \mathbf{X}, \boldsymbol{\beta})}{h_0(t)}\right\} = \boldsymbol{\beta}' \mathbf{X}$$

The cumulative hazard function is given by:

$$H(t) = H_o(t)\exp(\boldsymbol{\beta}' \mathbf{X})$$

From model $\log\left\{\frac{h(t,x,\beta)}{h_0(t)}\right\} = \beta' x$, we obtained the survivor function given by:

$$S(t, \mathbf{X}, \boldsymbol{\beta}) = [S_O(t)]^{\exp(\boldsymbol{\beta}' \mathbf{X})}$$

where $S_o(t)$ is a baseline survival function.

3.5.4 Fitting the Proportional Hazard Model

As with logistic regression, the Maximum Likelihood (ML) estimates of the Cox model parameters are derived by maximizing a likelihood function usually denoted as *L*. The likelihood function is a mathematical expression which describes the joint probability of obtaining the data actually observed on the subjects in the study as a function of the unknown parameters (the $\boldsymbol{\beta}$'s) in the model being considered. *L* is sometimes written notationally as $L(\boldsymbol{\beta})$ where $\boldsymbol{\beta}$ is a vector of unknown parameters.

The formula for the Cox model likelihood function is actually called a "partial" likelihood function rather than a (complete) likelihood function since it considers probabilities only for those subjects who fail, and does not explicitly consider probabilities for those subjects who are censored. Thus the likelihood for the Cox model does not consider probabilities for all subjects, and that is why it is called a "partial" likelihood.

In particular, the partial likelihood can be written as the product of several likelihoods, one for each of, say, *k* failure times. Thus, at the j^{th} failure time, l_j denotes the likelihood of failing at this time, given survival up to this time. Note that the set of individuals at risk at the j^{th} failure time is called the "risk set," $R(t_{(j)})$, and this set may change actually get smaller in size as the failure time increases.

$$l(\beta) = \prod_{j=1}^{k} l_j$$

Here l_j is the j^{th} failure time given the risk set $R(t_{(j)})$

In a very general sense, the partial likelihood is given by the expression

$$l_p(\boldsymbol{\beta}) = \prod_{i=1}^{n} \left[\frac{e^{\mathbf{x_i}\boldsymbol{\beta}}}{\sum_{j \in R(t_i)} e^{\mathbf{x_j}\boldsymbol{\beta}}} \right]^{C_i}$$

where the summation in the denominator is over all subjects in the risk set at time t_i denoted by $R(t_i)$. The expression above assume that there are no tied times, and it is often modified to exclude terms when $c_i=0$, yielding

$$l_p(\boldsymbol{\beta}) = \prod_{i=1}^{m} \left[\frac{e^{\mathbf{x_{(i)}}\boldsymbol{\beta}}}{\sum_{j \in R(t_i)} e^{\mathbf{x_j}\boldsymbol{\beta}}} \right]$$

where the product is over the m distinct ordered survival time and $x_{(i)}$ denoted the value of the covariance for the subject with ordered survival time $t_{(i)}$.Once the likelihood function is formed for a given model, the next step for the computer is to maximize this function. This is generally done by maximizing the natural log of *L*, which is computationally easier. The log partial likely function is given by:

$$L_p(\boldsymbol{\beta}) = \sum_{i=1}^{m} \left\{ \mathbf{x_{(i)}}\boldsymbol{\beta} - \ln \left[\sum_{j \in R(t_{(j)})} e^{\mathbf{x_j}\boldsymbol{\beta}} \right] \right\}$$

The maximization process is carried out by taking partial derivatives of log of *L* with respect to each parameter in the model, setting to zero and then solving the resulting system of equations

for parameters and hence the result follows. The solution may be carried out using iteration when it is possible to solve analytically**.** That is, the solution is obtained in a stepwise manner, which starts with a guessed value for the solution, and then successively modifies the guessed value until a solution is finally obtained. Thus, it requires special methods like Newton Raphson iteration method. These iterative methods are programmed into available survival packages like SPSS and STATA.

Relative Risk

Once the ML estimates are obtained, we are usually interested in carrying out statistical inferences about hazard ratios defined in terms of these estimates. In general, a hazard ratio (*HR*) is defined as the hazard for one individual divided by the hazard for a different individual. The two individuals being compared can be distinguished by their values for the set of predictors, that is, the *X*'s. We can write the hazard ratio as the estimate of h (t, $\boldsymbol{X}^*$) divided by the estimate of $h(t, \mathbf{X})$, where $\boldsymbol{X}^*$ denotes the set of predictors for one individual, and **X** denotes the set of predictors for the other individual.

$$\hat{HR} = \frac{\hat{h}(t, \boldsymbol{X}^*)}{\hat{h}(t, \boldsymbol{X})}$$

In this study, a multiple covariate analysis were used for investigating the relationship between the dependent variable and a series of other variables (those common factors scores obtained in multivariate analyses) simultaneously. For this analysis, we shall use the application of different software packages such as STATA and SPSS.

3.5.5 Model Building Strategies for proportional Hazard model

In modeling with many independent variables, one is usually concerned with the goal of selecting those variables that result in the "best" model within the scientific context of the problem. Having a basic plan to follow in selecting the variables for the model and assessing the adequacy of the model both in terms of the individual variables and from the point of view of the overall fit of the model is required for achieving this "best" model. It is also highlighted in Hosmer and Lemeshow (1998) that successful modeling of a complex data set is part science, part statistical methods, and part experience and common sense.

In this study, model building starts from single covariate analysis as suggested by Collet (1994). Collet recommended the approach of first doing a single covariate analysis to "screen" out potentially significant variables for consideration in the multi covariate model in order to identify the importance of each predictor. All variables that are significant at 25% level, the modest level of significance from one explanatory single covariate regression model are taken into multi covariate model. The purely statistical method is to use an automatic process ('stepwise' regression), which can be 'forward': the variables are added successively (the most significant at each step) until no variable adds significant information and can be 'backward': all the variables that are significant at 25% level of significance are included in the model at the beginning and are removed according to the significance criteria. For this study we fit multivariable Cox proportional hazards regression model using the statistical package SPSS "Method = Backward Stepwise (Likelihood ratio). Finally, the importance of each variable included in the multi covariate model should be verified by different model assessment techniques.

3.5.6 Assessing Model Adequacy for proportional Hazard model

Once a model has been developed through the various steps indicated in the above section, we now would like to know how effective the model is in describing the outcome of the variable. So, we need to assess the goodness of fit of the model (Agresti, 1996). Some of the methods for the assessment of a fitted proportional hazards model can equally be used for parametric regression models. There are basically a requirements for model adequacy considered in this study. They are:

Methods for Testing the Assumption of Proportional Hazards

The proportional hazards assumption is vital to the interpretation and use of a fitted proportional hazards model. An easy way to check the assumption that the effect of a variable X is constant in time is to create a new time-dependent variable to represent the interaction of X with the time, such as X *log(t) or X *t, to add it to the model, and test if this new variable adds significant information. If it is the case, it means that the proportional hazard assumption is not satisfied, and the model has to be adjusted for this. If X is not the main factor of the study, it is advisable to use it as a stratification variable. See details in David *et al*. (1996) and Hosmer and Lemeshow (1998).

Another method of testing the validity of the Cox proportionality assumption is to plot the scaled Schoenfeld residuals against the log of time, If this plot shows some trend the assumption is violated, whereas if the plot demonstrates randomness around the reference line then the assumption is satisfied.

Goodness-of-Fit of Proportional Hazard Model

To check the measure of goodness of fit for the final model we used the following tests: the partial likelihood ratio and Score tests.

The partial likelihood ratio (LR) test: to use this we need to fit both the unrestricted and the restricted models. We shall obtain the value of the log-partial likelihood function $\boldsymbol{LL_P}(\hat{\boldsymbol{\beta}})$ in the unrestricted model and $\boldsymbol{LL_P}(\hat{\boldsymbol{\beta}} = 0)$ when the model imposes the restrictions under H_O. The test statistic for H_O is based on the difference of the log-likelihood values. Under H_O, the test statistic in this case 'θ_{LR}' is asymptotically distributed as χ^2 with number P degrees of freedom.

$$Q_{LR} = 2\left[\boldsymbol{LL_P}(\hat{\boldsymbol{\beta}}) - \boldsymbol{LL}(0)\right] \quad \sim \quad \chi^2(P)$$

The Score test: For testing the hypothesis that the model fits the data, other common approaches is the Score tests (Q_S). Under H_O, the statistic is asymptotically distributed as χ^2 with number P degrees of freedom. If chi-square is significant, the variable is considered to be a significant predictor in the equation. The test statistics is:

$$Q_S = U'_{H_0}\, I^{-1}_{P\times P}(0)\, U_{H_0} \quad \sim \quad \chi^2(P)$$

where $I^{-1}_{P\times P}(0)$ is matrices of dimension p×p, extracted from the inverse of the observed information matrix evaluated at $\hat{\boldsymbol{\beta}} = 0$ and U_{H_0} is the score function under H_O. Q_S under H_0 have approximately χ^2 distribution with P degrees of freedom.

Checking for Influential and Linearity of Covariates

A thorough evaluation of regression diagnostic statistic is to identify, if any, subjects: (1) have unusual configuration of covariates or (2) have undue influence on the estimates of the Cox regression parameters or (3) have an unusual configuration of the covariates is carried out using score residuals. Leverages are diagnostic statistics that measure how "unusual" the values of the covariates are for an individual. Leverages, similar to what is obtained in logistic regression, are also adapted into proportional hazards regression through the score residuals as defined by Hosmer and Lemeshow (1998). Thus, the score residual is assessing subject-specific diagnostic or the influential subjects by observing how large the deviation is. The larger the deviation the more distant the residual is to the mean. The plot of the score residuals looks like a basic hourglass shape, fanning out from its narrowest point at approximately the mean of the covariate.

Finally, nonlinearity, that is, an incorrectly specified functional form in the parametric part of the model, is a potential problem in Cox regression as it is in linear and generalized linear models (Fox, 2003). In order to assess the linearity assumption on the part of the covariates, we plot martingale residuals compared by excluding the covariate to be checked for linearity against the values of the covariate. If the plot is not a definite pattern or the smoothed curve is almost a horizontal line through the origin, the covariate shows approximate linearity.

4. RESULTS AND DISCUSSION

4.1 Descriptive Statistics

There were 387 patients in the cohort study out of which 54 (14%) died and the remaining 333(86%) were censored. There were 236 females and 151 males. Out of those dead patients 46.3% were females and 53.7% are males. Out of the 54 dead patients 38.9% were bedridden, 25.9% were ambulatory and 35.2% were working.

There were 89(23.3%) TB-positive and 293(76.7%) TB-negative patients; out of the dead patients 24(44.4%) were TB-negative and 30(55.6) were TB-positive. Out of the dead patients 70.4% were anemia-positive and 29.6% were anemia-negative. The average CD4 count at the start of treatment for the dead patients was 128.29, with a maximum of 322; censored average CD4 count was 164.38 with a maximum of 497. There were 65(16.8%) patients in WHO stage I, 95(24.5%) in WHO stage II, 176(45.5%) in WHO stage III and 51(13.2%) patients in WHO stage IV; out of the dead patients 37% were in WHO stage IV, 33.3% were in WHO stage III, 20.4% were in WHO stage II and 9.3% were in WHO stage I. HIV-deaths among individuals who showed risk behaviors like not using condom was 55% and risk factor(smoking tobacco, drinking alcohol and using hard/soft drugs) was 59.7%.

There were 233(60.2%) patients whose baseline WBC count was ≥1200 and 154(39.8%) patients whose baseline WBC count was below 1200. Among the dead patients 53.7% had WBC count less than 1200 and 46.3% had WBC count ≥1200. Out of those dead patients 20(37%) had weight below 45kg and 34(63%) had weight 45kg and higher.

The Chi-square test showed that survival status of a patient were significantly associated with sex, baseline functional status, baseline WHO stage, anemia status, condom use, adherence type,

risk factor, baseline CD4 count, TB status, baseline WBC count, and baseline weight (p-value < .005). Table A4.1 in Appendix 4, Table 4.1 and Table 4.2 below reveal all details about descriptive statistics.

Table 4. 1: Summary results of HIV/AIDS death events vs socio-economic and Demographic and Risk variables at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	Number of death (%)	Number of Censored(%)	Total (%)	Chi-Square P-value
Age				0.222
[15-40)	39(72.2)	265(79.6)	304(78.6)	
≥40	15(27.8)	68(20.4)	83(21.4)	
Sex				0.017*
Female	25(46.3)	211(63.4)	236(61.0)	
Male	29(53.7)	122(36.6)	151(39.0)	
Marital Status				0.836
Never married	8(14.8)	43(13.0)	51(13.3)	
Married	26(48.1)	173(52.4)	199(51.8)	
Divorce/ Windowed	20(37.0)	114(34.5)	134(34.9)	
Educational level				0.209
No education	13(24.5)	100(30.5)	113(29.7)	
Primary	11(20.8)	91(27.7)	102(26.8)	
Secondary and above	29(54.7)	137(41.8)	166(43.6)	
Functional Status				0.000*
Bedridden	21(38.9)	12(3.6)	33(8.5)	
Ambulatory	14(25.9)	56(16.9)	70(18.1)	
Working	19(35.2)	264(79.5)	283(73.3)	
Residence				0.693
Rural	7(13.0)	50(15.0)	57(14.7)	
Urban	47(87.0)	283(85.0)	330(85.3)	
Partner's HIV Status				0.384
Negative	2(3.7)	18(5.4)	20(5.2)	
Positive	15(27.8)	66(19.8)	81(20.9)	
Unknown	37(68.5)	249(74.8)	286(73.9)	
Knowledge of ART				0.078
No	4(9.1)	9(3.4)	13(4.2)	
Yes	40(90.9)	259(96.6)	299(95.8)	
VCT				0.846
No	6(13.0)	36(12.0)	42(12.2)	
Yes	40(87.0)	263(88.0)	303(87.8)	
Risk Factor				0.000*
No	7(15.9)	117(44.3)	124(40.3)	
Yes	37(84.1)	147(55.7)	184(59.7)	

(*) The association is significant at $\alpha=0.05$

Table 4. 2: Summary results of HIV/AIDS death events vs different health and risk behavior variables at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	Number of death (%)	Number of Censored (%)	Total (%)	Chi-Square P-value
TB Status				0.000*
Negative	24(44.4)	269(82.0)	293(76.7)	
Positive	30(55.6)	59(18.0)	89(23.3)	
WHO Clinical Stage				0.000*
Stage I	5(9.3)	60(18.0)	65(16.8)	
Stage II	11(20.4)	84(25.2)	95(24.5)	
Stage III	18(33.3)	158(47.4)	176(45.5)	
Stage IV	20(37.0)	31(9.3)	51(13.2)	
Baseline WBC Count				0.024*
<1200 cells/mm^3	29(53.7)	125(37.5)	154(39.8)	
≥1200 cells/mm^3	25(46.3)	208(62.5)	233(60.2)	
Baseline CD4 Count				0.010*
<200 cells/ μl	44(81.5)	203(63.6)	247(66.2)	
≥200 cells/ μl	10(18.5)	116(36.4)	126(33.8)	
Baseline Weight				0.017*
<45 kg	20(37.0)	72(22.0)	92(24.1)	
≥45 kg	34(63.0)	255(78.0)	289(75.9)	
Anemia status				0.000*
Normal	16(29.6)	269(80.8)	285(73.6)	
Severe/mild/moderate	38(70.4)	64(19.2)	102(26.4)	
Regimen Type				0.154
D4T-3TC-NVP	8(14.8)	88(26.5)	96(24.9)	
D4T-3TC-EFV	12(22.2)	36(10.8)	48(12.4)	
AZT-3TC-NVP	10(18.5)	78(23.5)	88(22.8)	
AZT-3TC-EFV	10(18.5)	42(12.7)	52(13.5)	
TDF-3TC-NVP	7(13.0)	41(12.3)	48(12.4)	
TDF-3TC-EFV	6(11.1)	43(13.0)	49(12.7)	
Other	1(1.9)	4(1.2)	5(1.3)	
Condom use				0.022*
Never	22(55.0)	170(73.0)	192(70.3)	
Sometimes/Always	18(45.0)	63(27.0)	81(29.7)	
Regimen Change				0.194
No	23(42.6)	172(52.1)	195(50.8)	
Yes	31(57.4)	158(47.9)	189(49.2)	
Adherence				0.000*
Good	30(55.6)	307(96.5)	337(90.6)	
Fair	10(18.5)	4(1.3)	14(3.8)	
Poor	14(25.9)	7(2.2)	21(5.6)	

(*) The association is significant at α=0.05

4.2 Survival time of HIV/AIDS patients

4.2.1 Comparison of Survival Time for HIV/AIDS patients

In this section the discussion is based on Figure 1.1 in Appendix 1 and results in various tables. Since above 50% of the observations are censored, comparison is made based on mean survival time. Females had higher survival compared with men. Results based on the given log-rank test in Table 4.3 show that there is a significant difference between male and female with respect to survival time (p-value=0.040). Patients with risk behaviors like smoking tobacco, drinking alcohol and drug abuse had short survival time. The log-rank test for survival difference were also significant (p-value=0.002). The information presented above is summarized in Table 4.3.

