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Determinants of Survival Time of Adult HIV/AIDS Patients and Modelling Progression of HIV/AIDS Disease Stages: The Case of Debre Berhan Health Center, Amhara Region, Ethiopia

[1]Wudneh Ketema , [2]Murali Dharan, [3]Zelalem Meraf,

[1]Wudneh Ketema, Debre Berhan University, college of natural sciences, department of statistics.
[2] Murali Dharan, Debre Berhan University, college of natural sciences, department of statistics.
[3] Zelalem Meraf, Aksum University College of natural sciences, department of statistics.

ABSTRACT
The expansion of HIV/ADIS epidemic has now become a burning issue globally. HIV infection has changed from a fatal condition to a manageable chronic illness mainly because of the event of antiretroviral therapy (ART). Whether or not ART treatment has shown significant clinical importance by meeting the goal of therapy, but still increases variety of deaths thanks to certain socio-demographic and clinical factors. The aims of this study was to spot determinant factors for the Survival time of adult HIV/ADIS Infected Patients under the follow-up of antiretroviral therapy (ART) at Debere Berhan clinic and model the progression of HIV/AIDS disease of a personal patient under ART follow-up supported CD4 level using Markov process processes.

A retrospective study was undertaken on a sample of 301 HIV/AIDS patients were selected supported simple sampling technique for this study. Within the followed up period, 43 (14.3%) patients died and 258 (85.7%) patients were censored. From the whole death the bulk of death 13(4.3%) and 10(3.3%) deaths occurred within six months and twelve months of ART initiation, respectively. The Cox PH regression result indicated that the survival time of the HIV patient was significantly related with legal status, TB history, employment status, OIs, WHO stage, Regimen type, and Hemoglobin level. To determine Progression of HIV/AIDS Disease States, States of the stochastic process are defined by the seriousness of the sickness supported the CD4 counts. The states will be state I: CD4 count > 500 cells/μL, state II: 350 < CD4 count ≤ 500 cells/ μL, state III: 200 < CD4 count ≤ 350 cells/ μL, state IV: CD4 count ≤ 200 cell/ μL and Death. The primary four states are named pretty much as good states and Death were bad or absorbing state. There have been transitions between good states to the following worse state. From the above four state, in state IV there have been high number of deaths compared to others state. This means that the probability of dying increase with decreasing CD4 counts over time.
Keywords: Antiretroviral Therapy, Cox Proportional Hazard Model, AIDS Progression

Background

Human immunodeficiency virus (HIV) and bought immune deficiency syndrome (AIDS) has posed the best global public health challenges over the half-moon century (Strauss and Thomas,

2008). Although global commitment to manage the HIV and AIDS pandemic has increased significantly in recent years, some evidence suggest that the virus continues to spread and far remains to be done to reverse these trends (Bertozzi, et al., 2006). By the tip of 2010, an estimated 34 million people worldwide were living with HIV infection or disease. In 2010, close to 2.7 million new HIV infections including 390,000 among children and 1.8 million AIDS deaths occurred (UNAIDS 2010).

The earliest well documented case of Human Immunodeficiency Virus in human dates back to 1959.The virus may are present within the us as early as 1966(Kolata, Gina, 2001) but the overwhelming majority of infections occurring outside sub Saharan Africa (including the U.S.) will be traced back to one unknown individual who got infected with HIV in Haiti then brought the infection to the us sometime around 1969.

Countries in geographic region (e.g., Kenya, Uganda and Tanzania) are experiencing a decline in HIV incidence rates and a steadiness in terms of HIV-prevalence. as an example, Kenya's HIV-prevalence declined to between 6-8% from approximately 15% within the 1990s. Latest reports from Ethiopia and Tanzania indicates HIV prevalence rates of 1.4% and 6.5%, respectively. However, despite Uganda and Kenya being among the countries that first experienced a decline in HIV-prevalence, recent estimates shows a re-emergence of the epidemic (and NASCOP and MoH, 2008).

