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Statistical Modeling for the Survival of HIV/AIDS Patients Treated with Highly Active Anti-Retroviral Therapy (HAART): A Case Study at Dilchora Hospital, Dire Dawa, Ethiopia

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Abstract

The introduction of Highly Active Anti Retro Viral Treatment has brought about a significant reduction in the morbidity and mortality of patients living with HIV/AIDS infection. However, the mortality rate of patients treated with Highly Active Anti Retro Viral Treatment is still high in developing country. The study has reviewed patient forms and follow-up cards of 1437 patients treated with Highly Active Anti Retro Viral Treatment in Dilchora Hospital in Dire Dawa from January, 2010 to December, 2016 G.C and used to identify factors leading to mortality and statistically modeling the survival of patients with HIV/AIDS treated under Highly Active Anti Retro Viral Treatment. Survival of patients was significantly related with gender, functional status, marital status, educational level, WHO clinical stage, place of residence and baseline CD4 cell count. Results of both Cox Proportional Hazard and parametric lognormal regression model revealed that; male, being bedridden, WHO clinical stage-IV, lived in rural residence and patients with lower baseline CD4 count had significantly higher risk of death or shorter survival time than their counterparts. Based on Akaike information criteria (AIC) parametric lognormal regression model best fits the dataset and used to predict survival experience of patients.

Keywords: Akaike information criteria; Baseline CD4; HAART; Lognormal regression model

Introduction

Background of the study

Acquired immune deficiency Syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). The revolution in HIV treatment brought about by combination antiretroviral therapy in 1996 had altered the course of the disease among those living with HIV in high-income countries but had only reached a fraction of people in low and middle-income countries. In resource-poor countries, access to antiretroviral therapy (ART) has improved during the last years and mortality rates among treated patients have declined substantially [1].

HIV/AIDS is an epidemic that affects every part of the globe. According to UNAIDS figures an estimated 39.5 million people are living with HIV. There were 4.3 million new infections in 2006 with 2.8 million (65%) of these occurring in Sub-Saharan Africa and 2.9 million people died of AIDS-related illnesses. Declines in national HIV prevalence are being observed in some Sub-Saharan African countries, but such trends are currently neither strong nor widespread enough to diminish the epidemics. Almost three quarters (72%) of all adult and child deaths due to AIDS in 2006 occurred in Sub-Saharan Africa [2,3]. A study conducted in Sub-Saharan Africa based on data from 18 published cohort studies containing 39,536 HIV/AIDS patients had employed the Kaplan-Meir method to assess the proportion of survival time and random-effects model to find hazard ratio of prognostic variables [4]. Thus, a result of the study suggested advanced WHO clinical stage and low CD4 cell count as indicator of high mortality. Similarly, a study in Malawi based on 1308 patients employed Kaplan-Meier method to assess the probability of survival and the Cox proportional hazards model to assess the potential predictors of death. The study found low body-mass index, WHO clinical stage IV, male gender, and baseline CD4 count lower than 50 cells/ml as independent determinants of death [5].

One of Sub-Saharan Africa country hit by HIV/AIDS epidemic, next to South Africa and Zambia, is Ethiopia. Based on the report obtained from ministry of health (MOH), 1.3 million people are living with the virus, 744,100 are orphaned due to AIDS, and 277,800 are in need of antiretroviral treatment (ART) in 2005. AIDS accounted for an estimated 34% of all young adult deaths in rural Ethiopia and 66.3% of all young adult deaths in urban Ethiopia. In 2003, the Government of Ethiopia introduced its ART program with the goal of reducing HIV-related morbidity and mortality, improving the quality of life of people living with HIV, and mitigating some of the impact of the epidemic [6]. The country has scaled up its ART program and is planning to decentralize the service further to existing health facilities providing ART reaching 517 in December 2009 and the adult prevalence of HIV was estimated to be 1.5% in 2011 [7,8]. HAART has provided dramatic reductions in hospitalization and mortality rates. It has also increased the quality of life for many individuals living with HIV [9].

Nevertheless, mortality has been high compared to high-income countries and factors contributing to this high mortality are poorly understood in resource-limited countries like Ethiopia. However, most of these studies were done in untreated patients. Few studies have evaluated the usefulness of such simple markers as predictors of clinical events in patients receiving highly active antiretroviral therapy (HAART) [10]. In Ethiopia, we treated and followed patients using the WHO clinical stage, hemoglobin level, and the Total Lymphocyte Count (TLC) as criteria for beginning treatment [11].

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An Antiretroviral medication is designed to inhibit the reproduction of HIV in the body. HAART is a customized combination of different classes of medications that a physician prescribes based on such factors as the patients viral load (how much virus is in the blood), the particular strain of the virus, the CD4+ cell count and other considerations. HAART can control viral load, delaying or preventing the onset of symptoms or progression to AIDS, there by prolonging survival in people infected with HIV [12]. Although the treatments are not a cure and continue to present new challenges with respect to side-effects and drug resistance ART as disease modifying therapy for established HIV infection has produced dramatic effects on morbidity and mortality among HIV-infected patients. As a result of the widespread use of ART, the HIV/AIDS pandemic which was once regarded as an infectious disease with an almost universal fatal outcome has been transformed into a manageable chronic infectious disease [13,14]. But there is no proper understanding of these factors of paramount importance in tackling the factors of mortality after initiating ART. The aim of this study was to modeling and assesses predictors of survival rate in HIV patients treated under HAART.