Differences of survival time in patients by WHO clinical stage can be seen from Table 4.4. Among different WHO clinical stage, patients in WHO stage 4 had lowest survive time. The log-rank test also shows that there is a significant difference among the WHO clinical stage groups (p-value=0.001). Kaplan-Meier survivor estimates for TB and anemia status, baseline CD4 count, baseline lymphocyte count and baseline weight are also plotted. The results depict that patients with poor health indicators like TB-and anemia-positive , low baseline CD4 count, low baseline lymphocyte count and low baseline weight had low survival time; also all of these are significant with (p-value=0.000, p-value=0.000, p-value=0.008, p-value=0.016 and p-value=0.003), respectively.

The Kaplan-Meier survivor estimate for regimen changes shows that patients who did not change regimen had higher survival than those patients who did otherwise. The log-rank test in Table 4.4 shows that there is a statistically significant differences in the survival of patients who changed the regimen and who did not (p-value=0.002). The Kaplan-Meier survivor estimate based on adherence shows that patients with high level of adherence had higher survival than those

patients whose adherence were fair and poor. Differences of survival time of patients by functional status can be seen in Table 4.3. Patients whose functional status was bedridden had the shortest survive time than those patients whose functional status was ambulatory or working. The log-rank test for survival difference were highly significant (p-value < .000). The information presented above is summarized in Table 4.3 and Table 4.4.

Similar analysis was performed to investigate differences in survival time among patients with respect to residence, condom use, educational level, VCT(voluntary counseling and testing), age, partner HIV status and marital status. The Kaplan-Meier curves in Figure 1.1 (Appendix 1) show that the curves cross each other indicating that survival time may not differ for these groups. The log-rank tests also show that there were no statistically significant differences in the survival of a patient.

Table 4. 3: Comparison of survival experience of AIDS patients for socio-economic and demographic and risk behavior variable at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	Mean Survival time(in month)	95% CI for the Mean Survival time	Log-rank p-value
Age			0.367
[15-40)	99.741	95.62-103.86	
≥40	93.995	85.08-102.91	
Sex			0.040*
Female	101.893	97.46-106.32	
Male	93.365	86.66-100.07	
Marital Status			0.996
Never married	97.865	87.73-108.00	
Married	97.637	91.60-103.67	
Divorced/ Windowed	96.461	90.66-102.26	
Educational level			0.204
No education	101.605	95.36-107.85	
Primary	97.684	91.491-103.88	
Secondary and above	94.571	88.29-100.85	
Functional Status			0.000*
Bedridden	49.945	38.82-61.07	
Ambulatory	93.508	85.39-101.63	
Working	105.684	101.68-109.68	
Residence			0.929
Rural	86.999	79.46-94.54	
Urban	98.457	94.36-102.51	
Partner's HIV Status			0.063
Negative	90.263	77.46-103.06	
Positive	74.295	67.66-80.93	
Unknown	100.323	96.27-104.38	
VCT			0.281
No	105.200	98.92-111.48	
Yes	98.570	94.10-103.05	
Risk Factor			0.002*
No	104.905	100.54-109.27	
Yes	91.870	85.62-98.12	

(*) The mean Survival time difference is significant at $\alpha=0.05$

Table 4. 4: Comparison of survival of AIDS patients for health variables at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	Mean Survival time	95% CI for the Mean Survival time	Log-rank p-value
TB Status			0.000*
Negative	105.547	102.34-108.75	
Positive	68.010	59.46-76.56	
Baseline CD4 Count			0.008*
<200 cells/ μl	92.913	88.16-97.67	
≥200 cells/ μl	104.850	99.53-110.16	
Baseline Weight			0.003*
<45 kg	87.207	78.79-9562	
≥45 kg	100.953	96.88-105.02	
WHO Clinical Stage			0.001*
Stage I	104.985	97.52-112.45	
Stage II	99.449	93.08-105.82	
Stage III	97.950	93.12-102.78	
Stage IV	79.090	69.11-89.06	
Baseline WBC Counts			0.016*
<1200 cells/mm^3	91.468	84.30-98.64	
≥1200 cells/mm^3	102.540	98.30-106.72	
Knowledge of ART			0.171
No	74.260	52.43-96.10	
Yes	97.980	93.26-102.69	
Anemia status			0.000*
Normal	107.580	104.54-110.62	
Severe/mild/moderate	74.470	66.12-82.82	
Regimen Type			0.140
D4T-3TC-NVP	102.846	97.47-108.22	
D4T-3TC-EFV	88.531	77.02-100.04	
AZT-3TC-NVP	94.396	88.86-99.93	
AZT-3TC-EFV	83.851	74.946-92.757	
TDF-3TC-NVP	94.490	82.38-106.59	
TDF-3TC-EFV	96.790	86.17-107.41	
Other	81.000	45.94-116.06	
Condom use			0.081
Never	89.340	85.13-93.55	
Sometimes/Always	87.270	78.75-95.79	
Regimen change			0.002*
No	102.838	98.57-107.09	
Yes	85.843	80.16-91.53	
Adherence			0.000*
Good	103.460	99.80-107.13	
Fair	51.480	31.60-71.36	
Poor	41.080	93.89-101.82	

(*) The mean Survival time difference is significant at α=0.05

4.2.2 Single Covariate Analysis for survival time

The relationship between each single covariate and survival time of AIDS patients are presented in Table 4.5. As can be seen from this table, survival is significantly related with sex, functional status, risk factor, TB status, anemia status, baseline CD4 counts, WHO clinical stage, baseline weight, baseline lymphocyte counts, adherence and regimen change. The covariates age, religion, residence, educational level, condom use, regimen types and marital status are not statistically significant at 5% significance level.

Table 4. 5: Single covariate analysis of Cox proportional hazards on the time to event of AIDS patients at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	$\hat{B}$	SE	Wald	Df	Sig.	$\hat{HR}$	95% CI for HR
Sex	-0.553	0.273	4.107	1	0.043	0.575	0.34-0.98
Age	0.014	0.013	1.241	1	0.265	1.015	0.99-1.04
Marital Status	0.005	0.200	0.001	1	0.980	1.005	0.68-1.49
Educational Level	0.259	0.170	2.310	1	0.129	1.295	0.93-1.81
Residence	0.036	0.406	0.008	1	0.929	1.037	0.47-2.30
VCT	-0.475	0.445	1.137	1	0.286	0.622	0.26-1.49
Partner's HIV Status	-0.327	0.224	2.132	1	0.144	0.721	0.46-1.12
TB Status	-1.740	0.278	39.047	1	0.000	0.175	0.10-0.30
Baseline Weight	-0.042	0.016	7.171	1	0.007	0.959	0.93-0.99
Baseline CD4	-0.006	0.002	10.705	1	0.001	0.994	0.91-0.99
Baseline WHO Stage	0.483	0.158	9.390	1	0.002	1.621	1.19-2.21
Condom Use	-0.549	0.319	2.964	1	0.085	0.578	0.31-1.08
Risk Factor	-1.183	0.413	8.207	1	0.004	0.306	0.14-0.69
Functional Status	-1.284	0.168	58.741	1	0.000	0.277	0.20-0.39
Baseline WBC	-0.647	0.273	5.604	1	0.018	0.524	0.31-0.89
Knowledge of ART	0.710	0.529	1.797	1	0.180	2.033	0.72-5.74
Anemia Status	1.975	0.298	43.833	1	0.000	7.204	4.02-12.93
Regimen Type	0.113	0.079	2.076	1	0.150	1.120	0.96-1.31
Regimen Change	-0.843	0.283	8.876	1	0.003	0.430	0.25-0.75
Adherence	1.328	0.152	76.499	1	0.000	3.774	2.80-5.08

HR: Hazard Ratio
SE: Standard Error
CI: Confidence Interval
Df: Degrees of freedom

4.2.3 Multiple Covariates Analysis for survival time

One problem of single covariate approach is that it ignores the possibility that a collection of variables, each of which is weakly associated with the outcome, can become an important predictor of the outcome when taken together. In statistical modeling, when the number of variables is relatively large, it can be computationally expensive to fit all possible models. Thus, one of the options is fitting a multivariable model containing the variables that are significant at a modest level of significance in a univariable analysis. We use a α-value of 0.25 to select candidate variables for the multi-covariate analysis from the single covariate findings. As a result, 20 univariable Cox proportional hazards models, each containing one explanatory variable, were fitted.

The estimated coefficients $\widehat{\boldsymbol{\beta}}_i$ for the covariates in the final model, their standard errors and the adjusted hazard ratio corresponding are given in Table 4.6. As can be seen from this table, survival is significantly related with TB status, baseline CD4 count, anemia status, functional status, sex and adherence. The values of the Wald statistic for individual **β** coefficients support that the estimated values $\widehat{\boldsymbol{\beta}}_i$'s are significantly different from zero at α=0.05 level of significance for all the above six covariates.

Results about model adequacies are presented in Section 4.2.4; they show that model fit is good. The Cox regression hazard in the final model are interpreted as follows. The following interpretations are based on Table 4.6. After adjusting for other covariates, the hazard rate of male patients were about 81% more likely to die than female patients (adjusted HR=1.81, CI=0.99-3.29). The hazard rate of TB positive patients was 3.6 times that of TB negative

(adjusted HR=3.58, CI=1.96-6.53). The hazard rate of the normal anemic patients was about 73% lower relative to sever/moderate anemic patients (adjusted HR=0.27, CI= 0.14-0.50).

Bedridden patients were 5.1 times more likely to die than working patients (adjusted HR=5.06, CI=2.57-9.98). For ambulatory patients the hazard rate of patients was 29.6% higher than that of working patients (adjusted HR=1.29, CI=0.60-2.79). The hazard rate of patients whose adherence was good was 89% lower than that of patients whose adherence was poor (adjusted HR=0.11, CI=0.05-0.21). The hazard rate of patients whose adherence was fair was 53% lower than that of patients whose adherence was poor (adjusted HR=0.47, CI=0.19-1.14). Baseline CD4 count is also another covariate which has a significant effect on the survival of patients (adjusted HR=0.994, 95% CI: 0.991-0.998,p-value=0.004). The adjusted hazard ratio for a 50 cells/µl increase in the baseline CD4 count is $\exp(-0.006*50)=0.741$, and the corresponding 95 % CI for the hazard ratio is 0.609 to 0.901. The interpretation is that patients whose CD4 count is higher by 50 cells/µl on the baseline are dying at a hazard rate 26% lower than for patients with lower count.

Table 4. 6: Multiple Covariate Analysis for socio-economic, health and demographic variables that affect survival time of AIDS patients at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	Df	$\hat{B}$	Error	Wald	Sig.	aHR	95% CI for HR
Sex							
Male	1	0.594	0.304	3.809	0.050	1.812	0.99-3.29
Female (reference)						1	
Baseline CD4 Count	1	-0.006	0.002	8.291	0.004	0.994	0.991-0.998
TB Status							
Positive	1	1.276	0.306	17.359	0.000	3.581	1.96-6.53
Negative (reference)						1	
Anemia Status							
Normal	1	-1.310	0.320	16.780	0.000	0.270	0.14-0.50
Sever/Moderate (reference)						1	
Functional status							
Bedridden	1	1.623	0.346	22.028	0.000	5.067	2.57-9.98
Ambulatory	1	0.260	0.392	0.440	0.507	1.296	0.60-2.79
Working (reference)						1	
Adherence							
Good	1	-0.289	0.371	37.998	0.000	0.105	0.05-0.21
Fair	1	-0.757	0.452	2.801	0.094	0.469	0.19-1.14
Poor (reference)						1	

aHR: adjusted Hazard Ratio
SE: Standard Error
CI: Confidence Interval
Df: Degrees of freedom

4.2.4 Assessment of model adequacy for survival time

The formal test applied to the model presented in Table 4.7 shows the time-dependent covariates (interaction of covariates with logarithm of time) were not significant which justifies the proportional hazard assumption holds at 5% level of significance. The plot of the scaled Schoenfeld residuals in Figure 2.1 in Appendix 2 also shows that the residuals are random without any systematic pattern and the smoothed plot approximates a horizontal line. Thus, there is no violation of proportional hazards assumption.

Table 4. 7: Statistical test for Proportional hazards assumption of multiple covariates and their interaction with log of time for the survival time of the patient at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	B	SE	Wald	Df	Sig.	aHR	95% CI for HR
Sex	-0.868	0.806	1.158	1	0.282	.420	0.09-2.04
Baseline CD4 count	-0.008	0.005	3.023	1	0.082	.992	0.98-1.00
TB Status	-1.698	0.919	3.410	1	0.065	.183	0.03-1.11
Anemia Status	1.023	0.945	1.174	1	0.279	2.782	0.44-17.71
Baseline Functional Status	-0.380	0.410	0.856	1	0.355	.684	0.31-1.53
Adherence	1.597	0.457	12.192	1	0.000	4.940	2.02-12.11
Sex*ln(T)	0.051	0.235	0.048	1	0.826	1.053	0.66-1.67
Baseline CD4 count*ln(T)	0.001	0.001	0.645	1	0.422	1.001	0.99-1.04
TB Status*ln(T)	0.155	0.270	0.330	1	0.566	1.168	0.68-1.98
Anemia Status*ln(T)	0.103	0.270	0.145	1	0.703	1.108	0.65-1.88
Baseline Functional Status*ln(T)	-0.150	0.125	1.435	1	0.231	0.861	0.67-1.10
Adherence*ln(T)	-0.167	0.144	1.343	1	0.247	0.846	0.64-1.12

aHR: adjusted Hazard Ratio
SE: Standard Error
CI: Confidence Interval
Df: Degrees of freedom

The residuals plots can be used to check the linearity assumption and to check for the presence of influential and outlier observations. As can be observed in Figure 2.2 in Appendix 2 some observations have large spikes. These observations are suspected to have undue influence on the parameter estimates. To check their influence the suspected observations were removed one at a time and the model was refitted. There were no large changes in the model estimates and hence we conclude that these observations are not as such influential outliers and then retained in the model. From Figure 2.3 in Appendix 2 there is no definite pattern in the scatter plots; the smoothed curve is almost a horizontal line through the origin. These are indicators of approximate linearity in the covariates.