Methods

Source of data and description of the study area

The data of this study was collected from registered documents (patients' cards) of HIV positive patients who started antiretroviral treatment between September 1, 2010 and March 30, 2019 G.c at ART program unit of Debre Berhan health facility. The study were retrospective that done on patients under the follow of ART at Debre Berhan hospital between September 1, 2010 and April 2019G.c, Debre Berhan, Amhara Region, Ethiopia.

Simple sampling (SRS) could be a basic probability selection scheme during which a predetermined numbers of units from a population list are selected, in order that each unit thereon list has an equal chance of being included within the sample. A random method of selection is one which provides each of the N (total number of the population) units within the population to be covered a calculable probability of being selected.

Variables in the study

The response/dependent variable in the statistical analysis of this study is "survival time" of adult HIV/AIDS patients taking ART.

Definition: - The survival time is defined as the length of time between a patient initiation of ART and the end of the study period with status either death or censured, and measured in month. Predicting whether an event occurred or not and identifying the variables in making the prediction is an important step in carrying out the study. The independent variables that are used in the study were classified as demographic, socio-economic covariates and other variables. Variables such as

age, sex, etc… are considered as demographic variables, while others like economic status of family considered as socio-economic variables. Moreover, as some studies revealed, most independent variables which is included in this study are expected to show marked differential in the survival time of adult HIV/AIDS patient.

Statistical methods of data analysis

There are a number of multivariate statistical models that can be used to predict a dependent variable from a set of independent variables. Since survival time of HIV/AIDS patient data is time to event data by this reason the Statistical Model to predict a dependent variable from a set of independent variables used is Survival analysis.

Survival analysis is a statistical method for data analysis where the outcome variable of interest is the time to the occurrence of an event (Hosmer et. al., 2008). Survival analysis is also referred to as "time to event analysis", "durational analysis", "transition data analysis" or "event history analysis". It is the analysis of the duration for the occurrence or non-occurrence of an event during the risk period and an individual can only be eligible to experience an event if there was a period during which they were at 'risk' of experiencing the event e.g. in order for an individual to be at risk of getting divorced they have to be married. In this regression analysis the dependent variable measures the time to the occurrence of an event of interest and examines how covariates affect the length of time between consecutive events (Hosmer, et.al. 2008). In survival analysis, the interest is therefore on how various treatments or demographic characteristics affect survival times (Wooldridge, 2001).

Survival analysis models fall in three main categories: Nonparametric models, Semi parametric models and parametric models

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 β's) in the model being considered. L is sometimes written notational as L (β) where β denotes the collection of unknown parameters.

Results

Descriptive results

A total of 937 patients were treated with ART in Debre Berhan hospital during the study period from September 1, 2010 to March30, 2019. From this the study included 301 HIV/AIDS patients who were followed up during the time from 2010 to 2019 using an appropriate sample size determination formula at Debre Berhan ART center. The accounted death and censored of patients within the study period was 43 (14.3%) and 258 (85.7%), respectively. Since patients might survive beyond the study period, lost to follow up and might die thanks to other causes, the observations follow right censoring mechanism, random type in particular.

The response variable was the length of your time from start of treatment to death. The general mean estimated survival time of patients under the study was 76.949(95% CI: 72.231-

81.667) months with variance 2.407 months shown in Table 1.
The variable included during this study is categorized into two parts for better description. These are socio-demographic characteristics and clinical characteristics.
Figure 1: The plot of the overall estimate of Kaplan-Meier survivor function of HIV patients under ART in DB Health center 2011. From the above Figure 1 we depicted that the estimate for overall Kaplan-Meier survivor function represents that, relatively, an oversized number of the deaths occurred at the sooner months of ART treatment; and therefore the same graph showed the decrement over a follow up period.
A separate graph of the estimates of the Kaplan-Meier survivor functions is built for various covariates. It's possible to look at the existence of difference in survival experience between the indicated categories of people. In general, the pattern of 1 survivorship function lying above another means the group defined by the upper curve had a much better survival than the group defined by the lower curve.

