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Cox PH Regression and Homogeneous Semi-Markov Models for Identification of Risk Factors of HIV/AIDS Patients Taking HAART and Assessing the Disease Progression

HAART Alan HIV/AIDS Hastalarının Risk Faktörlerinin ve Hastalık Progresyonunun Tanımlanması İçin Cox PH Regresyonu ve Homojen Semi-Markov Modelleri

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ABSTRACT Objective: The objectives of the study were to identify the determinant factors for survival time of Human immunodeficiency virus (HIV) infected patients treated with highly active antiretroviral therapy (HAART) and to observe the HIV progression of HIV infected patients in Hawassa City Adare hospital, Ethiopia. **Material and Methods:** This was a retrospective cohort study of 330 patients who started ART between 2008 and 2014 at Hawassa City Adare Hospital. Data were extracted from paper based medical records database and the survival of patients was estimated by the Kaplan-Meier method. Predictors of mortality were identified by Cox proportional hazards model and the progression of the AIDS patients by Homogeneous Semi-Markov Stochastic model. **Results:** Survival of patients was significantly related with age, sex, Tuberculosis (TB) status, HIV disclosure, functional status, substance use, baseline World Health Organization (WHO) clinical stage, baseline weight and baseline cluster of differentiation 4 (CD4) count. Results of the Cox PH model revealed that; older, TB co-infected, substance user patients, and patients with lower baseline CD4 count and weight had significantly higher risk of death or shorter survival time than their counterparts. The results of Homogeneous Semi-Markov Stochastic model indicated that AIDS patients in the first state of the disease had the highest survival probability as compared to the patients in the second, third and fourth stage of the disease. **Conclusion:** To minimize deaths, more attention should be given during the early phases of treatment of HIV/AIDS patients on HAART.

Keywords: Cox proportional hazard model; HIV progression; Semi-Markov model

ÖZET Amaç: Bu çalışmada, Etiyopya Hawassa Şehri Adare Hastanesi'nde yüksek düzeyde aktif antiretroviral tedavi (HAART) ile tedavi edilen, insan immün yetmezlik virüsü (HIV) enfeksiyonu ile enfekte hastaların sağkalım süreleri için belirleyici faktörlerin tanımlanması ve HIV ile enfekte hastalarda HIV progresyonunun gözlemlenmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bu, Hawassa Şehri Adare Hastanesi'nde 2008-2014 yılları arasında antiretroviral tedavi başlanan 330 hastanın retrospektif bir kohort çalışmasıydı. Veriler, kağıt bazlı tıbbi kayıtlar veri tabanından çıkarılmış ve hastaların sağkalımları Kaplan-Meier metodu ile tahmin edilmiştir. Mortalitenin öngördürücüleri Cox orantılı risk modeli ile ve kazanılmış bağışıklık yetersizliği sendromu (AIDS) hastalarının progresyonu homojen semi-Markov stokastik modeli ile tanımlanmıştır. **Bulgular:** Hastaların sağkalımı yaş, cinsiyet, tüberküloz (TB) durumu, HIV durumu, işlevsel durum, madde kullanımı, Dünya Sağlık Örgütü'ne (DSÖ) göre başlangıçtaki klinik evre, başlangıç kilosu ve farklılaşma kümesi 4 (CD4) sayısı ile anlamlı olarak ilişkiliydi. Cox orantılı risk modelinin sonuçlarına göre; daha yaşlı, TB ile birlikte enfekte olmuş, madde kullanan hastalar ve daha düşük başlangıç CD4 sayısı ve ağırlığı olan hastalar benzerlerine göre daha yüksek ölüm oranlarına veya daha kısa sağkalım süresine sahiplerdi. Homojen semi-Markov stokastik modelin sonuçları, hastalığın birinci evresindeki AIDS hastalarının, hastalığın ikinci, üçüncü ve dördüncü evresindeki hastalara kıyasla en yüksek sağkalım olasılığına sahip olduğunu göstermiştir. **Sonuç:** Ölümleri en aza indirmek için, HAART tedavisi gören HIV/AIDS hastalarının tedavisinin erken evrelerinde daha fazla dikkat gösterilmelidir.