Most of the studies undertaken in our country focused on the prevention of the disease and the factors that increase the chance of contracting the disease among others. Retrospective cohort study conducted at Jimma University specialized Hospital from February 2009 to July 2014 to determine the follow up status and associated factors of HAART treatment for HIV infected tuberculosis patients showed that showed baseline weigh, smoking status and functional status were factors that have significant effect for the death of the patients using multinomial logistic model [15]. The result of study in Tikur Anbessa Specialized Hospital, Ethiopia showed that number of medications, baseline functional status, CD4 counts, antiretroviral treatment, age, gender and weight had significant impact on the survival experience of patients applying semi-parametric survival analysis [16]. Another study carried out in Central Zone Tigray concluded that Rural residence, unemployment, functional status and baseline hemoglobin level <11 mg/dL were independent predictors of HIV-related mortality, and Late diagnosis of HIV has increased mortality [17]. In Italy, Logistic regression analysis was employed to identify factors associated with recent HIV infection (RHI). The time from sero-conversion to crucial to allow introduction of antiretroviral therapy (cART) initiation was compared in RHI and NRHI overall and after stratification by calendar period to analyze in survival analysis. The HIV sero-conversion could be estimated for 2608/12,616 patients: 981/2608 (37.6%) were RHI and Proportion of RHI increased in recent calendar periods and was associated with younger age, baseline higher HIV-RNA and CD4+ count [18]. Also, A cross-sectional study was carried out at Mekelle Hospital during June 2012. A total of 422 participants were recruited by systemic random sampling by daily patient load of ART clinic. Bivariate and multiple logistic regression analysis were done to determine factors associated with drug adherence suggested that the mean age of participants was 38.44 years and on average they were on ART for 3 years and 5 months on ART. A total adherence level was 63.4% and HIV positive who had their own income (2.1 95% CI: 1.2, 3.9), urban residence (2.3 95% CI: 1.2, 4.5) and being diagnosed in Mekelle Hospital (1.8 95% CI: 1.2, 2.9) were independently predicts HAART adherence and patients place of residence, economic status and being diagnosed in Mekelle hospital were independent predictors for adherence [19].

Though studies conducted in our country (Ethiopia) addressed factors associated with mortality rate, defaulters and incidence to HIV/AIDS using binary models. Even using Cox proportional hazards does not give baseline distribution for the survival time to death of patients with HIV/AIDS treated with HAART. The factors associated with time to death of patients with HIV/AIDS have different baseline distribution and patients under HAART had their own survival time in study period which should be modeled by survival analysis. This study was intended to identify baseline distribution and model the survival time of HIV/AIDS patients' death of Adults in Dire Dawa Dilchora hospital using survival analysis framework. The primary variable in survival analysis is survival time, time to death of adults under HAART for this study. It was investigated to model and the major risk factors of adult death which will help to guide health professionals and health policy makers to identify indicators for monitoring adult survive strategy and applying necessary preventive and appropriate measures to decrease adult death, and may ultimately it will helps to reduce adult mortality rate. The survival approach used for this, were non-parametric, semi-parametric and parametric survival with (exponential, Weibull and log-logistic distribution) and the model best fit the data were selected using Akaike information criteria (AIC).

Study Design and Procedure

Source of data

The data for the study was obtained from Dire Dawa Dilchora Hospital from HIV/AIDS Clinic, Dire Dawa, Ethiopia. HIV/AIDS patients who were adult age (18 and above) on HAART from January, 2010 to December, 2016 G.C. were included for the analysis. The study population includes all adults under HAART those who were admitted to HIV/AIDS Clinic at Dire Dawa Dilchora Hospital from January, 2010 to December, 2016 G.C. were eligible. Among 2146 total patients during the time period 1437 that fulfill the inclusion criteria were considered for the study. Thus, the study was merely based on adults due to insignificant number of infants and children, and presumed that all deaths are caused by HIV/AIDS.

Variables of the study

The response/outcome variable is the survival time of HIV patients, the length of time from ART start date until the date of death/censor measured in months. The response variable for the i^{th} individual is represented by Yi and it measures duration to event and it is defined by status variable (event or censoring variable). Survival time measures the follow-up of time from a defined starting point to the occurrence of a given event. This observation time has two components, the beginning point of the study time and the observation of time to the end. In survival analysis, the outcome of interest (death in this study) is the duration of time until death occurs measured in months. There are also, different covariates and baseline clinical outcomes that we expected as associate factors that predicts the survival time of the patients were given in Table 1 below.

Variables	Code and Values of variables
Sex	Female and male
Age (in years)	Years
Religion	Muslim, orthodox, protestant and others
Base line CD4	Rural and urban
Residence	count cell counts per mm^3
Base line weight	kilograms
Marital status	Single, married, separated, windowed and divorced
Educational level	Not educated, primary, secondary, tertiary and above
WHO clinical stage	Stage I, II, III and IV
Functional status	Working, ambulatory and bed ridden

Table 1: Covariates that were considered in this study.

Ethical considerations

This study obtained ethical approval from the Haramaya University College of Computing and Informatics, department of Statistics. In addition, the medical directors' offices of Dilchora referral hospital granted permission to use the patients' data for this study. All data had no personal identifiers and were kept confidential and Verbal informed consent was obtained from the participants prior to participation in the study, and data collection was conducted confidentially.

Method of Data Analysis

Survival models

Survival analysis is defined as a branch of statistics which deals with data related to time to an event. Survival analysis is the phrase used to describe the analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point. The use of survival analysis, as opposed to the use of other statistical method, is most important when some subjects are lost to follow up or when the period of observation is finite certain patients may not experience the event of interest over the study period. Once this method was developed in modeling human life time where the target event is death, it has been serving as a powerful methodology that appropriately uses data from all observations.

In the analysis of survival data, interest centers on the risk of hazard of failure at any time after the time origin of the study. As a consequence, the hazard function is modeled directly in survival analysis. There are two broad reasons to model survival data. One objective of the modeling process is to determine which combinations of potential explanatory variables affect the form of the hazard function. Another reason for modeling the hazard function is to obtain an estimate of the hazard function itself for an individual from a set of explanatory variables [20].

A variety of models and methods have been developed for doing this sort of survival analysis using either parametric or semi-parametric approaches. One of the most popular types of regression models used in survival analysis is the Cox proportional hazard model [21]. The Cox Proportional Hazard (PH) Model is a multiple regression method and is used to evaluate the effect of multiple covariates on the survival. Cox proposed a semi-parametric model for the hazard function that allows the addition of covariates, while keeping the baseline hazards unspecified and can take only positive values.