Finally, the results of the likelihood ratio test (chi-square=149.19, p-value < .000) and Score test (chi-square=248.376, p-value < .000) shows that the model fit is good, i.e. significant at 5% level of significance. Thus, from all results we can say that our model fits the data very well.

4.2.5 Discussion About survival time

This study identified variables/factors that are significantly associated with increased risk of mortality. Identifying patients at a higher risk of death has the advantage that due attention will be given to the risk group during their follow up to minimize the risk of mortality while they are taking ART.

The Cox's proportional hazard model fitted using complete case analysis identified six variables that jointly serve as predictive factors of the survival of AIDS patients. These variables are sex, TB status, baseline CD4 count, baseline functional status, anemia status and adherence. The hazard rate of male patients is about 81% more likely to die than female patients. This result agrees with the result obtained from previous study where men had lower survival time compare to women Sieleunou *et al*.(2009) from Cameron, Dias *et al*. (2007) from Portugal and Mee-Kyung *et al*. (2009) from Korea.

The hazard rate of TB-positive patients was 3.6 times greater than TB-negative. This result concurs with a study by Begovac *et al*. (2006) in America and Dias *et al*. (2007) in Portugal. The hazard rate of patients who had normal anemia was 73% lower than those patients who have severe/mild anemia. This result agrees with a study from England (Moyle, 2002) showing that anemia is a significant predictor of survival of AIDS patients.

Baseline CD4 count determines the level of resistance to different opportunistic diseases. The higher the CD4 count, the lower the risk of death. The result of this study showed that patients

whose CD4 count is higher by 50 cells/mm^3 died at a hazard rate 26% lower than for patients with lower count. This result is similar with the study from Uganda by Brain *et al*. (2009), Ethiopia by Nuredin and Eshetu (2007) showing that baseline CD4 count is a significant predictor of survival of AIDS patient.

The hazard rate of patients whose functional status was bedridden was five times more likely to die than that of working patients. The hazard rate of patients whose functional status was ambulatory was 29% more likely to die than that of working patients. These results are similar with the study from Ethiopia by Nurilegn et al.(2013), which indicated that baseline bedridden and ambulatory had low survival relative to working patients. The hazard rate of patients whose adherence was categorized as "good" were 89% less likely to die than patients whose adherence was "poor". Similarly, the hazard rate of patients whose adherence was classified as "fair" was 53% lower than patients with "poor" adherence. This result is similar to the study done by Nurilegn et al. (2013).

4.3 Immunological recovery time of HIV patients

4.3.1 Comparison of Immunological Recovery Time

The following comparison is made based on the results in Tables 4.8 and 4.9 and Kaplan-Meier survival estimates in Appendix 5.1 in order to investigate for significant differences between immunological recovery times of patients. Kaplan-Meier survivor estimates for the two genders shows that females had shorter median recovery time compared with men. The log-rank test result in Table 4.8 shows that there is a significant difference between male and female with respect to immunological recovery time. The differences of recovery time of patients by functional status shows that patients whose functional status was working had shorter median recovery time than ambulatory and bedridden. Baseline CD4 count >200cell/µl, TB-negative, total lymphocyte count ≥1200 cell/mm^3 and baseline weight ≥45kg contributed to a shortening time to immunological recovery. A low baseline CD4 count ≤200cell/µl, TB-positive, patient in WHO stage IV and being anemic contributed to a longer time to immunological recovery at 5% of significant level.

Based on Table 4.9 patients who did not change regimen had a shorter median recovery time than those patients who changed regimen. The log-rank test shows that there is statistically significant difference in the recovery of patients. Patients whose adherence was "good" had a shorter recovery time than those patients whose adherence were "fair" and "poor". The log-rank test showed a significant recovery difference.

Similar analysis is performed to investigate difference in the recovery time among the patients with respect to, residence, condom use, educational level, VCT (voluntary counseling and testing), age, partner HIV status, marital status, risk factor, knowledge of ART and regimen type. The respective Kaplan-Meier curves in Figure 5.1 in Appendix 5 show that the curves

cross each other implying the possibility that survival time may not differ for these groups. Also, the log-rank test results show that there is no statistically significance difference in the recovery.

Table 4. 8: Comparison of immunological recovery time for socio- demographic and risk behavior variables at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	Median Survival time	95% CI for the Median time	Log-rank p-value
Age			0.139
15-39	9.00	7.98-10.02	
>=40	12.00	8.47-15.52	
Sex			0.002*
Female	9.00	7.84-10.13	
Male	12.00	8.38-15.61	
Marital Status			0.811
Never married	10.00	6.16-13.84	
Married	10.00	7.92-12.087	
Divorce/ Windowed	10.00	7.83-12.17	
Educational level			0.168
No education	10.00	7.42-12.58	
Primary	9.00	7.29-10.70	
Secondary and above	11.00	8.35-13.65	
Functional Status			0.002*
Bedridden	20.00	8.14-31.86	
Ambulatory	10.00	7.57-12.43	
Working	9.00	7.85-10.15	
Residence			0.941
Rural	10.00	8.43-11.56	
Urban	9.00	6.73-11.26	
Partners HIV Status			0.212
Negative	14.00	11.28-16.72	
Positive	11.00	5.93-16.07	
Unknown	10.00	8.78-11.21	
VCT			0.052
No	9.00	6.95-11.05	
Yes	10.00	8.40-11.59	
Risk Factor			0.934
No	10.00	8.15-11.85	
Yes	10.00	8.00-11.99	

(*) The Median Immunological Recovery time difference is significant at $\alpha=0.05$

Table 4. 9: Comparison of Immunological recovery for health variables at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	Median Immunological Recovery time	95% CI for the Median time	Log-rank p-value
TB Status			0.001*
Negative	10.00	8.77-11.22	
Positive	12.00	7.21-16.78	
Baseline CD4 Count			0.041*
<200	11.00	9.71-12.28	
>= 200	6.00	5.34-6.66	
Baseline Weight			0.002*
<45	15.00	12.04-17.96	
>= 45	9.00	7.98-10.02	
WHO Clinical Stage			0.006*
Stage I	10.00	7.76-12.23	
Stage II	9.00	7.26-10.74	
Stage III	10.00	8.29-11.71	
Stage IV	16.00	10.27-21.73	
Baseline WBC Counts			0.001*
<1200	13.00	10.55-15.44	
>=1200	9.00	7.91-10.09	
Knowledge of ART			0.498
No	15.00	7.04-22.96	
Yes	10.00	8.73-11.27	
Anemia status			0.000*
Normal	9.00	7.92-10.08	
Sever/mild/moderate	15.00	9.66-20.34	
Regimen Type			0.222
D4T-3TC-NVP	10.00	7.68-12.32	
D4T-3TC-EFV	8.00	5.97-10.02	
AZT-3TC-NVP	9.00	6.26-11.74	
AZT-3TC-EFV	11.00	8.56-13.44	
TDF-3TC-NVP	10.00	5.06-14.94	
TDF-3TC-EFV	11.00	3.81-18.19	
Other	15.00	0.00-30.59	
Condom use			0.445
Never	10.00	8.31-11.68	
Sometimes/Always	9.00	5.86-12.14	
Regimen change			0.003*
No	9.00	7.79-10.20	
Yes	11.00	8.74-13.26	
Adherence			0.003*
Good	10.00	8.69-11.30	
Fair	15.00	8.17-21.82	
Poor	24.00	10.34-33.78	

(*) The Median Immunological Recovery time difference is significant at $\alpha=0.05$

4.3.2 Single covariate analysis for immunological recovery time

The relationship between single covariates and recovery time of AIDS patients are presented in Table 4.10. As can be seen from this table, time to immunological recovery is significantly related with sex, functional status, TB status, anemia status, baseline CD4 count, WHO clinical stage, baseline weight, baseline lymphocyte counts, adherence and regimen change. The covariates age, residence, educational level, condom use, regimen types, marital status, VCT (voluntary counseling and testing), partner's HIV status, risk factor and knowledge of ART are not statistically significant at 0.05 significant level.

Table 4. 10: Single Covariate Analysis for socio-economic health and demographic variables that affects time to immunological recovery of AIDS patients at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	$\hat{B}$	SE	Wald	Df	Sig.	$\hat{HR}$	95% CI for HR
Sex	0.346	0.120	8.369	1	0.004	1.414	1.12-1.79
Age	-0.010	0.007	2.195	1	0.138	0.990	0.97-1.00
Marital Status	0.047	0.088	0.284	1	0.594	1.048	0.88-1.25
Educational Level	-0.113	0.068	2.717	1	0.099	0.894	0.78-1.02
Residence	-0.012	0.168	0.005	1	0.994	0.998	0.71-1.37
VCT	0.323	0.174	3.468	1	0.063	1.382	0.98-1.94
Partner's HIV Status	0.174	0.105	2.780	1	0.095	1.191	0.97-1.46
TB Status	0.450	0.146	9.508	1	0.002	1.568	1.17-2.08
Baseline Weight	0.023	0.006	14.597	1	0.000	1.023	1.01-1.04
Baseline CD4	0.003	0.001	17.602	1	0.000	1.003	1.001-1.004
Baseline WHO Stage	-0.173	0.062	7.928	1	0.005	0.841	0.76-0.95
Condom Use	0.109	0.149	0.531	1	0.466	1.115	0.83-1.49
Risk Factor	-0.010	0.132	0.006	1	0.937	0.990	0.77-1.28
Baseline Functional Status	0.310	0.097	10.238	1	0.001	1.364	1.13-1.65
Baseline WBC	0.370	0.120	9.459	1	0.002	1.448	1.14-1.83
Knowledge of ART	-0.209	0.324	0418	1	0.518	0.811	0.43-.53
Anemia Status	-0.455	0.137	11.048	1	0.001	0.634	0.48-0.83
Regimen Type	-0.053	0.032	2.643	1	0.104	0.949	0.89-1.01
Regimen Change	-0.344	0.117	8.635	1	0.003	0.709	0.56-0.89
Adherence	0.332	0.117	8.096	1	0.004	1.393	1.11-1.75

HR: Hazard Ratio
SE: Standard Error
CI: Confidence Interval
Df: Degree of freedom

4.3.3 Multiple Covariates Analysis for immunological recovery time

The following discussion is based on Table 4.11. After adjusting for other covariates, the hazard of attaining immunological recovery for male patients was about 26.7% lower than for female patients (adjusted HR=0.73, CI= 0.570-0.940). The adjusted hazard ratio for a 50 cells/µl increase in the baseline CD4 count is $\exp(0.002*50)=1.11$, and the corresponding 95 % with CI 1.002-1.22. That is, for a 50 CD4 cell/µl increase of baseline CD4 count, the rate of attaining immunological recovery increased by 11%. For a 5kg increase of baseline weight of the patients, the rate of attaining immunological recovery increased by 13.3% (adjusted HR for 5kg change=1.13, CI=1.058-1.213). The rate of attaining immunological recovery decreased by a 8% for a 5 year increase in age. The adjusted hazard ratio and the corresponding 95% CI for a 5 year increase in age are adjusted HR=0.92, CI=0.862-0.988.

The rate of attaining immunological recovery for not anemic patients was about 34.4% higher than those patients with severe/moderate anemic (adjusted HR=1.34, CI=1.020-1.780). The rate of attaining immunological recovery for patients with a total lymphocyte count <1200 cells/mm^3 was about 23% lower than a patient with a total lymphocyte count of ≥ 1200 cells/mm^3 (adjusted HR=0.77, CI=0.600-0.980). The rate of attaining immunological recovery for patients who were in WHO stage I was about 88% higher than those patients who were in WHO stage IV (adjusted HR=1.88, CI=1.170-3.030); for patients who were at WHO stage II it was about 67% higher (adjusted HR= 1.67, CI=1.070-2.580), for patient who were in WHO sage III was about 64% higher than those patients who were at WHO stage IV. Finally the hazard of attaining immunological recovery for patients who changed the regimen was about 31% lower than those patients who do not changed the regimen (adjusted HR=0.69,CI=0.540-0.870).

Table 4. 11: Multiple Covariate Analysis for socio-economic, health and demographic variables that affect time to immunological recovery of HIV patients at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	df	$\hat{B}$	SE	Wald	Sig.	aHR	95.0% CI for HR
Sex							
Male	1	-0.311	0.128	5.886	0.015	0.733	0.57-0.94
Female (reference)						1	
Age	1	-0.016	0.007	4.461	0.035	0.984	0.97-0.99
Baseline CD4 count	1	0.002	0.001	14.123	0.000	1.020	1.01-1.04
Baseline Weight	1	0.025	0.007	14.272	0.000	1.026	1.01-1.04
Baseline WHO Stage							
Stage I	1	0.633	0.242	6.825	0.009	1.884	1.17-3.03
Stage II	1	0.510	0.224	5.175	0.023	1.665	1.07-2.58
Stage III	1	0.496	0.208	5.663	0.017	1.642	1.09-2.47
Stage IV (reference)						1	
Baseline WBC							
<1200	1	-0.264	0.126	4.436	0.035	0.768	0.60-0.98
≥1200 (reference)						1	
Anemia Status							
Normal	1	0.295	0.143	4.256	0.039	1.344	1.02-1.78
Sever/Moderate (reference)						1	
Regimen change							
Yes	1	-0.373	0.121	9.562	0.002	0.688	0.54-0.87
No (reference)						1	

aHR: adjusted Hazard Ratio
SE: Standard Error
CI: Confidence Interval
Df: Degree of freedom

4.3.4 Assessment of model adequacy for immunological recovery time

The formal test applied to the model presented in Table 4.12 shows that the time-dependent covariates (interaction of covariates with logarithm of time) were not significant thereby justifying that the proportional hazard assumption holds at 5% level of significance. The plot of

the scaled Schoenfeld residuals in Figure 6.1 in Appendix 6 also show that the residuals are random without any significant systematic pattern and the smoothed plot approximating a horizontal line.

Table 4. 12: Statistical test for Proportional hazards assumption of the covariate and their interaction with log of time for time to immunological recovery of the patient at Felege-Hiwot Referral Hospital during 2006-2013.

Variables	$\hat{B}$	SE	Wald	df	Sig.	aHR	95%CIfor HR
Sex	0.373	0.467	0.636	1	0.425	1.452	0.58-3.63
Age	-0.030	0.027	1.229	1	0.268	0.970	0.92-1.02
Baseline Weight	-0.001	0.025	0.002	1	0.960	0.999	0.95-1.05
Baseline CD4 count	0.002	0.001	4.835	1	0.028	1.002	1.000-1.005
Baseline WHO Stage	-0.137	0.259	0.279	1	0.597	0.872	0.52-1.45
Baseline WBC	-0.158	0.453	0.122	1	0.727	0.854	0.35-2.07
Anemia Status	-0.555	0.533	1.085	1	0.298	0.574	0.20-1.63
Regimen change	0.161	0.447	0.130	1	0.718	1.175	0.50-2.82
Sex*ln(T)	-0.022	0.203	0.012	1	0.912	0.978	0.66-1.45
Age*ln(T)	0.013	0.013	1.031	1	0.310	1.013	0.98-1.04
Baseline CD4count*ln(T)	0.000	0.001	0.080	1	0.778	1.000	0.999-1.001
Baseline WHO Stage*ln(T)	-0.005	0.118	0.001	1	0.969	0.995	0.79-1.25
Baseline WBC*ln(T)	0.147	0.201	0.534	1	0.465	1.158	0.78-1.72
Anemia Status*ln(T)	0.169	0.231	0.536	1	0.464	1.184	0.75-1.86
Baseline Weight*ln(T)	0.014	0.011	1.584	1	0.208	1.014	0.99-1.04
Regimen change*ln(T)	-0.036	0.200	0.032	1	0.857	0.965	0.65-1.43

Residuals plots can be used to check the validity of the linearity assumption as well as to check the presence of influential and outlier observations. As can be observed in Figure 6.2 in Appendix 6 some observations have large spikes; these are suspected to have undue influence on the parameter estimates. To check their influence the suspected observations were removed

one at a time and model was refitted. It was noted that there were no significant changes in the model estimates leading to the conclusion that they are not as such influential outliers, and therefore, can be retained in the model. Figure 6.3 in Appendix 6 shows no definite pattern in the scatter plots, and the smoothed curve is almost a horizontal line through the origin. These are indicators of approximate linearity in the covariates.