Cox Proportional hazards model results and analysis

Interpreting the results we use the multiplicative type of the equation headed by Exp (β), which is termed the hazard ratio. The Values of Exp (β) but one indicates that the variable under study may be a significant think about decreasing the chance of death of patient under ART.
The coefficient of a categorical explanatory variable within the model may be interpreted supported the ratio of the hazard of death to reference group. In other words, comparison is created with the reference category and between groups for the specific covariates. We start by legal status of the patient. The reference category for covariate legal status was 'Never married'. Patients with their legal status divorced are dying at a rate 61.7% times greater than patients with legal status never married or patients with legal status divorced are 38.3% less likely to die than patients with legal status never married. The 95% confidence interval of hazard ratio is as large as 2.01 and as small as 1.190.

Patients with their legal status widowed are dying at a rate 3.56 times greater than patients with legal status never married. The 95% confidence interval indicates that the hazard rate goes to a maximum of 12.6 and a minimum of 1.004.
Similarly, variables that are found to be significantly related to the survival of patients within the fitted Cox regression model are TB co-infection. The hazard ratio for TB co-infected patients in relevance those that are uninfected with TB is 4.22 (95% 1.897-9.396). It means the patients infected with TB have about 4 times higher rate than patients without TB infection.
The estimated hazard ratios for a patient with working part time and not working thanks to illness as compared with working full time are 0.229 (95%CI: 0.061-0.854) and 0.885 (95%CI: 0.306-2.556) respectively. This means that patient with employment status working full time are 77.1% and 11.5% less likely to die than patient in working part time and not working thanks to illness respectively

Analysis of Clinical Progression of AIDS

DiseaseAn HIV infected individual enters the study with an HIV state defined by CD4 cell counts levels. Because the patient initiates treatment therapy, the patient is either in state 1, 2, 3 or 4 and these states is mutually exclusive. At time Δt the patient in state i is predicted to either maintain his state (i=1,2,3,4), transition to state of higher helper cell counts (i-1, $i \neq 1$) (or remain at rock bottom state) or transit to a state of lower helper cell counts (i+1, i=1,2,3,4) (or remain at the best state). These possible transitions are supported the belief that not all patients initiated into ART recover their T lymphocyte counts levels.

This study considered that an infected patient can move among the subsequent immunological marker stages associated with CD4 count: state I: CD4 count > 500 cells/micro liter, state II: 350 < CD4 count ≤ 500 cells/micro liter, state III: 200 < CD4 count ≤ 350 cells/micro liter, state IV: CD4 count ≤ 200 cells/micro liter. Moreover, the patient death added as an absorbing state. Among four state of the disease, Patient started the treatment under any state incorporates a possibility to succeed in the other state. If there's an improvement on CD4 count, the patient features a recovery from the state or patient may visit death from any working state. The transition of the patient in numerous states occurs at any time.

Discussion of Clinical Progression of AIDS Disease

The semi-Markov model may be a great tool to predict the clinical progression of a disease. It consists mainly of computing the probability of a patient being into one in every of the possible stages of the disease for a particular time and therefore the probability that the patient might survive for a time t.

The number of death observed from the successive working state i.e. I, II, III, and IV was 7, 5, 9 and 22, respectively. These are from SI to D, SII to D, and SIII to D and SIV to D. The probability of dying for a patient who is within the American state were 0.046, for a patient who is within the second state, 0.031 for a patient who is within the third state and 0.042 for a patient who is within the fourth state were 0.128. Comparable study in Italy Giuseppe et al., 2010 that contained data refers to subjects selected from a series of 766 HIV positive intravenous drug users who attended the AIDS clinics in Rome between January 1989 and December 1996 for 87 month, 6 patients died from stage I, 8 patients died from stage II, 31 patients died from each stage III and stage II.

Patients show improvement from state IV to III, II and that i were 0.244, 0.215 and 0.1046 respectively. Patients show improvement from state IV to III, from state III to II and from state II to I with probability 0.244, 0.192 and 0.190, respectively were direct improvement. This Comparable study in Italy Giuseppe et al., 2010 also shows an improvement from state IV to state III, state II and state I with probability 0.3951, 0.211, and 0.1743 respectively.