Non-parametric survival analysis: The Kaplan-Meier (KM) estimator is the standard non-parametric estimator of the survival function (t), proposed by Kaplan and Meier [22], and is also called the Product-Limit estimator. 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. suppose $t_1, t_2, \ldots t_n$, be the survival times of independent observations $t_1 \leq t_2 \leq \ldots t_m$, m≤n and be the distinct ordered birth times. The Kaplan-Meier estimator of the survivorship function (or survival probability) at time t, s $(t)=P(T> t)$ is defined as:

$$\hat{s}(t) = \Pi_{t(j)\leq t}\left(\frac{nj-rj}{nj}\right) = \Pi_{t(j)\leq t}\left(1-\frac{nj-rj}{nj}\right) \quad (1)$$

With the convention that $\hat{s}(t)$ for $t<t_{(1)}$. Where n_j is the number of individuals who are at risk at time t_j and r_j is the number of individuals who occurs an event at time t_j.

The cox proportional hazard model: The Cox proportional hazards model is a semi-parametric model for fitting survival data which describes the relation between the event incidence, as expressed by the hazard function and covariates that influence survival time. Let t denote a continuous non-negative random variable representing survival time. The basic Cox model is written as,

$$h(t) = h_o(t)exp\{\beta_1 z_1 + \beta_2 z_2 + \cdots \beta_p z_p\} \quad (2)$$

Where $h(t)$ is the hazard function at time t with covariates $z=(z_1, z_2, \ldots z_p)$, $h_o(t)$ is the arbitrary baseline hazard function that characterizes how the hazard function changes as a function of survival time or the value of the hazard if all the covariates are equal to zero, $\beta=(\beta_1, \beta_2, \ldots \beta_p)$ is a column vector of p regression parameters associated with explanatory variables.

Estimation of parameters in proportional hazard model: Full maximum likelihood requires that we maximize with respect to the unknown parameter of interest β, and unspecified baseline hazard and survival functions. This indicates that unless we explicitly specify the baseline hazard, $h_o(t)$ we cannot obtain the maximum likelihood estimators for the full likelihood. But, Cox [21] proposed using an expression he called "partial likelihood function" that depends only on the parameter of interest. Partial likelihood is a technique developed to make inference about the regression parameters in the presence of nuisance parameters ($h_o(t)$) in the Cox PH model.

Let $t_1, t_2, \ldots t_n$ be the observed survival time for n individuals. Let the ordered event experiencing time of r individuals be $t_{(1)}<t_{(2)}<, t_{(r)}$ and let $R(t_{(j)})$ be the risk set just before t_j and r_j for its size. So that $R(t(j))$, is the group of individuals who are alive and uncensored at a time just prior to t_j. The conditional probability that the i^{th} individual experiences the event at t_j given that one individual from the risk set on $R(t_{(j)})$ dies at t_j is:

$$\begin{aligned}
&pr\left(individual\, i\, experiences\, the\, event\, at\, t_{(j)}\, one\, of\, the\, event\, from\, the\, risk\, set\, R_{t_{(j)}}\, at\, t_{(j)}\right)\\
&= \frac{pr\left(individual\, i\, experiences\, the\, event\, at\, t_{(j)}\right)}{pr\left(one\, event\, at\, t_{(j)}\right)}\\
&= \frac{pr\left(individual\, i\, experienced\, the\, event\, at\, t_{(j)}\right)}{\sum_{k\in R_{(j)}} pr\left(individual\, k\, experienced\, the\, event\, at\, t_{(j)}\right)}\\
&= \frac{pr\left(individual\, i\, experienced\, the\, event\ at\left(t_{(j)}, t_{(j)}+\Delta t\right)/\Delta t\right))/\Delta t\right)}{\sum_{k\in R_{(j)}} pr\left(individual\, k\, experienced\, the\, event\left(t_{(j)}, t_{(j)}+\Delta t\right)\right)\Delta t\right)}\\
&= \frac{lim_{\Delta t\to 0} pr\left(individual\, i\, experienced\, the\, event\, at\left(t_{(j)}, t_{(j)}+\Delta t\right)/\Delta t\right))/\Delta t\right)}{lim_{\Delta t\to 0}\sum_{k\in R_{(j)}} pr\left(individual\, k\, experienced\, the\, event\ t_{(j)}, t_{(j)}+\Delta t\right)\Delta t\right)}\\
&= \frac{h_i\left(t_{(j)}\right)}{\sum_{k\in R_{(j)}} h_k\left(t_{(j)}\right)}\\
&\cong \frac{h_o\left(t_{(j)}\right)exp\left(\beta' z_i t_{(j)}\right)}{\sum_{k\in R_{(j)}} h_o\left(t_{(j)}\right)exp\left(\beta' z_k t_{(j)}\right)} = \frac{exp\left(\beta' z_i t_{(j)}\right)}{\sum_{k\in R_{(j)}} exp\left(\beta' z_k t_{(j)}\right)}
\end{aligned}$$

Then the partial likelihood function for the Cox PH model is given:

$$L(\beta) = \prod_{j=1}^{r}\left\{\frac{\exp(\beta' z_i(t_{(j)}))}{\sum_{k\in R_{t_{(j)}}}\exp(\beta' z_i(t_{(j)}))}\right\} \quad (3)$$

Where $z_i t_{(j)}$ is the vector of covariate values for individual I who experience the event at $t_{(j)}$.

The general method of partial likelihood was discussed by Cox [21]. Note that this likelihood function is only for uncensored individuals. Let $t_1 \leq t_2 \leq \ldots \ldots \ldots \ldots, t_n$ be the observed survival time for n individuals

and δ_i be the event indicator, which is zero if the i^{th} survival time is censored and unity otherwise.

The likelihood function in equation (3) can be expressed by:

$$L(\beta)=\left[\prod_{J=0}^{r}\frac{\exp(\beta' z_i(t_{(j)}))}{\sum_{k\in R_{i(j)}}\exp(\beta' z_i(t_{(j)}))}\right]^{\delta_i} \quad (4)$$

Where $R_{(tj)}$ is the risk set at time t_j. The partial likelihood is valid when there are no ties in the data set. That means are no two subjects who have the same event time.

Parametric regression modeling

The basis of this method was to avoid having to specify the hazard function completely. However, there may be settings in which the distribution of the survival time is in specific parametric distribution that justifies the use of a fully parametric model to better address the goal of the analysis.

Baseline exponential distribution: The exponential distribution, with only one unknown parameter and it is the simplest of all life distribution models. In the exponential model, the conditional probability is constant over time. In other words, the main feature of exponential distribution is that the instantaneous hazard does not vary over time. Modeling the dependency of the hazard rate on covariates entails constructing a model that ensures a non-negative hazard rate (or non-negative expected duration time). The exponential PH model is a special case of the Weibull model when γ=1. The hazard function under this model is to assume that it is constant over time.