Finally, the results of the likelihood ratio test (chi-square=69.79, p< .000) and Score test (chi-square=68.549, p< .000) shows that the model fit is good, i.e. significant at 5% level.

4.3.5: Discussion about time to immunological recovery

The Cox's proportional hazard model, showed that baseline CD4 counts, anemia status, sex, baseline lymphocyte counts, baseline weight, age, regimen change and baseline WHO stage jointly predict time to immunological recovery of AIDS patients.

A baseline total lymphocyte count of at least 1200 cells/mm^3 was found to be associated with a short median time to immunological recovery. The rate of attaining immunological recovery for a patient with a total lymphocyte count below 1200 cells/mm3 was about 23% lower than a patient with a total lymphocyte count of 1200 cells/mm^3 and more. Brain et al., (2009) identified a significant association between total lymphocyte count below 1200 cells/mm3 and subsequent poor immunological recovery, disease progression or mortality.

The current study found that the rate of attaining immunological recovery for male patients is about 27% lower than for female patients. This result agrees the earlier findings reported by Lorna et *al*. (2011), Moges *et al.* (2013) and Puthanakit et al. (2012). This study showed that the rate of attaining immunological recovery decreased by 8% for a 5 year increase in age. Our result agrees the earlier findings reported by Nguyen et al. (2008) and Gebo et al. (2008).

The rate of attaining immunological recovery for not anemic patients was about 34% higher than those patients who had severe/mild level of anemia. This result is in agreement with a study from England (Moyle, 2002) and another from USA (Patrick, 2002) showing that anemia is a very significant predictor of immunological recovery of AIDS patient. The current study found that, for a 50 CD4 *cells/ μl* increase in the baseline CD4 counts, the rate of attaining immunological recovery increased by 11%. The finding is consistent with other studies where it was found that immunological recovery is largely dependent on baseline CD4 count, and thus the timing of ART initiation is important in order to maximize the CD4+ T-cell response to therapy (Brain *et al*., 2009; Lawn *et al*., 2006; Moges *et al*., 2013; Antonella *et al*., 2010).

Baseline weight determines resistance to different opportunistic diseases. We found that for a 5 kilogram increase in baseline weight of patients, the rate of attaining immunological recovery increased by 13%. This result agrees with an earlier finding reported by Mair et al. (2007). Clinical WHO stage is also a predictor of time to immunological recovery of AIDS patients. The rate of attaining immunological recovery for patients who were in WHO stage I was about 88% higher than those patients who were in WHO stage IV, the rate of attaining immunological recovery for patients who were in WHO stage II was about 67% higher than those patients who were in WHO stage IV while the rate of attaining immunological recovery for patient who were in WHO sage III was about 64% higher than those patients who were in WHO stage IV. This result agrees with the findings reported by Adrian et al. (2013).

This study found that the rate of attaining immunological recovery for patients who changed the regimen was about 31% lower than those patients who did not change regimen. This result agrees with the earlier findings reported by Eric et al. (2012).

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

The aim of ART is to improve the health condition and survival of HIV/AIDS patients. The objective of this study were two: (i) to compare survival time and time to immunological recovery among groups, and (ii) to examine factors that may affect survival and recovery of a patients under ART. The Cox regression analysis showed that the major factors that affect the survival of HIV/AIDS patients are gender, TB status, anemia status, baseline CD4 counts, functional status and adherence to treatment. Males had lower survival time compared to women patients. Patients with poor health indicators like being TB-and anemia-positive, having low CD4 count, being in WHO stage IV and poor adherence to treatment had lower survival.

The results also indicated that survival probability of patients is not statistically different among groups classified by age, marital status, knowledge of ART, residence, VCT(voluntary counseling and testing), educational level, regiment type, risk factor, weight, WBC, condom use, regimen change, partner's HIV status, and risk factor behavior.

The Cox regression analysis for the immunological recovery showed that the major factors affecting time to immunological recovery of HIV/AIDS patients were sex, age, anemia status, baseline CD4 count, baseline lymphocyte count, baseline weight, baseline WHO stage and regimen change. Female patients had shorter time to immunological recovery compared with male patients. Similarly, TB-and anemia-positive, low baseline CD4 count and low baseline lymphocyte count, low weight and elder patients could not attain immunological recovery fast.

The results indicated that the probability of immunological recovery of a patient was not statistically different among groups classified by, marital status, knowledge of ART, residence,

VCT(voluntary counseling and testing), educational level, regiment type, risk factor, condom use, adherence to treatment, partner's HIV status, risk factor and functional status.

5.2 Recommendations

ART clinics are now widespread in all corners of Ethiopia. Patients are being treated in the ART clinics to extend their lives. But parallel to this, due to many reasons, patients are still dying under ART follow up. According to the results of this study the main predictive factors for the survival and time to immunological recovery probability of AIDS patients are more of clinical variables. So, health workers should be cautious when a patient has lower CD4 count, lower weight, lower lymphocyte count, and is TB-or anemia-positive. When this is the case appropriate clinical and non-clinical measures like medicine and other support should be provided. For those patients with low economic status, stakeholders need to find way of supporting the patients with respect to improving their income, nutrition and living conditions.

Being bedridden and in WHO clinical stage IV are strong indicators of the progression of the disease. Therefore, patients should be informed about the need for early diagnosis of HIV infection should be advised to start treatment early. A separate treatment program for drug user patients is important and has to be carefully monitored with respect to drug adherence, as the effect of the treatment is highly dependent on adherence. Also, the greater risk of mortality associated with drug use need be explored. Physicians need to be cautious about the most recent status of the disease while treating a given patient, as it may affect his/her survival and recovery time.

Most of the patients in the cohort studied here initiated their therapy with NVP-based regimens which are not recommended for patients co-infected with TB according to the ART guideline.

Thus, EFV-based regimen should be provided to patients with TB to improve their survival. In addition to this, special care should be given to TB/HIV patients.

6. REFERENCES

Adrian Alejandro Farias, Luis Emiliokremer, Luis Allende, Maria Belen Pisano, Marta Silvia(2013). Determinants of immunological and virological response to ART among HIV infected adults in central argentina. Journal of Royal socityof tropical medicine and hygine.

Agresti, A. (1996). An introduction to categorical data analysis. John Wiley and So, Inc., New York

Alemtsehai Abate and Eshetu Wencheko (2006). Association of HIV infection with some selected factors and modeling the chance of contracting HIV: The case of Hawassa and its surrounding. *Journal of Ethiop Stat Assoc*; 15: 27-48.

Allison A. (2006). ***HIV Laboratory Monitoring***www.aidsalliance.org/publications.

Ana,S. and MD.Guimarães (2005). Factors associated with psychiatric treatment dropout in a mental health reference center, Belo Horizonte. *Bras Psiquiatr* 27(2):113-8.

Appay V, Sauce D. 2008: Immune activation and inflammation in HIV-1 infection: causes and consequences. J Pathol, 214:231-241.

Antonella Castagna, Laura Galli, Carlo Torti, Antonella D'arminio et al. 2010. Predicting the magnityde of short-term CD4+ T-cell recovery in HIV-Infected patients duringfirst line HAART. Antivira Therapy 2010 15:165-175.

Azzoni L, Chehimi J, Zhou L, Foulkes AS, June R, Maino VC, Landay A, Rinaldo C, Jacobson LP, Montaner LJ. 2007. Early and delayed benefits of HIV-1 suppression: timeline of recovery of innate immunity effector cells. AIDS, 21:293-305.

Barre-Sinoussi, F., JC. Chermann, F. Rey, MT. Nugeyre, S. Chamaret, J. Gruest, C. Dauguet, C. Axler-Blin, , F. Vezinet-Brun, C. Rouzioux, W. Rozenbaum, L. Montagnier. (1983). Isolation of a T-lymphotropic retrovirus from a patient at risk for AIDS. *Science*, 220: 868-71.

Baker JV, Peng G, Rapkin J, Krason D, Reilly C, Cavert WP, Abrams DI,MacArthur RD, Henry K, Neaton JD. 2008: Poor initial CD4+ recovery with antiretroviral therapy prolongs immune depletion and increases risk for AIDS and non-AIDS diseases. J Acquir Immune Defic Syndr,48:541-546

Begovac, J., M. Lisi, D. Lukas, T. Mareti, T. Kniewald and T.E. Novotny (2006). Marked improvement in survival among adult croatian AIDS patients after the introduction of highly active antiretroviral treatment. *Coll. Antropol* 30 (1): 175–179.

Biadgilign S, Reda AA, Digafe T (2012) Predictors of mortality among HIV infected patients taking antiretroviral treatment in Ethiopia: a retrospective cohort study. AIDS Res Ther 9: 15.

Brian, K., S. Samwel, M. Peter, and N. Betty (2009). The effect of AIDS defining conditions on immunological recovery among patients initiating antiretroviral therapy at Joint Clinical Research Centre, Uganda. *AIDS Research and Therapy* 6:17.

Braitstein, P., M. Brinkhof, F. Dabis (2006). Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* 367: 817–824.

Bucy RP, Hockett RD, Derdeyn CA, et al. **1999.** Initial increase in blood CD4+ lymphocytes after HIV antiretroviral therapy reflects redistribution from lymphoid tissues. J Clin Invest; 103:1391–8.

Cain KP, Anekthananon T, Burapat C, Akksilp S, Mankhatitham W, Srinak C,et al 2009. Causes of death in HIV - infected person who have tuberculosis. Emereging infectious diseases;15: 258-64.

Cairns G. Long-term CD4 increase on HAART averages 250–350 cells, plateaus after 3–4 years; Presented at: 12th Conference on Retroviruses and Opportunistic Infections; February 22–25, 2005; Boston, MA.

Central Statistics Authority. (2008). Summary and statistical report of 2007 population and housing census. *Addis A*beba, Ethiopia. 113 p.

Cochran, W. (1977). Sampling technique. New York. John Wiley & Sons, Inc.

Collett, D. (1994). Modeling survival data in medical research. London: Chapman & Hall.

Country Progress Report on HIV/AIDS Response, FHAPCO, Addis Ababa, Ethiopia, 2012.

Cox, DR. (1972). Regression models and life-tables (with discussion). *J R Stat Soc* 34**:**187-220.

Cox, DR. and EJ. Snell (1989) The analysis of binary data. 2nd edition, Chapman and Hall, Londin, UK.

David, M., M. Pever, and MA. Martin (1996). Survival analysis, 4th edition, Lippincott – Raven, Philadelphia, USA.

Detels, R., A. Mun˜oz, and G. McFarlane. (2010). Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. *JAMA* 280:1497–503.

Dias, S., V. Andreozzi, R.O. Martins, and J. Torgal (2007). A hierarchical survival model to describe patterns and factors associated with HIV/AIDS Portuguese Referral Hospitalization. M.Sc thesis. New university of Lisbon. Portugal.

Egger M, May M, Chêne G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet. 2002;360:119–129. [PubMed]

Eric Balestre Serge P. Eholie, Amani Lokossue, Papa Salif Sow, Man Charurat, Albert Minga, Joseph Drabo, Francois Dabis, Didier K. Ekouevi, Rodolphe Thie´baut. Effect of age on immunological response in the first year of antiretroviral therapy in HIV-1-infected adults in West Africa. AIDS 2012, 26:951–957.

Fieldman J.G., Nicolas R.T., Benard H., Robert K., (2006). ***Association of cigarret smoking with HIV prognosis among women in the HAART era. A report from the women's interagency HIV study***. American journal of public health. p 96, 1061-1065.

Florence E, Lundgren J, Dreezen C, Fisher M, Kirk O, Blaxhult A, Panos G,Katlama C, Vella S, Phillips A. 2003: Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study.HIV Med 2003, 4:255-262.

Fox, J. (2003). Cox proportional hazards regression for survival data: appendix to and R and S-plus companion to applied regression.

Galai, N., M. Safaeian, D. Vlahov, A. Bolotin and D. Celentano (2003). Longitudinal patterns of drug injection behavior in the ALIVE study cohort, 1988–2000: description and determinants. *Am J Epidemiology* 158: 695–704.

Gandhi RT, Spritzler J, Chan E, Asmuth DM, Rodriguez B, Merigan TC, et al. Effect of baseline- and treatment-relatedfactors on immunologic recovery after initiation of antiretroviral therapy in HIV-1-positive subjects: results from ACTG 384. J Acquir Immune Defic Syndr 2006; 42:426–434.

Gebo KA (2008) Epidemiology of HIV and response to antiretroviral therapy in the middle aged and elderly. Aging health 4: 615–627.

Grabar S, Kousignian I, Sobel A, Le Bras P, Gasnault J, et al. (2004) Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. AIDS 18: 2029–2038.

Greenbaum AH, Wilson LE, Keruly JC, Moore RD, Gebo KA (2008) Effect of age and HAART regimen on clinical response in an urban cohort of HIV-infected individuals. AIDS 22: 2331–2339.

Grinspoon S, Mulligan K (2003) Weight loss and wasting in patients infected with human immunodeficiency virus. Clin Infect Dis 36: S69–78.

Guerreiroa M, R. Ligia, S. Rosa and C. Marcondes (2011). Survival of adult AIDS patients in a reference Referral Hospital of a metropolitan area in Brazil. Rev *Saúde Pública* 36(3):278-84

Habtamu Ashenafi and Eshetu Wencheko (2012). Factors affecting the survival of HIV-infected children after ART initiation in Bahir-Dar, Ethiopia. Ethiop.j. Health Dev. 26(3): 193-199

Harries AD, Zachariah R, Corbett EL, Lawn SD, Santos-Filho ET, Chimzizi R et al. 2010. The HIV-associated tuberculosis epidemic–when will we act? *Lancet*;375:1906–19. doi:10.1016/S0140-6736(10)60409-6 PMID:20488516

Hawkins C, Achenbach C, Fryda W, Ngare D, Murphy R. Antiretroviral durability and tolerability in HIV-infected adults living in urban Kenya. J Acquir Immune Defic Syndr. 2007;45:304–310. [PubMed]

Hirschel B, Opravil M (1999) The year in review: antiretroviral treatment. AIDS 13: S177–S187.

Holmes, C., E. Losina, R. Walensky, Y. Yazdanpanah, KA. Freedberg. (2003). Review of human immunodeficiency virus type 1-related opportunistic infections in sub-saharan Africa. *Clin Infect Dis* 36: 652-62.

Hosmer, D. and S. Lemeshow (1998). Applied survival analysis: Regression Modeling of Time to Event Data. Wiley New York.

Huges R., Stanford J., (2007). Long-term trends in CD4 counts in Patients starting HAART. UK- CHIC study**.** Eleventh EACS Conference, abstractno. P14.4/04/BPD,2007.