Anahtar Kelimeler: Cox oransal risk modeli; HIV progresyonu; Semi-Markov modeli

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Human immunodeficiency virus/Acquired immunodeficiency syndrome (HIV/AIDS) is among the health issues with which Ethiopia continues to combat. In Ethiopia, the HIV prevalence among women and men aged 15-49 has decreased from 1.5% in 2011 to 0.9% in 2016. The prevalence was 1.4% in 2005.[1] The prevalence of HIV was relatively low in the 1980's but it increased rapidly in the 1990's.[2,3]

A study on HIV-infected patients that have started antiretroviral therapy (ART) revealed that being male, severe malnutrition and World Health Organization (WHO) stage IV were associated to progression to death.[4] A similar retrospective cohort study also revealed that registered year, clinical status, cluster of differentiation 4 (CD4) group, and ARV drug group were all significantly related to death.[5]

Another study conducted to assess the probability of survival and the independent predictors of death of patients on highly active antiretroviral therapy (HAART) identified low body mass index (BMI), WHO stage IV, sex, and baseline CD4 count as independent determinants of death in the first 6 months. However, age at HAART initiation and regimen types were not significantly associated with early death.[6]

To examine the event of mortality, clinical characteristics and outcome of co-infection with HIV and Tuberculosis (TB), a cross-sectional study of co-infected cases reported from nine domestic hospitals throughout mainland China, provided treatments for 241 TB and HIV patients and mortality attributable to co-infection was reported for 15.8% of the cases.[7] HIV/TB co-infection was linked to high mortality even for those on HAART and/or drug therapy. Accounting for potential confounders, another study revealed that, including CD4 cell count and viral load, the risk of AIDS-related death was more for the person-time with TB compared to the person-time without TB.[8]

A cohort study of patients who started ART, with a median CD4 cell count of 252 cells/ml, showed that high viral load, advanced clinical stage, past history of tuberculosis, low BMI, low hemoglobin and low CD4 cell count were independent risk factors for mortality and/or severe morbidity at baseline. Moreover, low CD4 cell count and persistently detectable viral load were the risk factors during follow-up.[9]

To determine the connection between the risk of mortality and the CD4 cell response to ART, a cohort of 2,423 patients on ART who had a median baseline CD4 count of 105 cells/μl were followed for up to 5 years of ART. Older age, WHO clinical stage 4, updated CD4 cell counts and detectable updated viral load measurements were all significantly related with mortality risk in both the crude analyses and the multivariate analysis with the exception of sex which was significant in the crude analysis only though updated CD4 cell counts were most strongly associated with death.[10]

Mortality rates among drug users have been significantly higher than the rates for the general population. Common causes of death among drug users include bacterial infection, overdose, accidents, and AIDS[18]. Although HIV-infected drug users are less likely to initiate taking ART, their response to therapy is comparable to that for other exposure groups, provided that adherence to treatment is satisfactory.[11]

The factors associated with survival of AIDS patients are baseline CD4 count and baseline lymphocyte and WHO clinical stage.[12] Patients with a small baseline CD4 count had a mortality risk two times as high as those with higher CD4 count, patients in WHO stage III and IV were two to four times more likely to die than patients in stage I and II.[12] The reports show that the survival probability of AIDS patients would improve with increased CD4+ count.[13] Baseline CD4 count (> 200 cells/μl) and baseline total lymphocytes count ($\geq$1200 cells/mm^3) were identified as determinants that favored a good immunological recovery process after ART initiation.[14]

In the case of Ethiopia, there is little research and literature on the survival of patients with ART. A cohort study at Adama Referral Hospital conducted to assess the major factors of death status of HIV/AIDS patients revealed that some health, economic and risk behavior factors influence the survival of patients.[15] Moreover, a study at Arbaminch Referral Hospital identified WHO clinical stage, total lymphocyte count (TLC), BMI and weight loss as predictors of early death in HIV-positives.[16]

Although Ethiopia is making efforts to supply ART drugs to people who are living with HIV/AIDS, in order to reduce opportunistic infectious diseases, HIV/AIDS-related deaths and to improve quality of life of those infected with HIV, research on the factors that influence the survival/death status of a person given she/he is already HIV positive and is under the follow up of ART is scanty.