For the time data and skewed to the right with exponential distribution, the time of survival for a set of covariate X, which is called, accelerated failure time is expressed as:

$$T=\exp(\beta' X+\varepsilon) \quad (5)$$

Where, ε ', is the error component

The exponential model ($t\sim$ exp (α)) is the simplest parametric model and assumes a constant risk or hazard over time, which reflects the property of the distribution appropriately called "lack of memory" because the hazard function h (t)=α does not depend on time. Hence the probability of failure in a time interval (t, t+δt) does not depend on previous interval. The survivorship function may be obtained by expressing in terms of time as: $S(t,X,\beta)=\exp(-te^{\beta X})$ and the hazard function of the exponential regression model is $h(t,X,\beta)=e^{(\beta' X)}$. For the exponential regression survival model, the hazard ratio for the dichotomous covariate is $HR(x=1, x=0)=e^{\beta}{}_1$.

Baseline Weibull distribution: Survival time t is a positive random variable with Weibull probability density function that can be expressed as:

$$f(t,\mu,\alpha)=\frac{\alpha}{\mu}\left(\frac{t}{\mu}\right)^{\alpha-1}\exp\left(\left(-\frac{t}{\mu}\right)^{\alpha}\right) \quad (6)$$

Where, $\mu>0$ and $\alpha>0$ and the baseline hazard function of the distribution becomes:

$$h(t,\mu,\alpha)=\frac{\alpha}{\mu}\left(\frac{t}{\mu}\right)^{\alpha-1} \quad (7)$$

This yield the following survivorship functions: $S(t)=\exp\left[-\left(\frac{t}{\mu}\right)^{\alpha}\right]$ and the cumulative hazard function become: $H(t)=\left(\frac{t}{\mu}\right)^{\alpha}$ on the value of α the hazard function can increase or decrease with increasing survival time. Hence the Weibull model can yield an accelerated failure time model. Independent observations (t_i,δ_i), i=1,….,n with survival time t_i and censoring indicator δ_i which has value of one if i^{th} observation is not censored and zero when the i^{th} observation is censored and let β be the unknown parameter. The likelihood function is:

$$L(\beta)=\prod_{i=1}^{n}\left\{f(t_i)^{\delta_i}(S(t_i))^{1-\delta_i}\right\}$$

$$=\prod_{i=1}^{n}\left\{\left(\frac{f(t_i)}{S(t_i)}\right)^{\delta_i}S(t_i)\right\}=\prod_{i=1}^{n}\left\{\{h(t_i)\}^{\delta_i}S(t_i)\right\}$$

$$=\prod_{i=1}^{n}\left\{\left(\frac{\alpha}{\mu}\left(\frac{t}{\mu}\right)^{\alpha-1}\right)\exp\left(\left(-\frac{t}{\mu}\right)^{\alpha}\right)\right\} \quad (8)$$

Re-parameterizing the Weibull distribution using $\lambda=\mu^{-\alpha}$ then $h_o(t)=\lambda\alpha t^{\alpha-1}$ will be the baseline hazard function. Now incorporate covariates X in the hazard function, the Weibull regression models become:

$$h(t,X,\beta)=\lambda\alpha^{\alpha-1}\exp(X\beta') \quad (9)$$

The model assumes that individual i and j with covariate xi and xj have proportional hazard function of the form $\frac{h(t,x_i)}{h(t,x_j)}=\frac{\exp(x_i\beta)}{\exp(x_j\beta)}=\exp((x_i-x_j)'\beta)$. A different parameterization is used with intercept ν and scale parameter σ and covariate effects γj having relationship with original parameterization as $\beta_j=\frac{-\gamma_j}{\sigma},\alpha=\sigma^{-1}$ and $\mu=\exp(\upsilon)$.

Baseline log-logistic distribution: Multiple covariate log-logistic accelerated failure time may be expressed as:

$$\ln(T)=\beta' X+\sigma\varepsilon \quad (10)$$

Where σ is the scale parameter and Ɛ is residual (unexplained) variation in the transformed survival times [23]. The survivorship function for the model (10) is: $S(t,X,\beta,\sigma)=\left[1+\exp(z)\right]^{-1}$ where z is the standardized log-time outcome variable that is; $z=\frac{(y-\beta_0-\beta_1 X)}{\sigma}$ and y=ln (t).

The odds of a survival time of at least t are, $OR=\frac{S(t,X,\beta,\sigma)}{1-S(t,X,\beta,\sigma)}=\exp(-z)$, assumes that the covariate is dichotomous and coded 0 or 1. The odds-ratio at time t from the ratio the odds of a survival time evaluated at x=0 and x=1 is:

$$OR(X=1,X=0)=\frac{\exp\left[-\frac{(y-\beta_0-\beta_1 x1)}{\sigma}\right]}{\exp\left[-\frac{(y-\beta_0-\beta_1 x0)}{\sigma}\right]}=\exp\left(\frac{\beta_1}{\sigma}\right) \quad (11)$$

This is independent of time.

Then the hazard rate is given as follows:

$$h(t,X,\beta)=\frac{\lambda p t^{p-1}\exp(X\beta)}{1+\lambda p t^{p}\exp(X\beta)} \quad (12)$$

Baseline lognormal distributions: The log-normal model may take censored time dependent variable that allows the hazard rate to increase and decrease [24]. The log-normal model assumes that ε~N (0,1). Let h (t) be the hazard function of T for ln (T)=β'x+∈ when β=0 i.e. β0=β1=…..=βp=0. Then, it can be shown that h (t) has the following functional form:

$$h(t) = \frac{\phi\left(\frac{\log(t)}{\delta}\right)}{1-\phi\left(\frac{\log(t)}{\delta}\right)} \quad (13)$$

Where, $\phi(t) = \frac{1}{\sqrt{2\pi}}\exp\left(-\frac{t^2}{2}\right)$ is the probability density function, and $\Phi(t) = \int_{-\infty}^{t}\frac{1}{\sqrt{2\pi}}\exp\left(-\frac{u^2}{2}\right)du$ is the cumulative distribution function of the standard normal distribution. Then, the log-hazard function of T at any covariate value X can be expressed as: $\log h(t/X) = \log h_{\circ}(te^{-\beta' x}) - \beta' x$.