Hunt PW, Martin JN, Sinclair E, Bredt B, Hagos E, Lampiris H,et al. T cell activation is associated with lower CD4R T cell gains in human immunodeficiency virus-infected patients with sustained viral suppression during antiretroviral therapy.J Infect Dis 2003; 187:1534–1543.

Ivers LC, Kendrick D, Doucette K. Efficacy of antiretroviral therapy programs in ressource-poor settings: a meta-analysis of the published literature. Clin Infect Dis 2005; 41:217–224.

Jacobson LP, Phair JP, Yamashita TE (2004) Virologic and immunologic response to highly active antiretroviral therapy. Curr HIV/AIDS Rep 1: 74–81.

Johnson, SA. (2010). HIV/AIDS mortality differential across provinces in Kenya and through time. Texas tech university. 15 p.

Kaufmann G, Perrin L, Opravil M, et al. Effect of 7 years of potent antiretroviral therapy on CD4 T-lymphocyte recovery; Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections; February 22–25, 2005; Boston, MA. Abstract 612.

Kaplan, E.L.; Meier, P.(1958)."Non parametric estimation from incomplete observations". J.Amer. Statist.Asn, 53(282):457-481. JS TOR 2281868.

Kim, TW., SG. Kertesz, NJ. Horton, N.Tibbetts, JH.Samet (2006). Episodic homelessness and health care utilization in a prospective cohort of HIV-infected persons with alcohol problems. *BMC Health Serv* 6:19.

Laurent C, Ngom Gueye NF, Ndour CT, Gueye PM, Diouf M, Diakhate´ N, et al. Long-term benefits of highly active antiretroviral therapy in Senegalese HIV-1-infected adults. J Acquir Immune Defic Syndr 2005; 38:14–17.

Lawn SD, Myer L, Bekker L-G, Wood R (2006) CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa. BMC Infect Dis 6.

Laxmi Bhatta, Elise Klouman, Keshab Deuba, Rachana Shrestha, Deepak Kumar Karki, Anna Mia Ekstrom, and Luai Awad Ahmed (2013) Survival on antiretroviral treatment among adult HIV-infected patients in Nepal: a retrospective cohort study in far-western Region, 2006–2011.BMC Infect Dis. 2013; 13**:** 604**.**

Li N, Spiegelman D, Drain P, Mwiru RS, Mugusi F, et al. (2012) Predictors of weight loss after HAART initiation among HIV-infected adults in Tanzania. AIDS 26: 577–585.

Lichtenstein KA, Armon C, Moorman A, et al. Initiation of antiretroviral therapy at higher CD4+ T cell counts reduces incidence of nucleoside analogue toxicities acutely and risk for later development with continued use of these agents in the HIV outpatient (HOPS) cohort; Abstracts of the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention; July 22–25, 2007; Sydney, Australia. Abstract MOPEB016.

Lorna Renner, Meghan Prin, Fang-Yong Li, Bamenla Goka,Veronika Northrup, and Elijah Paintsil. 2011. Time to and Predictors of CD4+ T-Lymphocytes Recovery in HIV-Infected Children Initiating Highly Active Antiretroviral Therapy in Ghana. AIDS Research and Treatment, Volume 2011, Article ID 896040, 9 pages doi:10.1155/2011/896040.

Manosuthi W, Tansuphaswadikul S, Prasithsirikul W, et al. Incidence and risk factors of major opportunistic infections after initiation of antiretroviral therapy among advanced HIV-infected patients in a resource-limited setting. J Infect. 2007;55:464–469. [PubMed]

Mair C., S. E. Hawes, H. D. Agne, P. S. Sow, I. N'doye, L. E.Manhart, P. L. Fu, G. S. Gottlieb and N. B. Kiviat. 2007. Factors associated with CD4 lymphocyte counts in HIV-negative Senegalese individuals.Clinical and Experimental Immunology, 151:432–440.

Mariz Cde A, Albuquerque Mde F, Ximenes RA, Melo HR, Bandeira F, et al. (2011) Body mass index in individuals with HIV infection and factors associated with thinness and overweight/obesity. Cad Saude Publica 27: 1997–20

May M, Sterne JA, Sabin C, et al. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. AIDS. 2007;21:1185–1197. [PMC free article] [PubMed]

Mee-Kyung, K., L. Jin-Hee, K. Eun-Jin, and L. Jiae (2009). Improvement in survival among HIV-infected individuals in the Republic of Korea: Need for an early HIV diagnosis. *BMC Infectious Diseases*, **9**:128-130.

Ministry of Health. (2006). AIDS in Ethiopia, sixth report, Addis- Ababa, Ethiopia. 150 p.

Mocroft, A., S. Madge, and AM. Johnson. (2007). A comparison of exposure groups in the EuroSIDA study: starting highly active antiretroviral therapy (HAART), response to HAART, and survival. *AIDS* 22:369–78.

Modjarrad K, Vermund SH (2010) Effect of treating co-infections on HIV-1 viral load: a systematic review. Lancet Infectious Diseases 10: 455–463.

Moges Derbel DP Monga and Deresse Daka. 2013. Immunological response among HIV/AIDS patients before and after ART therapy at Zewuditu Hospital Addis Ababa, Ethiopia American Journal of Research Communication vol 1 (1), 103-15.

Monge S, Jarrin I, Perez - Hoyos S, Ferreros I, Garcia - Olalla P, Muga R, et al. 2011. Education level and HIV disease progression before and after the introduction of HARRT: a cohort study in 989 HIV serovonverters in Spain. Sex Transm Infect.; 87: 571-6.

Merito-logo M and P. Patrizio (2006). Comparing costs and effectiveness of different starting points for highly active antiretroviral therapy in HIV-positive patients. *Acquir Immune Defic Syndr* 11: 197–202.

Moyle, G. (2002). Anemia in persons with HIV infection: prognostic marker and contributor to morbidity. *AIDS* 4:13-20.

Murphy EL, Collier AC, Kalish LA, Assmann SF, Para MF, et al. (2001) Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. Annals of Internal Medicine 135: 7–26

Nash D, Katyal M, Brinkhof MW, Keiser O, May M, Hughes R, Dabis F,Wood R, Sprinz E, Schechter M, Egger M. 2008 immunologic response to antiretroviral therapy in low-income countries: collaborative analysis of prospective studies. AIDS, 22:2291-2302

Ngo AT, Duc NH, Lan NH, Maynart M, Mayaud C, et al. 2007. Mechanisms and causes of death in 143 Vietnamese HIV-infected patients hospitalized for tuberculosis. Rev Pneumol Clin 63: 139-146

Nguyen N, Holodniy M. 2008. HIV infection in the elderly. Clin Interv Aging; 3: 453-72.

Nogueras M, Navarro G, Anto´n E, Sala M, Cervantes M,Amengual M, et al. Epidemiological and clinical features,response to HAART, and survival in HIV-infected patients diagnosed at the age of 50 or more. BMC Infect Dis 2006;6:159.

Nuredin Ibrahim and Eshetu Wencheko (2007). Evaluation of factor affecting the chance of survival/death status among HIV positive people under the antiretroviral treatment program: the case of Adama Referral Hospital. Journal of Ethiop.Stat.Assoc.16,29-43.

Nuriilign abebe, Kassahun A, Tadesse A, Amanuel A(2013). predictors of mortality among HIV positive adults on ART in Debre Markos Referal hospital. Journal of AIDS and HIV research.

Office of AIDS Research Advisory Council (OARAC) (2008). Guidelines for the use of antiretroviral agents in HIV-1 Infected Adults and Adolescents.

Orlando G, Meraviglia P, Cordier L, Meroni L, Landonio S, Giorgi R, et al. Antiretroviral treatment and age-related comorbidities in a cohort of older HIV-infected patients. HIV Med 2006; 7:549–557

Oyomopito R, Lee MP, Phanuphak P, Lim PL, Ditangco R, et al. (2010) Measures of site resourcing predict virologic suppression, immunologic responseand HIV disease progression following highly active antiretroviral therapy (HAART) in the TREAT Asia HIV Observational Database (TAHOD). HIV Medicine 11: 519–529

Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, et al. (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators Engl J Med 338: 853–860.

Pakker NG, Notermans DW, de Boer RJ, et al. **1998.** Biphasic kinetics of peripheral blood T cells after triple combination therapy in HIV-1 infection: a composite of redistribution and proliferation. Nat Med; 4:208–14.

Patrick Sullivan. 2002. Associations of Anemia, Treatments for Anemia, and Survival in Patients with Human Immunodeficiency Virus Infection. The Journal of Infectious Diseases 2002;185 (Suppl 2):S138–42.

Puthanakit. T, S. J. Kerr, J. Ananworanich, T. Bunupuradah, P. Boonrak, and V. Sirisanthana. 2012..Pattern and predictors of immunologic recovery in human immunodeficiency virusinfect ed children receiving non-nucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy,"Pediatric Pediatric Infectious Disease Journal,vol. 28, no. 6, pp. 488–492

Resino S, Bello´n JM, Sa´nchez-Ramo´n S, Gurbindo D, Ruiz-Contreras J, et al.(2002) Impact of antiretroviral protocols on dynamics of AIDS progression markers. Arch Dis Child 86: 119–124

Rizzardini G, Trabattoni D, Saresella M, Piconi S, Lukwiya M,Declich S, et al. Immune activation in HIV-infected Africanindividuals. Italian-Ugandan AIDS cooperation program. AIDS 1998; 12:2387–2396.

Robert F. (2003). ***September clinic psychiatry news, international media news***,London.

Sandra, K., C. Ling, V. Eric, V. Annie, D. Joshua and H. Mitchell (2009). Impact of housing on the survival of persons with AIDS. *BMC Public Health* 9:220.

Severe P, Juste MAJ, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. N Engl J Med. 2011;363:257–265. [PMC free article] [PubMed]

Seyler C, Anglaret X, Dakoury-Dogbo N, Messou E, Toure´ S,mDanel C, et al. Medium-term survival, morbidity and immunovirological evolution in HIV-infected adults receiving antiretroviral therapy, Abidjan, Coˆ te d'Ivoire. Antivir Ther 2003;8:385–393.

Sibhatu Biadgilign, Ayalu A Reda and Tesfaye Digaffe(2012**)** Predictors of mortality among HIV infected patients taking antiretroviral treatment in Ethiopia: a retrospective cohort study. *AIDS Research and Therapy* 2012, **9**:15 doi:10.1186/1742-6405-9-15

Sieleunou, I., M. Souleymanou, AM. Scho¨nenberger, J. Menten and M. Boelaer (2009). Determinants of survival in AIDS patients on antiretroviral therapy in rural centre in the Far-North Province,Cameroon. Tropical Medicine and International Health 14 (1):36–43.

Siegel K, Lekas H-M (2002) AIDS as a chronic illness: Psychosocial implications. AIDS 16: S69–S76.

Silverberg MJ, Leyden W, Horberg MA, DeLorenze GN, Klein D, et al. (2007) Older age and the response to and tolerability of antiretroviral therapy. Arch Intern Med 167: 684–691.

Tafese Z, Berhan Y, Abebe H (2012) Changes in nutritional, functional and immunological status of HIV-infected adults with antiretroviral therapy. Ethiop Med J 50: 75–87.

The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group (2008) Response to combination antiretroviral therapy: variation by age. AIDS 22: 1463–1473.

Tumbarello M, Rabagliati R, de Gaetano Donati K, Bertagnolio S, Montuori E, Tamburrini E, et al. Older age does not influence CD4 cell recovery in HIV-1 infected patients receiving highly active antiretroviral therapy. BMC Infect Dis 2004; 4:46.

United Nations Programme on HIV/AIDS (UNAIDS). (2013). Report on the Global HIV/AIDS Epidemic, Geneva.

United Nations Programme on HIV/AIDS (UNAIDS). (2006). Report on the Global HIV/AIDS Epidemic, Geneva

United Nations Programme on HIV/AIDS (UNAIDS). (2012). Report on the Global HIV/AIDS Epidemic, Geneva. 362 p.

Wang, C., D. Vlahov and N. Galai (2005).The effect of HIV infection on overdose mortality. *AIDS* 19:935–42.

World Health Organization (WHO). (2006,2011,2012,2013). Towards Universal Access by 2010: How WHO is Working with Countries to Scale-up HIV prevention, treatment, care and support. Geneva.

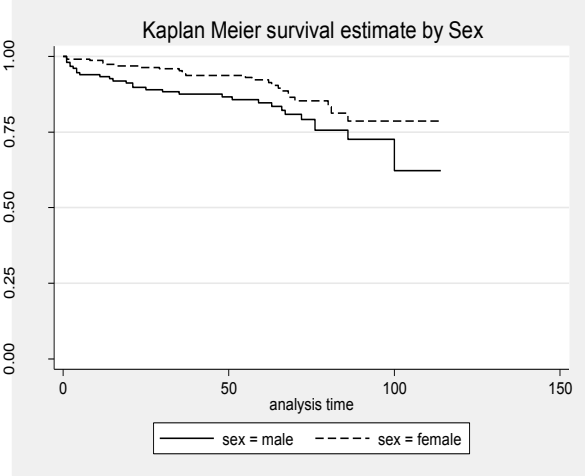
Yamashita TE, Phair JP, Mun˜oz A, Margolick JB, Detels R, et al. (2001) Immunologic and virologic response to highly active antiretroviral therapy in the Multicenter AIDS Cohort Study. AIDS 15: 735–746.

Zachariah R, Fitzgerald M, Massaquoi M, et al. Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. AIDS. 2006;20:2355–2360.

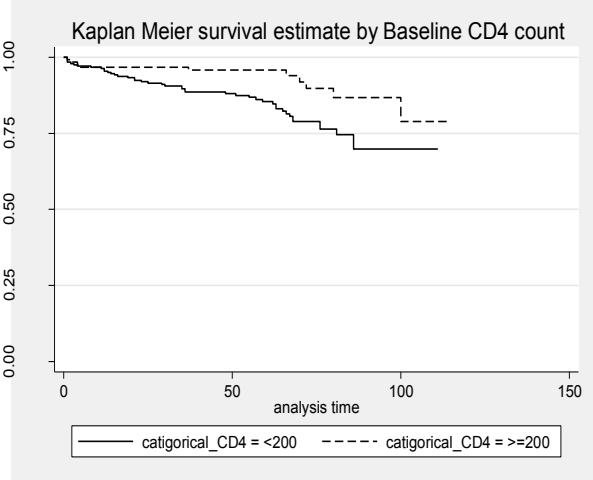
Zahang, C. (2007). HIV/AIDS relative survival analysis, M.Sc. thesis. Georgia state university, in the college of arts and sciences. 79 p.

7. APPENDICES

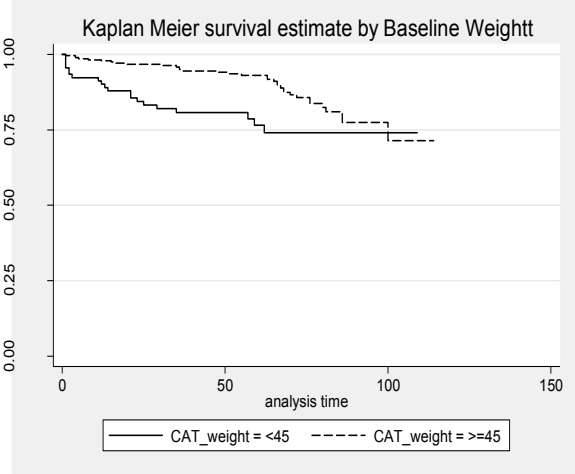
Appendix 1: The Kaplan-meier survival function estimates for survival time of HIV patients.