Most of the researches undertaken in Ethiopia focused on the prevention of the disease and the factors that increase the chance of contracting the disease among others. Almost all sought ways of preventing it before a person is HIV positive.

This study is motivated by the inadequacy of researches not only on the factors that influence the survival/death status of a person given she/he is already HIV positive and is taking HAART but also on the progression of the disease. The rationale behind such a research is to improve the success rate of ART programs run by different health institutions of the country and thereby minimize HIV related mortality. The question we want to address here is "Which social, demographic, economic and health related factors/variables affect the chance of survival/death of HIV-positive people taking ART? How is the progression of HIV/AIDS disease to death of HIV/AIDS patients on highly active antiretroviral therapy (HAART)?

DATA AND METHODOLOGY

STUDY DESIGN, AREA AND PERIOD

A retrospective cohort study was carried out on HIV/AIDS patients on HAART at Hawassa City Adare Hospital in Ethiopia from 2008 to 2014.

STUDY POPULATION AND SAMPLING DESIGN

All recorded patients of laboratory confirmed HIV/AIDS patients at Hawassa City Adare Hospital who were on antiretroviral therapy during 2008 - 2014 were the source of information.

At the time of data collection of this specific study, 2509 HIV/AIDS patients were in the hospital of which 1212 started ART service during 2008 to 2014. The patients were stratified on the basis of their ART starting time into three strata with the first stratum covering the period from 2008 to 2010(N_1 = 286), the second stratum from 2011 to 2012(N_2 = 348) and the third stratum from 2013 to 2014 (N_3 = 578).

SAMPLE SIZE DETERMINATION

The sample size determination formula by Cochran (1977) was adopted for this study after considering the ART starting time of the patients as stratification variable.

The proportions P_1, P_2 and $P_3 = 0.5$ represented the proportion of death among HIV/AIDS patients under ART in the first, second and third stratum respectively. In this study the population size (N) is 1212 with N_1= 286, N_2 = 348 and N_3 = 578. Thus, the stratum weights were calculated using the formula $w_i = \frac{N_i}{N}$ giving w_1= 0.236, w_2= 0.287 and w_3= 0.477. Consequently the sample size was calculated as $n = \frac{\sum_{i=1}^{3} \frac{w^2{}_i N_i P_i (1-P_i)}{w_i (N_i - 1)}}{V + \frac{\sum_{i=1}^{3} \frac{w_i N_i P_i (1-P_i)}{N_i - 1}}{N}}$ = 330 where V = $(\frac{d}{Z_{\alpha/2}})^2$, $Z_{\alpha/2}$ =1.96, and d=0.05

ALLOCATION OF SAMPLE SIZE

To determine the size of the sample from each stratum, proportional allocation has been used which resulted in a sample of 78 patients from the first stratum, 95 patients from the second stratum and a sample of 157 patients from the third stratum.

DATA

Data were obtained by reviewing the medical charts of the patients.

STUDY VARIABLES

The response/outcome variables are the survival time of HIV/AIDS patients that have started ART and HIV/AIDS disease progression that changes from state to state.

The predictor (independent) variables considered were baseline age, sex (male, female), marital status (unmarried, married, divorced, windowed, others), religion (Muslim, Orthodox, Protestant, Catholic), level of education (no education, primary, secondary and above), Employment status (yes, no), TB incidence (yes, no), HIV disclosure (yes, no), substance (tobacco, alcohol, others) use (yes, no), functional status (working, ambulatory and bedridden), baseline WHO clinical stage (Stage I, Stage II, Stage III and Stage IV), baseline CD4 cells count and baseline weight

METHODOLOGY

Data on a sample of 330 patients with HIV/AIDS taking ART at Hawassa City Adare Hospital during 2008-2014 were examined using Cox proportional hazards (PH) model and homogeneous Semi-Markov reliability stochastic model.