Statistical Data Analysis and Discussion

Baseline characteristics of the Study

The medical cards of 1437 patients have been reviewed of which 414 (28.81%) are death cases. A death proportion seems lower for males (12.60%) than for females (16.21%). Of the patients in the study, 444 (30.90%) were Muslim of which 137 (9.53%) were dead, 677 (47.11%) were Orthodox of which 189 (13.15%) were dead, 220 (15.31%) were Protestant of which 61 (3.24%) were dead and the rest 96 (6.68%) were others of which 27 (1.88%) were dead. There were 101 (7.03%) illiterate patients of which 21 (1.46%) were dead, 391 (27.21%) had Primary education of which 116 (8.07%) were dead, 751 (52.26%) had secondary education in which 206 (14.34%) were dead and the rest 194 (13.50%) had Tertiary and above level of education of which 74 (4.94%) were dead. The other covariates are summarized as in Table 1.

Comparison of survival experience

Generalized wilcoxon, Tarone-Ware and Peto-Peto-Prentice test were performed to investigate the significance of the observed difference in the Kaplan-Meier estimates of the survivor functions among different categories of the factors. The results presented in Table 2 showed that Gender, Marital status, Functional status, Residence and WHO clinical stage had significant effect on the survival of the patients under HAART at 5% level of significance. Educational level also, had a significant effect on the survival experience of patients under HAART at 10% level of significance. This implies there is a significant difference within the category of Gender, Marital status, Functional status,

Covariates	Category		Status		
			Death (%)	Censored (%)	Total (%)
	Female		233 (16.21)	629 (43.77)	862 (59.99)
Gender	Male		181 (12.60)	394 (27.42)	575 (40.01)
Age	15-24		51 (3.55)	126 (8.77)	177 (12.32)
	25-34		200 (13.92)	430 (29.92)	630 (43.84)
	35-44		110 (7.65)	325 (22.62)	435 (30.27)
	≥45		53 (3.69)	142 (9.88)	195 (13.57)
Marital status	Single		120 (8.35)	220 (15.31)	340 (23.66)
	Married		183 (12.73)	469 (32.64)	652 (45.37)
	Separated		28 (1.95)	50 (3.48)	78 (5.43)
	Divorced		57 (3.97)	173 (12.04)	230 (16.01)
	Widowed		26 (1.81)	111 (7.72)	137 (9.53)
Educational level	Not educated		21 (1.46)	80 (5.57)	101 (7.03)
	Primary		116 (8.07)	275 (19.14)	391 (27.21)
	Secondary		206 (14.34)	545 (37.93)	751 (52.26)
	Tertiary and above		71 (4.94)	123 (8.56)	194 (13.50)
Functional status	Ambulatory		129 (8.98)	226 (15.73)	355 (24.70)
	Working		242 (16.84)	752 (52.33)	994 (69.17)
	Bedridden		42 (2.99)	45 (3.13)	88 (6.12)
Residence	Rural		80 (5.57)	144 (10.02)	224 (15.59)
	Urban		334 (23.24)	879 (61.17)	1213 (84.41)
Religion	Muslim		137 (9.53)	307 (21.36)	444 (30.90)
	Orthodox		189 (13.15)	488 (33.96)	677 (47.11)
	Protestant		61 (3.24)	159 (11.06)	220 (15.31)
	Others		27 (1.88)	69 (4.80)	96 (6.68)
WHO clinical stage	I		35 (2.44)	87 (6.05)	122 (8.49)
	II		70 (4.87)	425 (29.58)	495 (34.45)
	III		88 (6.12)	217 (15.10)	305 (21.22)
	IV		221 (15.38)	294 (20.46)	515 (35.84)
	Minimum	Maximum	Mean	SE	95% CI
CD4 Count	2	902	161.33	3.79	[153.89,168.77]
Baseline weight	30	88	52.80	0.28	[52.26, 53.35]
SE: Standard error, CI: Confidence interval.					

Table 2: Summary results of HIV/AIDS Patients' death by different demographic, health and risk behavior variables.

Residence, WHO clinical stage and Educational level of patients under HAART in survival experience. In addition, the Kaplan-Meier survival plot found in Figures 1 and 2 below, indicate that there is survival differences between groups of functional status, Gender, clinical stage and Residence of patients under HAART.

Multiple covariate results of Cox proportional hazard models

In any kind of statistical analysis, it is commonly advisable to use univariate statistical analysis before doing multivariate statistical analysis. Results of Kaplan Meier survival experience and univariate Cox proportional hazard model showed that Gender, Marital status, Functional status, Residence, WHO clinical stage, CD4,Baseline weight and Educational level were significant at 10% level of significance which is candidate covariates for multivariable Cox proportional hazard models. Based on multiple covariate results survival of adults with HIV/AIDS under HAART was significantly related with Gender, Marital status, Functional status, Residence, WHO clinical stage, CD4,Baseline weight and Educational level. The values of the Wald-statistic for individual β coefficients support that the estimated values β_i's are significantly different from zero at 5% level of significance. Hazard ratio having 95% CI for Adults with HIV/AIDS under HAART whose Gender male, Functional status (working and bedridden), Widowed marital status, having tertiary and above Educational level, being WHO clinical stage II and IV and lived in urban Residence compared to those Adults who was female, single marital status, not Educated, WHO clinical stage I and lived in Rural Residence were 1.3415 (1.0900,1.6511), 0.6399 (0.5145, 0.7958), 1.5412 (1.0745, 2.2106), 0.5077 (0.3313,0.7779), 1.7944 (1.0982, 2.9318), 0.5727 (0.3793, 0.8647), 1.7997 (1.2541, 2.5825) and 0.7268 (0.5682, 0.9296) respectively. This implies, the risk of death for male Adults, functional status of bedridden, having Tertiary and above education level and being in WHO clinical stage IV were 34.15, 54.12, 79.44 and 79.97% more likely to die than those adults of female, functional status of ambulatory, not educated and being in WHO clinical stage I respectively. Also, the adults who were Widowed marital status, functional status of working, being in WHO clinical stage II and came from urban residence 49.23,36.01, 42.73 and 27.32 less likely to die than to those adults of single marital status, Functional status of ambulatory, being in WHO clinical stage I and came from rural residence respectively.