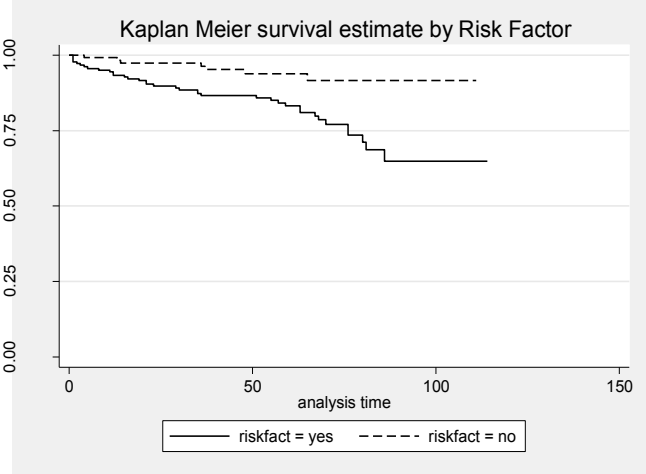
A) KM estimates of survival for the variable sex.



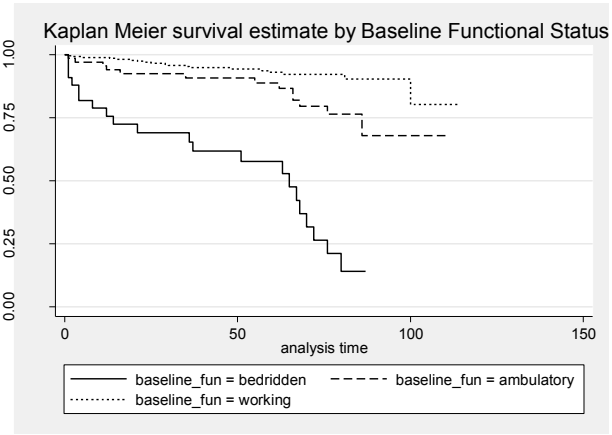
B) KM estimates of survival for the variable CD4 count.



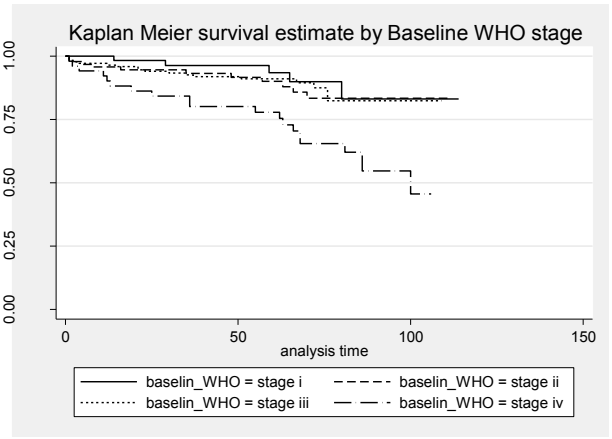
C) KM estimates of survival for the variable Baseline Weight.



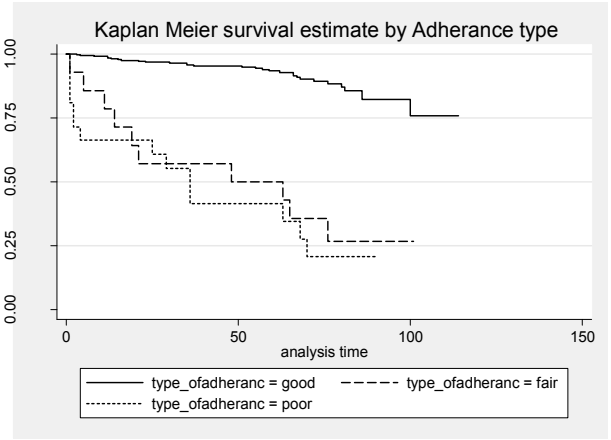
D)KM estimates of survival for the variable risk factor.
Risk Factor.



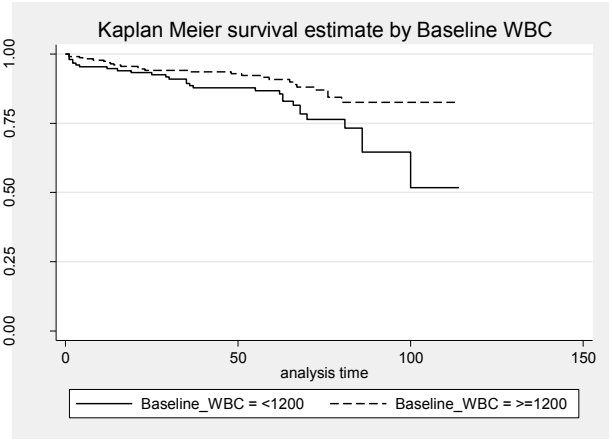
E) KM estimates of survival for the variable Baseline Functional status.



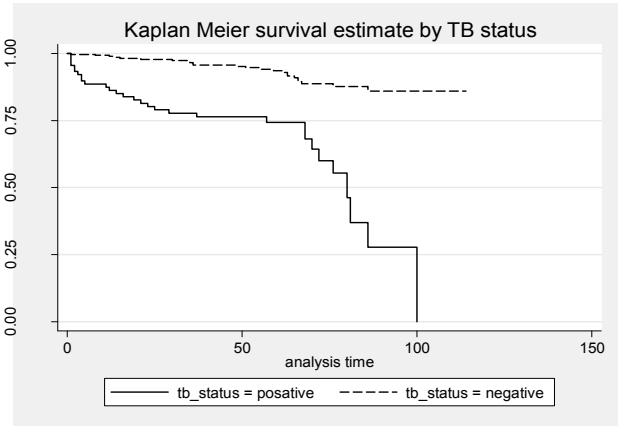
F) KM estimates of survival for the variable Baseline WHO stage.



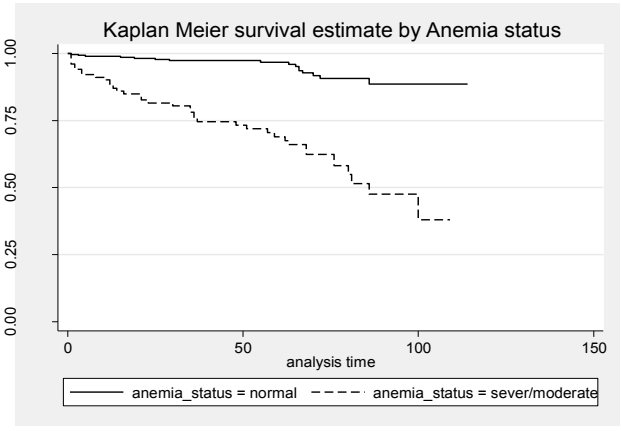
G) KM estimates of survival for the variable Adherence.



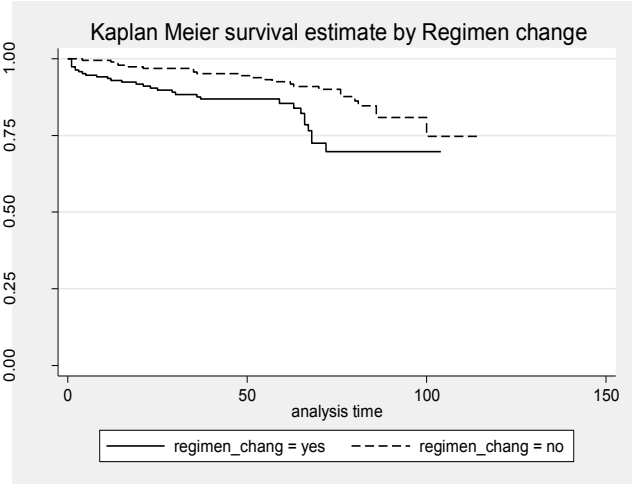
H) KM estimates of survival for the variable Baseline WBC.



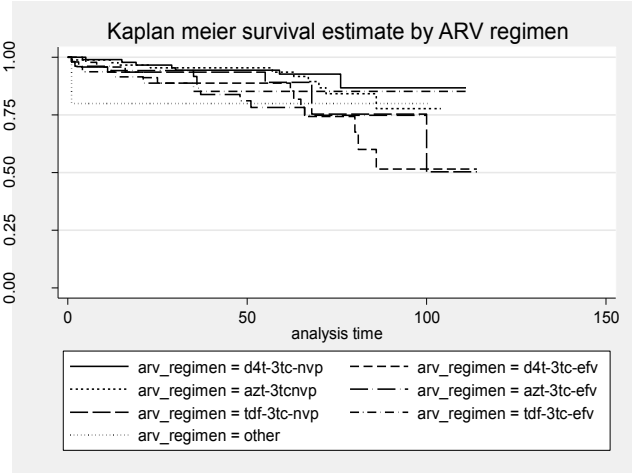
I) KM estimates of survival for the variable TB status.



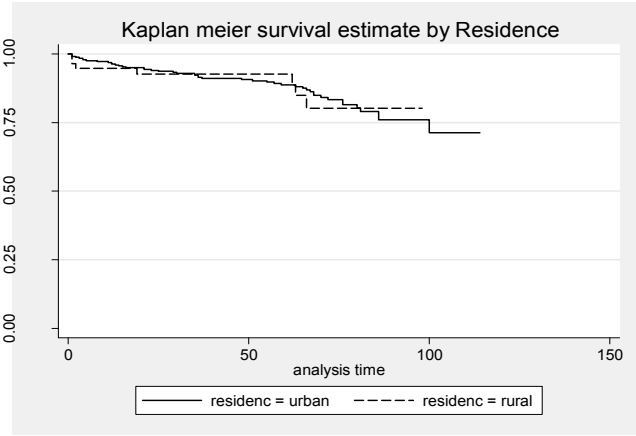
J) KM estimates of survival for the variable Anemia status.



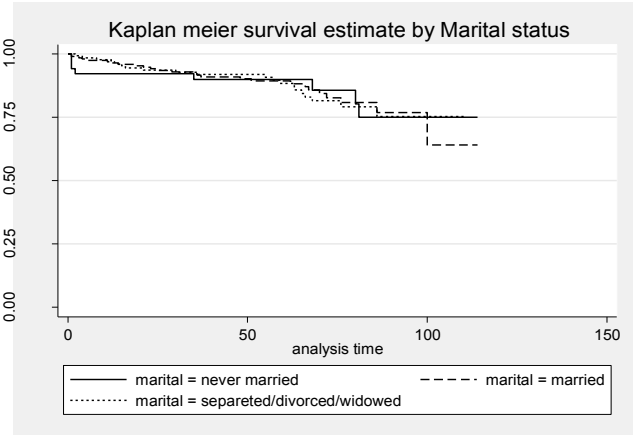
K) KM estimates of survival for the variable Regimen change.



L) KM estimates of survival for the variable ARV Regimen .



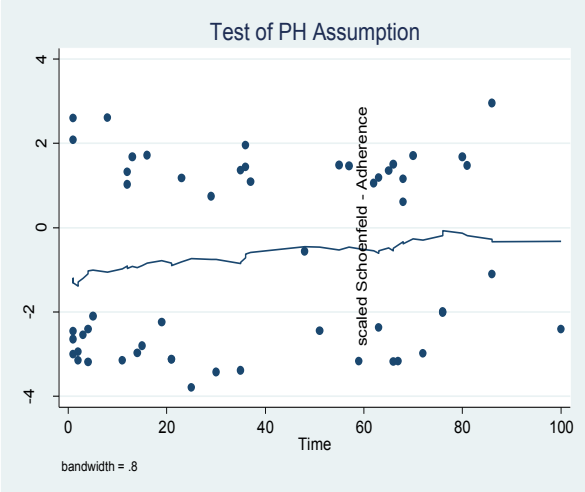
M) KM estimates of survival for the variable Residence.



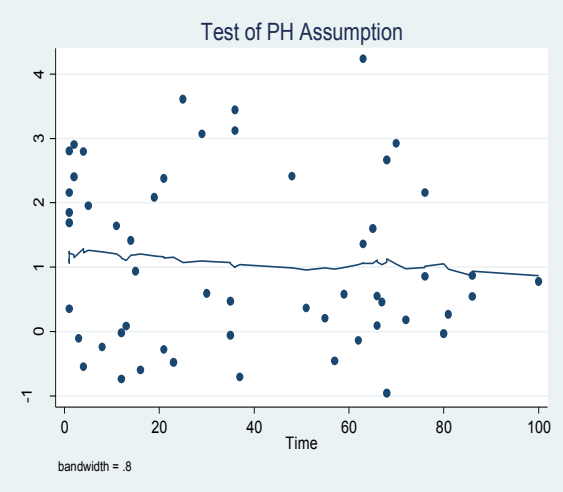
N) KM estimates of survival for the variable Marital Status.

Figure 1. 1: Kaplan-Meier survivor estimates for categorical variables for AIDS patients.

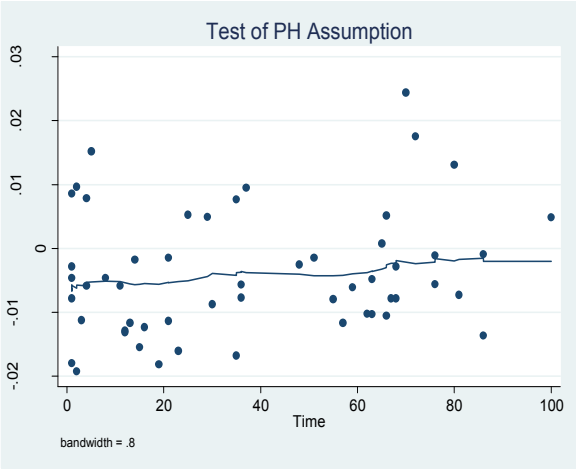
Appendix 2: Residual plots for model assessment for survival time



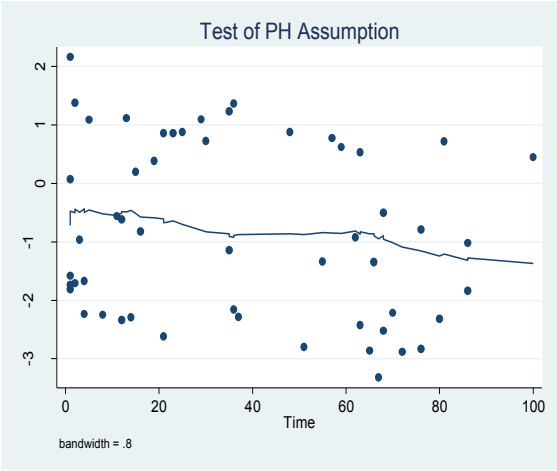
A) The plot of scaled Schoenfeld residual for sex to check the validity of the PH assumption



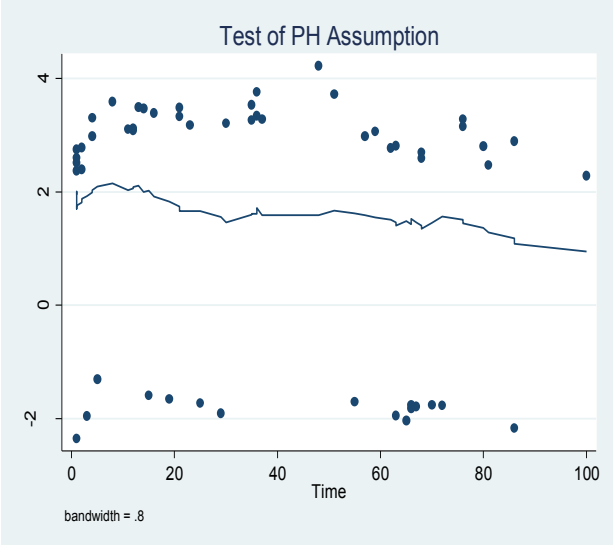
B) The plot of scaled Schoenfeld residual for adherence to check the validity of the PH assumption



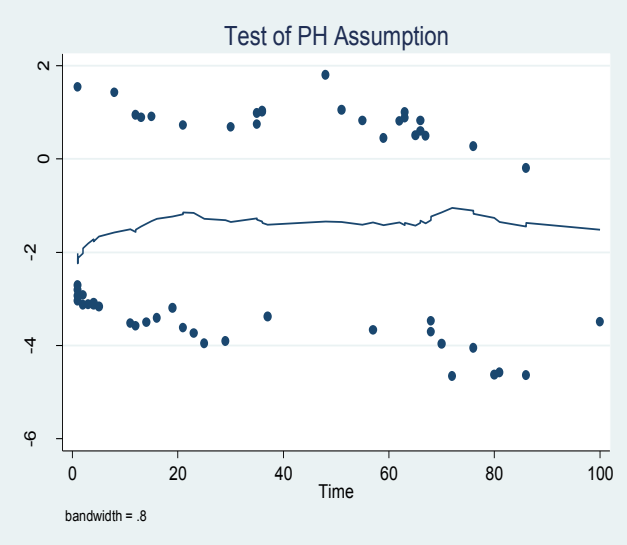
C) The plot of scaled Schoenfeld residual for Baseline CD4 count to check the validity of the PH assumption.