In this study a patient transition from state I to state II, from state I to state III, from state I to state

IV, from state II to state III, from state II to state IV and from state III to state IV occurs, we are saying a patient goes to the subsequent worse state. The probability of Transit from state I to state II is on top of the probability that a patient Transit from state II to state III, and from state III to state IV. The probability that a patient being in state i'll move to state II were 0.224.

The probability that a patient being in state it'll move to state III, in state i will be able to move to state IV, in state II will move to state III, in state II will move to state IV and being in state III will move to state were 0.145, 0.151, 0.233 and 0.166 respectively.

Conclusions

This study reflected on the final information about survival analysis of adult HIV/AIDS patients and modeling progression of HIV/AIDS disease stage just in case of Debre Berhan consultation room.

In this research, we will determine the factors before ART initiation that were most predictive of survival time in HIV/AIDS patients after initiation ART and see the progression of the disease supported CD4 in Debre Berehan hospital, Debre Berhan, Ethiopia. The aim of this study were to spot determinant factors for the Survival time of adult HIV/ADIS Infected Patients under the follow-up of antiretroviral therapy (ART) at Debere Berhan sickbay and model the progression of HIV/AIDS disease of a personal patient under ART follow-up supported CD4 level using Mark off process processes.

The semi-Markov process model is applied to capture the AIDS dynamic progression of a patient. The model considers the randomness of the time that a patient spends in an exceedingly given state of the disease. The survival probability of a patient depends on the immunological marker of CD4 T cell count. to try to to this progression we've got four states. This are state I: CD4 count > 500 cells/micro liter, state II: 350 < CD4 count ≤ 500 cells/micro liter, state III: 200 < CD4 count ≤ 350 cells/micro liter, state IV: CD4 count ≤ 200 cells/micro liter and death. Among the states of the semi-Markov process, the death state D is taken into account to be an absorbing state or bad state and therefore the other state are good state. Within the nice states, the transition probability from a given state to the following worse state increases at given period. Being within the fourth state (low CD4 counts) results in the very best probability of dying at a particular time as compared to the opposite states. More generally, the probability of dying decreases with increasing CD4 counts over time. For an HIV/AIDS patient during a specific state of the disease, the probability of being in same state decreases over time. However, the result had shown that probability of improving the clinical progression of AIDS disease by recovering the patients T lymphocyte count. The amount of death observed from the successive working state i.e. I, II, III, and IV was 7, 5, 9 and 22 respectively. A patient within the state I, II, III, and IV dies with probability 0.046, 0.0306, 0.042 and 0.1279 respectively within the above table. A patient from state I, II and III enters to state IV with probability 0.151, 0.166 and 0.141 respectively.

Abbreviations

ADLs: - Activities of Daily Living
AFT: - accelerated failure time
AIDS: - acquired immune deficiency syndrome
ART: -Antiretroviral Treatment
ARVs: -antiretroviral drugs
CDF: - cumulative distribution function
CSWs: - commercial sex workers
DTHSMP: - Discrete Time Homogeneous Semi-Markov Process
FHI: - Family Health International
FMOH: - Federal Ministry of Health
HAART: - Highly active antiretroviral therapy
HIV: - Human immunodeficiency virus
HSMP: - homogenous semi-Markov process
KM: - Kaplan Meier
ML: - Maximum likelihood
MOH: -Ministry of Health
PH: - proportional hazards
PLWHA: - People Living with HIV/AIDS
PMTCT: - prevention of mother-to-child transmission
SMP: - Semi-Markov process
SNNPR: - Southern Nation Nationalities and People's Regional state
SRS: - Simple random sampling
SSA: - Sub-Saharan Africa
STDs: - sexually transmitted diseases

Competing interests

The authors declare that they have no competing interests.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical clearance was taken from Debre Berhan University, school Post Graduate coordination ethical review board and official letter was written by the department of statistics to the Debre Berhan referral hospital in order to obtain the data from the hospital before planning and starting data collection. Official letter was given for concerned bodies and then confidentiality of the information was assured from all aspects.

Ethical statement

All relevant ethical safeguards have been met in relation to patient or subject protection, or animal experimentation.

Consent for publication

Not applicable.

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