Finally, base line CD4 counts and weight have also a significant effect on the survival of the patients. Keeping the effects of all other covariates constant, the hazard ratio having 95% confidence interval for CD4 cell count and Baseline weight were 0.9991 (0.9983,1.0000) and 0.9884 (0.9781,0.9987) respectively. An increase in CD4 count

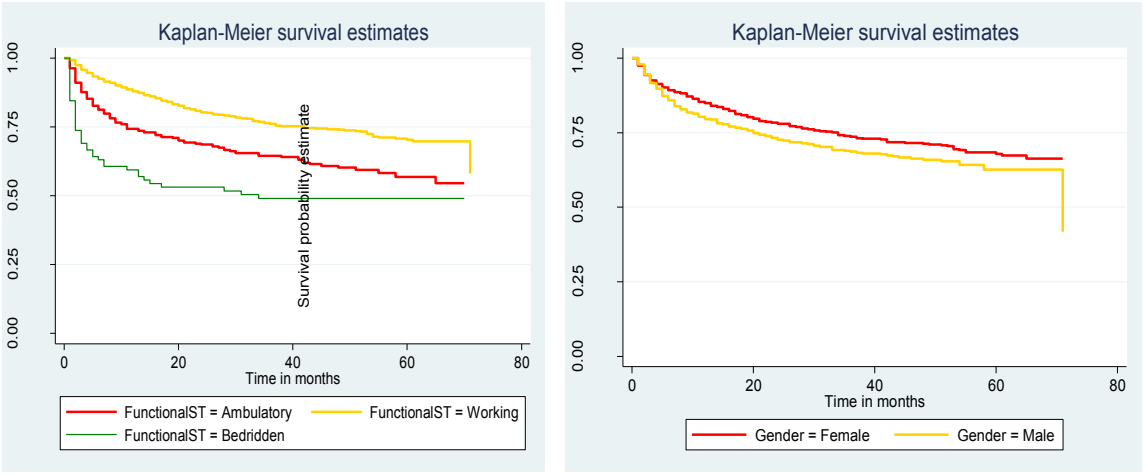

Figure 1: Kaplan Meier plots of survival function for Functional status and Gender category of HIV/AIDS patients under HAART.

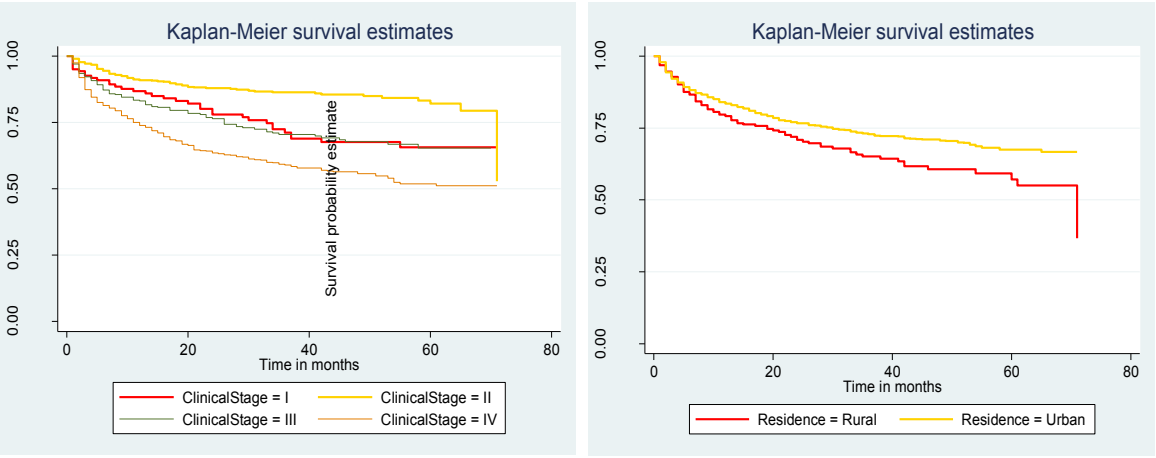

Figure 2: Kaplan Meier plots of survival function for Clinical stage and place of residence of HIV/AIDS patients under HAART.

decreased the hazard rate of patients by 0.09%, which means for every one CD4 count increased in the baseline CD4 counts of patients, the hazard rate decreased by 0.09% controlling the effects of all other covariates in the model. The hazard ratio for a one unit increase in baseline weight is around 98.84%, so that increasing adult's baseline weight, such that patients' weight goes up by one leads to a reduction in risk of death of 1.16% among patients under HAART survivors. An overall Goodness of Fit of model assessed using R^2 and partial likelihood ratio test. A perfectly adequate model has low R^2 due to the present of censored data (Cox, 1972). Thus; the model fitted in this study has a value of R^2 statistic of 0.1179 implying a good fit of the model. In addition to R^2, the results of the likelihood ratio test (chi-square=180.30, p-value<0.0001) suggests that model is in good fit, i.e. significant at 5% level of significance (Table 3).

Checking for the Linearity of Continuous Covariates in the model; In order to examine the scale of continuous covariates of CD4 cell count and baseline weight, martingale residuals plotted against covariates to detect for the correctness of the functional form. From the plot of martingale residuals versus covariate CD4 and Baseline weight, the plots do not show systematic patterns or trend, the resulting smoothed plots were approximately horizontal straight lines. Therefore the plots of martingale residual confirm that CD4 and baseline weight of adult with HIV/AIDS patients have an approximate linear relationship with the survival time (Figures 3 and 4).

Multiple covariate analysis of final lognormal regression model

In order to select parametric regression model that fit the data Akaike information criterion (AIC) and Bayesian information criteria (BIC) were performed as in Table 4. The lognormal regression model has the least (AIC=2715.802) and (BIC=2810.668) value which shows that the lognormal regression model well fitted to data of HIV/AIDS patients under HAART.