D) The plot of scaled Schoenfeld residual for Baseline functional status to check the validity of the PH assumption.

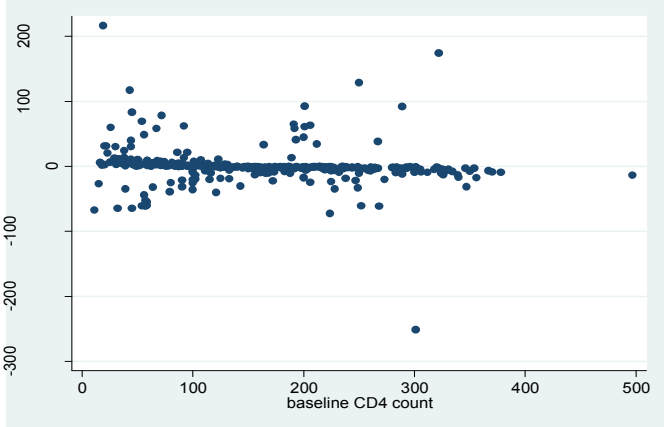


E) The plot of scaled Schoenfeld residual for Anemia status to check the validity of the PH assumption.



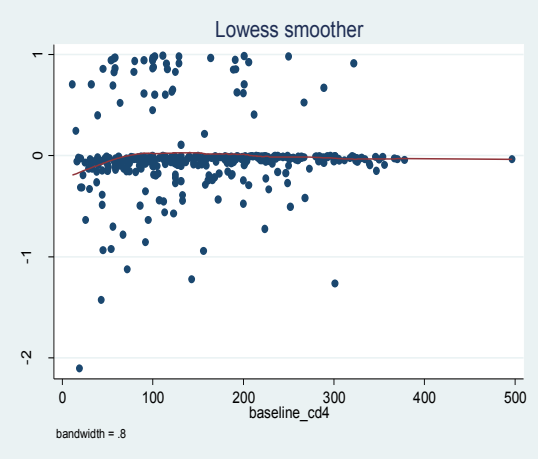
F) The plot of scaled Schoenfeld residual for TB status to check the validity of the PH assumption.

Figure 2. 1: Plots of scaled Schoenfeld residuals against transformed time for each covariate in Cox Proportional Hazards Model fit AIDS patients.



A) The score residual for baseline CD4 count to detect the existence of influential observations

Figure 2. 2: Plots of score residuals for each covariate in Cox proportional hazards model for the survival time of AIDS patients.



A) The plot of the martingale residual against the covariate Baseline CD4

Figure 2. 3: Plot of Martingale residuals against continuous variables to check linearity for the survival time of AIDS patients.

Appendix 3: Categorical variable coding

Table A3. 1: categorical variable coding

		Frequency	(1)	(2)	(3)	(4)	(5)	(6)
Sex	1=Male	89	1					
	2=Female	151	0					
Marital Status	1=Never Married	31	1	0				
	2=Married	131	0	1				
	3=Separated/Divorced/ Widowed	78	0	0				
Educational Status	1=No education	73	1	0				
	2=Primary	64	0	1				
	3=Secondary and above	103	0	0				
VCT	1=Yes	234	1					
	2=No	6	0					
Residence	1=Urban	211	1					
	2=Rural	29	0					
Baseline CD4 count	0=<200	161	1					
	1=>=200	79	0					
Baseline weight	1=<45	60	1					
	2=>=45	180	0					
Partner's HIV Status	1=Negative	13	1	0				
	2=Positive	56	0	1				
	3=Unknown	171	0	0				
Risk factor	1=Yes	160	1					
	2=No	80	0					
Baseline Functional Status	1=Bedridden	23	1	0				
	2=Ambulatory	34	0	1				
	3=Working	183	0	0				
Baseline WHO Stage	1=Stage I	43	1	0	0			
	2=Stage II	54	0	1	0			
	3=Stage III	120	0	0	1			
	4=Stage IV	23	0	0	0			
ARV regimen	1=D4T-3TC-NVP	61	1	0	0	0	0	0
	2=D4T-3TC-EFV	30	0	1	0	0	0	0
	3=AZT-3TCNVP	57	0	0	1	0	0	0
	4=AZT-3TC-EFV	30	0	0	0	1	0	0
	5=TDF-3TC-NVP	32	0	0	0	0	1	0
	6=TDF-3TC-EFV	28	0	0	0	0	0	1
	7=Other	2	0	0	0	0	0	0

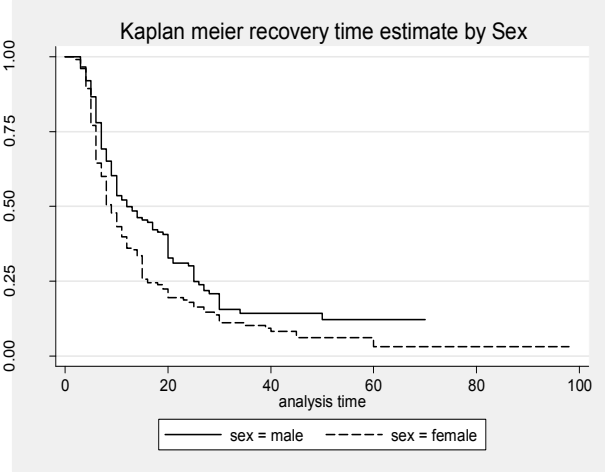
Condom use	1=Yes	73	1	
	2=No	167	0	
Knowledge of ART	1=Yes	236	1	
	2=No	4	0	
Type of Adherence	1=Good	215	1	0
	2=Fair	11	0	1
	3=Poor	14	0	0
Baseline WBC	0=<1200	97	1	
	1=>=1200	143	0	
TB Status	1=Positive	57	1	
	2=Negative	183	0	
Anemia Status	0=Normal	174	1	
	1=Sever/Moderate	66	0	
Age	1=<40	195	1	
	2=>=40	45	0	
Regimen change	1=Yes	119	1	
	2=No	121	0	

Appendix 4: Descriptive measures of the continuous covariates

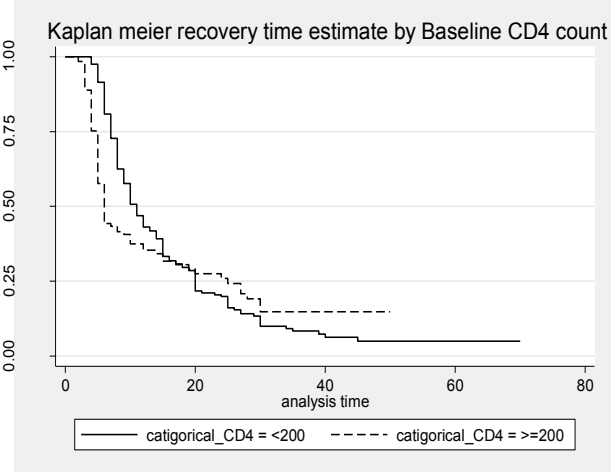
Table A4. 1: Descriptive Characteristics AIDS patients for the continuous covariates

	Statistics	**Age**	**Baseline Weight**	**Baseline CD4 count**
	Mean	35.48	49.00	128.296
	variance	121.08	110.91	5200.74
Dead	St.Dev.	11.00	10.53	72.12
	minimum	19	32.00	11.00
	maximum	80	90.00	322.00
	Mean	33.25	52.13	164.38
	variance	76.22	84.08	8458.78
Censored	St.Dev.	8.73	9.17	91.97
	minimum	16	24	16.00
	maximum	70	80	497.00

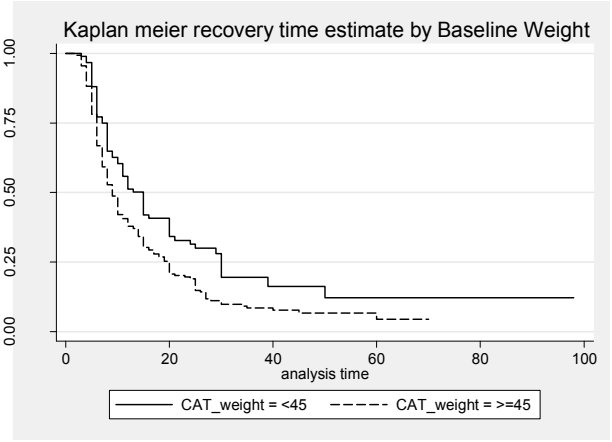
Appendix 5: The Kaplan-Meier survival function estimate for the immunological recovery time of AIDS patients.



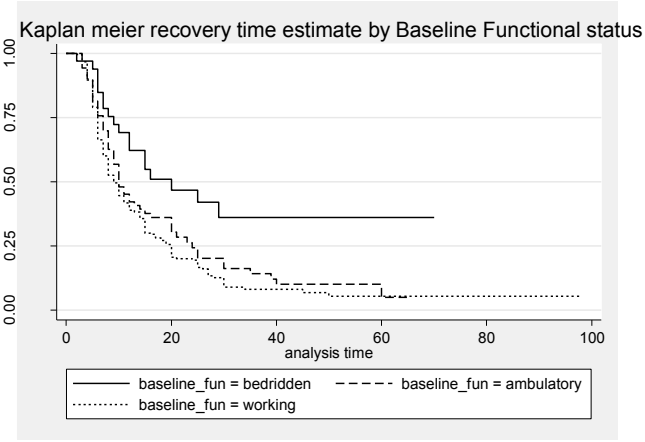
A) KM estimates of recovery time for the variable sex



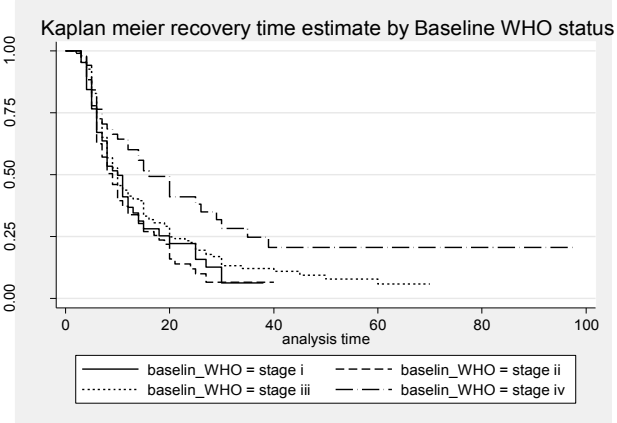
B) KM estimates of recovery time for the variable CD4 count.



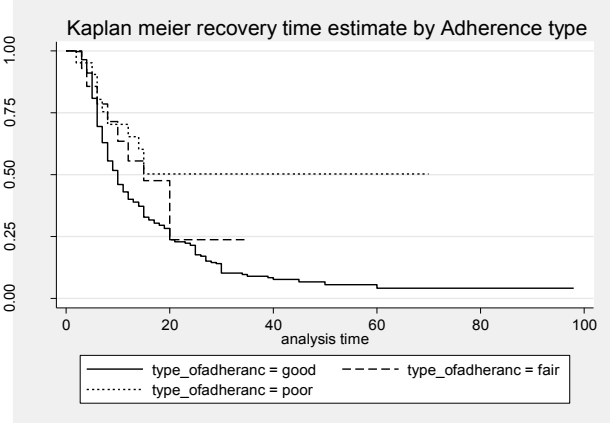
C) KM estimates of recovery time for the variable weight.



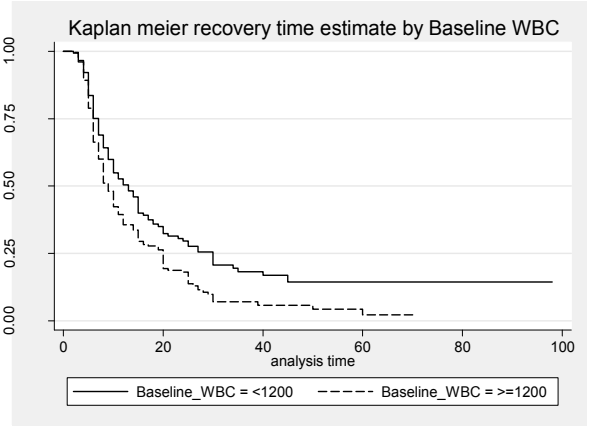
D) KM estimates of recovery time for the variable baseline functional status.



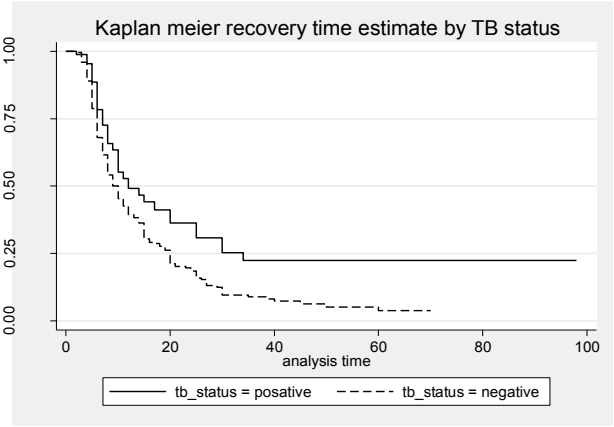
E) KM estimates of recovery time for the variable baseline WHO stage.



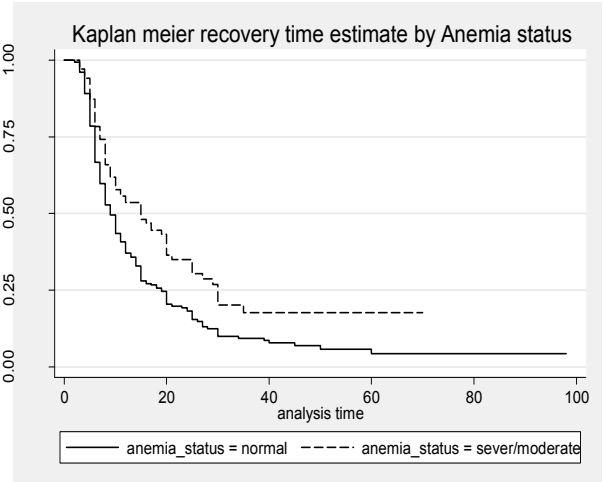
F) KM estimates of recovery time for the variable adherence.



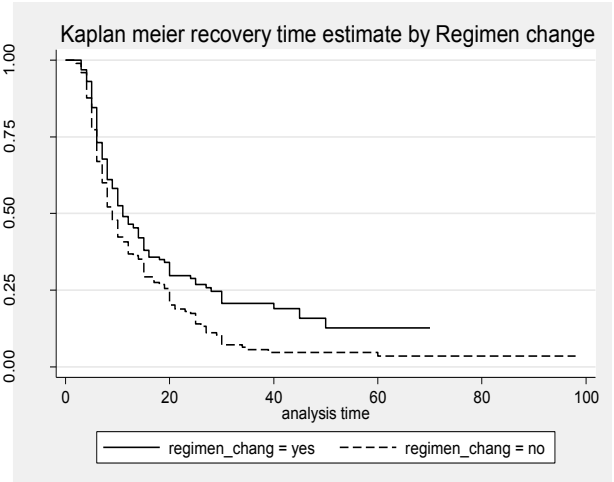
G) KM estimates of recovery time for the variable baseline WBC.



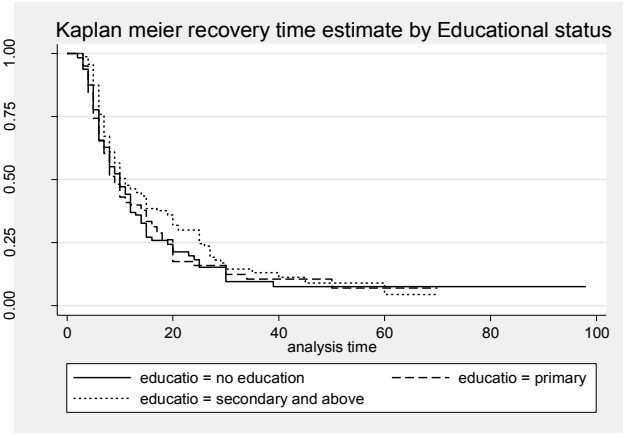
H) KM estimates of recovery time for the variable TB status.



I) KM estimates of recovery time for the variable anemia status.



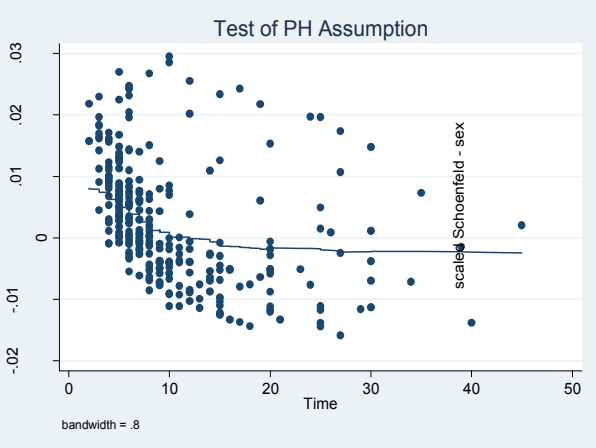
J) KM estimates of recovery time for the variable regimen change.



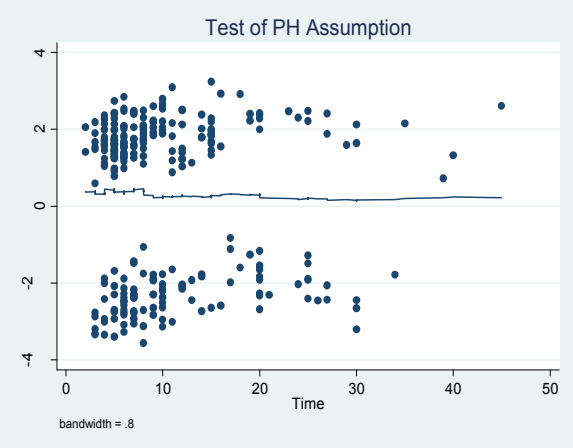
K) KM estimates of recovery time for the variable educational status.

Figure 5. 1: Kaplan Meier survivor estimates for categorical variables for AIDS patients.

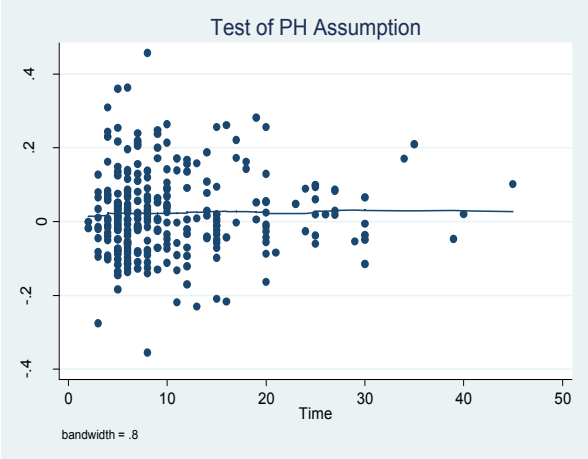
Appendix 6: Residual plots for model assessment for Recovery time.



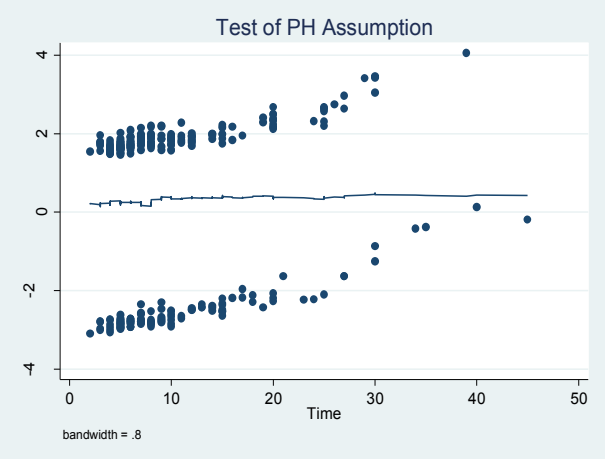
A) The plot of scaled Schoenfeld residual for Baseline CD4 to check the validity of the PH assumption.



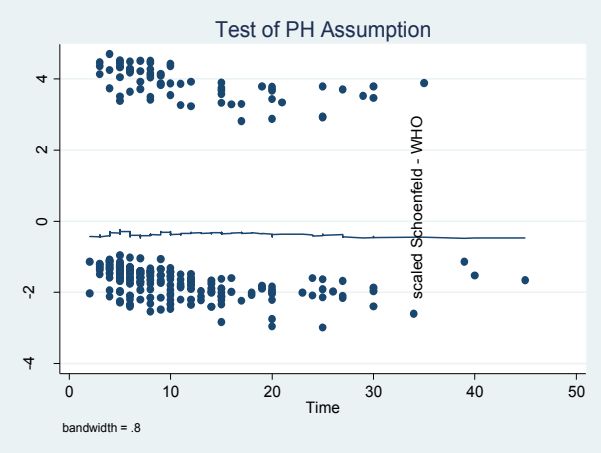
B) The plot of scaled Schoenfeld residual for Sex to check the validity of the PH assumption.



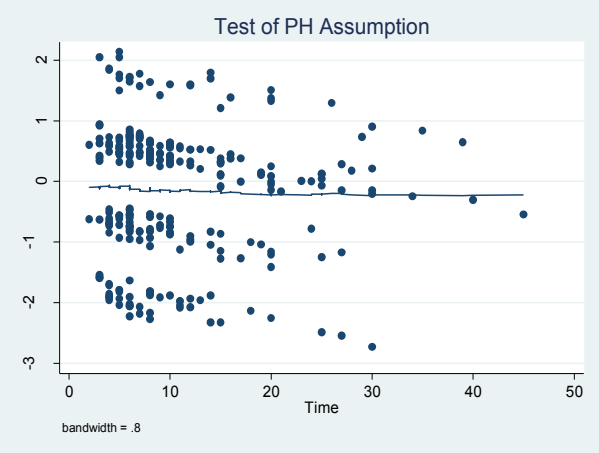
C) The plot of scaled Schoenfeld residual for Baseline Weight to check the validity of the PH assumption.



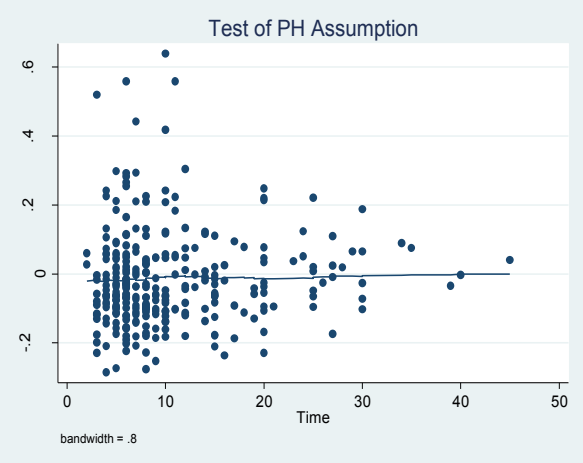
D) The plot of scaled Schoenfeld residual for Baseline WBC to check the validity of the PH assumption.



E) The plot of scaled Schoenfeld residual for Anemia status to check the validity of the PH assumption.

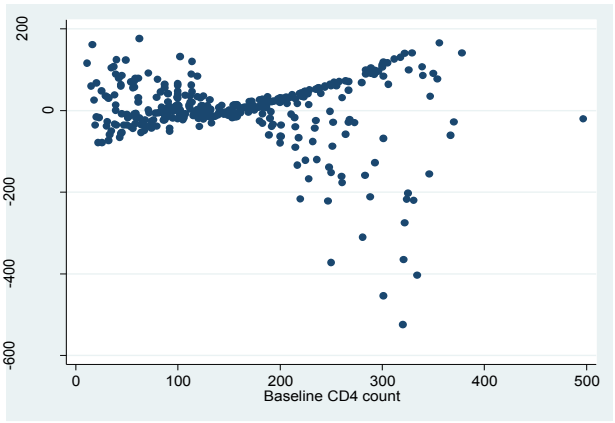


F) The plot of scaled Schoenfeld residual for baseline WHO stage status to check the validity of the PH assumption.

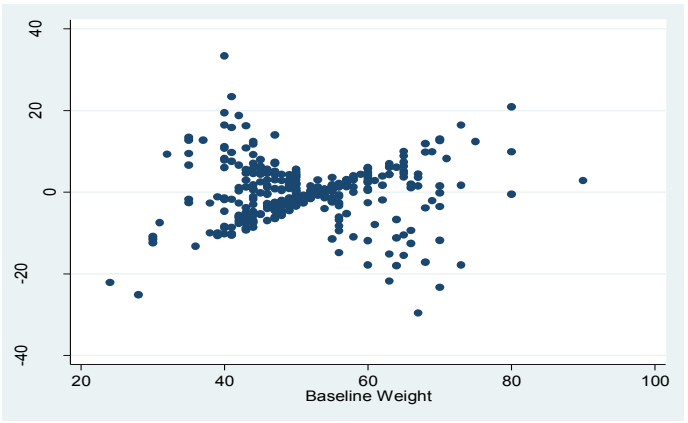


G) The plot of scaled Schoenfeld residual for age to check the validity of the PH assumption.

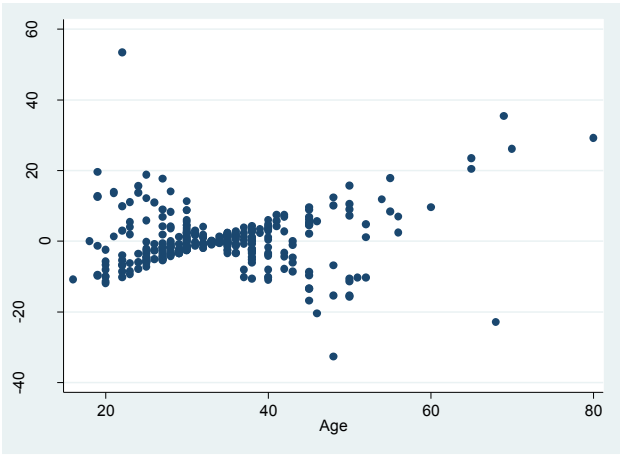
Figure 6. 1: Plots of scaled schoenfeld residuals against transformed time for each covariate in Cox Proportional Hazards Model fit AIDS patients.



A) The score residual for baseline CD4 count to detect the existence of influential observations.

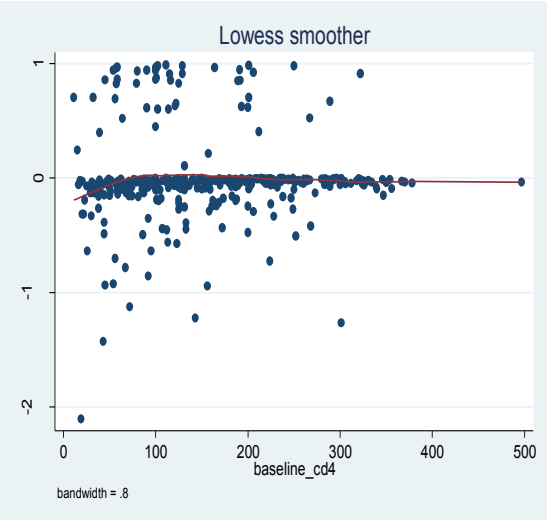


B) The score residual for baseline Weight to detect the existence of influential observations.

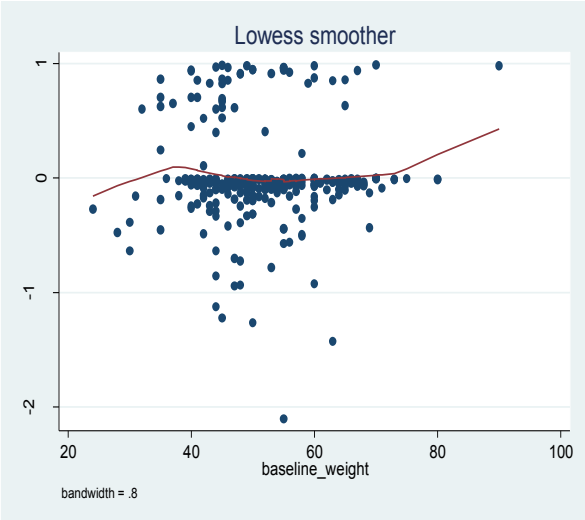


C) The score residual for age to detect the existence of influential observations.

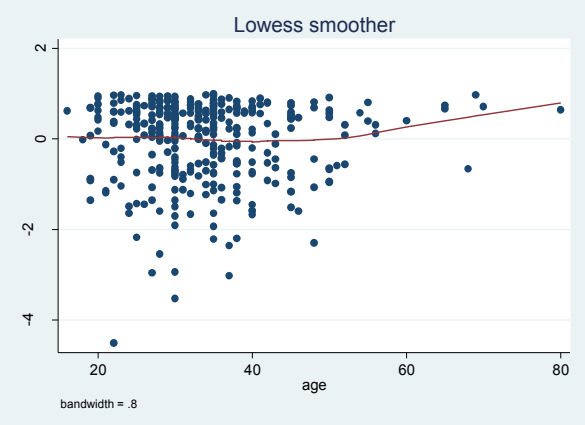
Figure 6. 2: Plots of score residuals for each covariate in Cox proportional hazards model for the survival time of AIDS patients.



A) The plot of the martingale residual against the covariate Baseline CD4 count.



B) The plot of the martingale residual against the covariate Baseline Weight.



C) The plot of the martingale residual against the covariate age.

Figure 6. 3: Plot of Martingale residuals against continuous variables to check linearity for the survival time of AIDS patients.