The relationship between covariates and survival probability of patients with HIV/AIDS under HAART modeled by lognormal regression model are presented in Table 5. The results of parametric lognormal showed that survival of the adults was significantly associated with gender, functional status, marital status, educational level, CD4 count, WHO clinical stage and place of residence of patients. Having the regression equation (13) and with the parameters found, the survival time of HIV/AIDS patients have lognormal distribution, which can be expressed as t~lognormal (μ, δ^2) and error term assumes $\mathcal{E}$~N (0,1). The two parameters, that is, intercept (μ) and scale (δ) are associated to lognormal distribution. From the result of lognormal regression model output in Table 5, intercept μ=3.6044 and scale δ=2.2038. The corresponding hazard h (t) be hazard function of time T and h (t) has functional form $h_{\circ}(t)=\frac{\phi\left(\frac{\log(t)}{\delta}\right)}{\left[1-\phi\left(\frac{\log(t)}{\delta}\right)\right]}=\frac{\phi\left(\frac{\log(t)}{2.2038}\right)}{\left[1-\phi\left(\frac{\log(t)}{2.2038}\right)\right]}$ which is the base line hazard function of adults with HIV/AIDS in every increase in time measured in months: where $\phi(t)=\frac{1}{\sqrt{2\pi}}\exp\left(-\frac{t^2}{2}\right)$ is the probability density function, and $\Phi(t)=\int_{-\infty}^{t}\frac{1}{\sqrt{2\pi}}\exp\left(-\frac{u^2}{2}\right)du$ is the cumulative distribution function of the standard normal distribution. The Lognormal regression model that predicts the survival of adults with HIV/AIDS patient treated under HAART with similar data settings were:

$$\text{Logh}(t/X)=\log\frac{\phi\left(\frac{\log(t)}{2.2038}\right)}{\left[1-\phi\left(\frac{\log(t)}{2.2038}\right)\right]}(te^{-\beta'X})-\beta'X \quad (14)$$

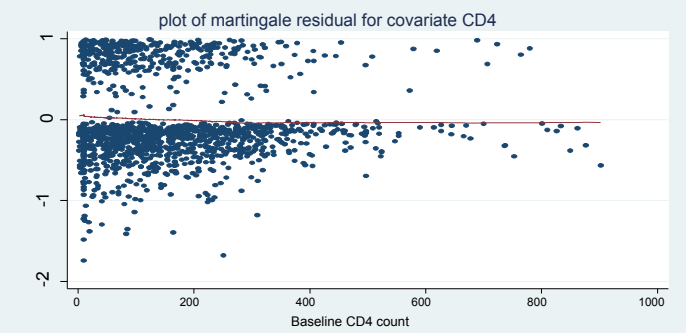

Figure 3: Plots of martingale residuals against the covariate Baseline CD4 count.

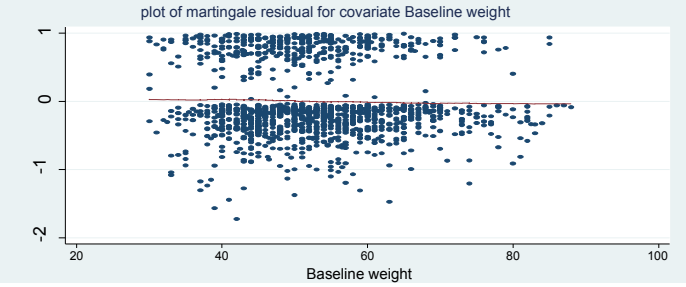

Figure 4: Plots of martingale residuals against the covariate Baseline weight.

Test for equality of survivor functions over group	Generalized wilcoxon			Tarone-Ware			Peto-Peto-Prentice		
Covariates	**Chi-square**	**Df**	**P-value**	**Chi-square**	**Df**	**P-value**	**Chi-square**	**Df**	**P-value**
Gender	5.09	1	0.0240	4.85	1	0.0276	4.67	1	0.0306**
Age group	4.50	3	0.2126	4.97	3	0.1738	5.85	3	0.1195
Marital status	16.66	4	0.0022	16.85	4	0.0021	17.04	4	0.0019**
Educational level	6.47	3	0.0910	6.95	3	0.0736	7.28	4	0.0634*
Functional status	76.63	2	0.0000	66.71	2	0.0000	65.35	2	0.0000**
Residence	4.36	1	0.0368	5.17	1	0.0230	5.68	1	0.0171**
Religion	1.39	3	0.7086	1.16	1	0.7634	1.07	1	0.7838
WHO clinical stage	89.10	3	0.0000	92.51	3	0.0000	91.79	3	0.0000**
Note: *Significance at 10% level of significance and **Significance at 5% level of significance.									

Table 3: Comparison of survival experience of HIV/AIDS Patients under HAART at Dilchora Hospital, Dire Dawa, Ethiopia.

Covariates	β	SE	HR	Wald	Df	p-value	95% CI for HR
Gender Ref (female) male	0.2939	0.1060	1.3415	7.6729	1	0.0060	[1.0900, 1.6511]
Functional status Ref (ambulatory)							
Working	-0.4464	0.1113	0.6399	16.0801	1	0.000	[0.5145, 0.7958]]
Bedridden	0.4325	0.1840	1.5412	5.5225	1	0.019	[1.0745, 2.2106]
Marital status Ref (single)							
Married	-0.2153	0.1194	0.8063	3.2400	1	0.0710	[0.6380, 1.0189]
Separated	0.0878	0.2119	1.0917	0.1681	1	0.6790	[0.7207,1.6538]
Divorced	-0.2547	0.1632	0.7751	2.4336	1	0.1190	[0.5629,1.0674]
Widowed	-0.6780	0.2177	0.5077	9.6721	1	0.0020	[0.3313,0.7779]
Educational level Ref (not Ed.)							
Primary	0.3767	0.2411	1.4578	2.4336	1	0.1180	[0.9087,2.3383]
Secondary	0.3129	0.2313	1.3673	1.8225	1	0.1760	[0.8690,2.1513]
Tertiary and above	0.5846	0.2505	1.7944	5.4289	1	0.0200	[1.0982, 2.9318]
CD4 count	-0.0009	0.0004	0.9991	4.3681	1	0.0370	[0.9983, 1.0000]
Baseline weight	-0.0117	0.0053	0.9884	4.8841	1	0.0270	[0.9781, 0.9987]
WHO clinical stage Ref (I)							
II	-0.5574	0.2102	0.5727	7.0225	1	0.0080	[0.3793, 0.8647]
III	0.2665	0.2037	1.3051	1.7161	1	0.1910	[0.8756, 1.9456]
IV	0.5876	0.1843	1.7997	10.1716	1	0.0010	[1.2541, 2.5825]
Residence Ref (Rural) urban	-0.3191	0.1256	0.7268	6.4516	1	0.0110	[0.5682, 0.9296]
**Partial likelihood ratio (LR) test=180.30, df=16, p ≤ 0.001 and R^2=0.1179; *CD: Cluster Differentiation, WHO: World Health Organization. *CD: Cluster Differentiation, WHO: World Health Organization							

Table 4: Results for multiple covariate Cox proportional hazard model of Patients under HAART.

Models	LL (null)	LL (model)	Df	AIC	BIC
Exponential	-1511.047	-1413.837	17	2861.674	2951.27
Weibull	-1460.555	-1368.737	18	2773.475	2868.340
Log logistic	-1452,900	-1353.694	18	2743.388	2838.253
Log normal	-1436.181	-1339.901	18	2715.802	2810.668

Table 5: Comparison of parametric models Using AIC and BIC.

Discussion of the results

HIV infection prevention is one of the most challenging tasks for clinicians and public health workers at any level. In order to improve the quality of life of HIV/AIDS infected patients and lengthen the survival interval from HIV infection /AIDS diagnosis to death of patients. The study found gender, functional status, marital status, educational level, CD4 count, WHO clinical stage and place of residence as statistically significant and strong predictors of mortality of HIV patients under HAART. Lognormal distribution is the best parametric baseline distribution to predict the survival of HIV patients under HAART as compared to others (exponential, Weibull and log logistic) distribution. The result showed that Gender is an important predictor that associated to HIV patients' mortality. The hazard ratio in Cox proportional hazards model for being male is 1.3415 times higher than female patients. That is, the risk of death for male is 34.15% more likely to die than those of female patients. This outcome is supported by study done earlier [16,25-27].

The functional status of patients can be seen as an indicator of the severity of the progression of the disease. Results Cox proportional hazard models and lognormal parametric regression models showed that functional status have significantly associated with survival time of HIV/AIDS patients under HAART. The result is in accordance with study done by Belay [17], concluded the death rate of functional status is (AHR=2.98) for bedridden and (AHR=2.54) for ambulatory patients,

which forecasts occurrences of deaths in HIV/AIDS patients. Others studies like studies of Sebu [15].

The marital status is a demographic prognostic factor that significantly predicts the survival time of HIV/AIDS patients. The result of both Cox proportional hazard and lognormal parametric model showed that widowed marital status was associated to time to death of patients under HAART. Married marital status also had significant effect on survival of patients when baseline distribution is specified as lognormal and the hazard rate indicates that married is 46.46% more likely to die than single patients treated under HAART. Another demographic variable associated with HIV/AIDS disease is educational level. In this study, having Tertiary and above educational level had significant effect on survival of HIV/AIDS patients as compared to illiterate patients.

CD4 cell count is an important clinical risk factors that significantly associated to time to death of patients with HIV/AIDS treated under HAART. Result of models, multiple covariate Cox proportional hazard and parametric lognormal models indicates that baseline CD4 cell count had significantly predicts the survival time of patients with the specified disease. Hazard ratio from Cox PH models showed that an increase in baseline CD4 count decreased the hazard rate of patients by 0.09% controlling the effects of all other covariates in the model. The result is comparable with earlier study done by Habtamu [28]. Other study also indicated that CD4 count is a laboratory predictor of mortality in the sense that higher CD4 counts are associated with longer survival time of HIV/AIDS patients [26,29].

Another important marker of the severity of the disease is the WHO clinical stage of patients. In this study, we found that the advanced WHO clinical stages II and IV were independent markers of mortality for HIV/AIDS patients on HAART. Results of Cox Proportional hazards and lognormal parametric regression model showed that the WHO clinical stage have significantly associated with survival time of patients with HIV/AIDS. This study confirmed with the study carried out by Zachariah and Ahmed concluded that WHO clinical stage was an independent marker of mortality in patients treated with HAART [30,31]. However, Shibre [32]; suggested that being in WHO clinical stages 3-4 have hazard rate of 2.39 (CI: 1.26, 5.31), higher than HIV/AIDS patients in WHO clinical stage 1 and 2.

Place of residence has been identified as an important factor for death in HIV/AIDS patients under HAART. Different studies showed that Residence was a factor that is affecting the survival of HIV/AIDS patients. According to Hadera [17], in Central Zone Tigray, northern Ethiopia mortality was associated to residence in which the associated risk rate of rural residence was 1.96 (CI: 1.05-3.68) and indicates that patients living in rural is about 96% more likely to die than those who live in urban residence patients. A study done by Kiday [19] recommended that awareness creation for rural residence should be created to increase adherence level.

Conclusions and Recommendations

Conclusion

In conclusion, HIV/AIDS patients under HAART was affected by gender, functional status, marital status, educational level, CD4 cell count, WHO clinical stage and place of residences and had significant impact on the survival experience of patients. Males, Functional status (ambulatory and bedridden), having Tertiary and above education level and being in WHO clinical stage IV lived shorter as compared to females, Functional status of working, not educated and being in WHO clinical stage I respectively whereas being in WHO clinical stage II and living in urban residence had longer survival than WHO clinical stage I and rural residence respectively. Lower CD4 was associated with higher risk of death and increase CD4 cell count have an association with better survival experience HIV/AIDS patients under HAART. Lognormal parametric regression model were the best model to predict the survival experience of patients with HIV/AIDS treated under HAART in the same dataset.

Recommendations

Accordingly, to control death from HIV/AIDS, governmental policy makers and non-governmental organizations should have a strong focus on identifying HIV/AIDS-infected individuals as early as possible. Having lower CD4 count, being bedridden and WHO clinical stage are indicators of the progression of the disease. Therefore, patients should be informed about the need for early diagnosis of HIV/AIDS infection and starting treatment early is very important. Finally, health workers and peer educators and data clerks, working with patients under HAART, should be given special training to improve the quality of the data records of patients. Moreover, attempt should be made to investigate the causes of deaths that occurred out of hospitals, and mechanisms should be devised to trace patients lost to follow up.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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