The Cox Proportional Hazards Model

The Cox proportional hazards regression model[17] can be written as follows:

$$h(t) = h_0(t)\exp(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p)$$

where h(t) is the expected hazard at time t, $h_0(t)$ is the baseline hazard and represents the hazard when all of the predictors (or independent variables) X_1, X_2 , X_p are equal to zero. Thus, the predicted hazard (i.e., h(t)), or the rate of suffering the event of interest in the next instant, is the product of the baseline hazard ($h_0(t)$) and the exponential function of the linear combination of the predictors.

Homogenous Semi-Markov Model

Homogenous Semi-Markov Processes[18] (HSMP) is a process that changes states according to a discrete time Markov Chain (X_n) but stays at each state for a random amount of time (T_n).

In the HSMP environment, two random variables run simultaneously:

$X_n : \Omega \rightarrow S, \qquad T_n : \Omega \rightarrow R$

where X_n with state space $S = \{S_1, S_2, \ldots, S_m\}$ represents the state at the n^{th} transition.

Thus, one cannot only consider the randomness of the states but also the randomness of the time elapsed in each state. The kernel $Q = (Q_{ij})$ associated with the process is

$Q_{ij}(t) = P[X_{n+1} = j, T_{n+1} - T_n \leq | X_n = i]$, where $P_{ij} = \lim_{t\rightarrow\infty} Q_{ij}(t)$, $i,j \in S$ is the transition matrix of the embedded Markov chain.

The probability that the process may leave state *i* in time *t* is

$$H_i(t) = P[T_{n+1} - T_n \leq t \,|\, X_n = i]$$

Similarly, the distribution function of the waiting time in each state *i*, given that the subsequently occupied state is known is

$$G_{ij}(t) = P[T_{n+1} - T_n \leq t \,|\, X_n = i, X_{n+1} = j]$$

Therefore,

$$G_{ij}(t) = \begin{cases} \frac{Q_{ij}(t)}{P_{ij}}, & if \ P_{ij} \neq 0 \\ 1 & if \ P_{ij} = 0 \end{cases}$$

For any HSMP X = (X (t), t∈ N) representing the state occupied by the process, the transition probabilities are defined as:

$$\phi_{ij}(t) = P[X(t) = j \mid X(0) = i]$$

We chose homogeneous Semi-Markov models because they are suitable for assessing the disease progression in the sense that they enable us to consider not only the randomness in different states in which the infection can progress into but also the randomness of the time spent in each state.

RESULTS AND DISCUSSION

DESCRIPTIVE STATISTICS

The study was based on a sample of 330 patients selected from a total population of 1212 HIV/AIDS patients who started ART treatment from 2008 to 2014. Out of the random sample of 330 patients 61(18.48%) were dead and 269 (81.52%) were censored during the follow-up study. The sample included 125 male patients of which 28(22.4%) were dead. Among the 205 females in the sample, 33(16.1%) were dead.

Among the patients in the sample, 136(41.21%) were TB co-infected of which 53(38.97%) were dead. Of 194(58.79%) non-TB-infected patients, 8(4.1%) were dead. Among the patients in the sample, 124(37.58%) used substance including tobacco, alcohol and chat, of which 56(45.16%) were dead. Out of 206 patients who did not use substance 5(2.43%) were dead. Patients in WHO clinical stage IV had the highest proportion (8.2%) of deaths than patients in other stages. The details of the distribution of HIV patients taking HAART by factors are presented in Table 1.

TABLE 1: The distribution of HIV patients treated with HAART in Hawassa City Adare Hospital by some important socio-demographic and clinical characteristics (categorical variables).

Variable	Category	Total N	N of Events	Censored (%)
Sex	Male	125	28	97 (77.6)
	Female	205	33	172 (83.9)
Marital status	Unmarried	61	14	47 (77.0)
	Married	155	28	127 (81.9)
	Others	114	19	95 (83.3)
Religion	Orthodox	196	34	162 (82.7)
	Muslim	31	6	25 (80.6)
	Protestant	97	20	77 (79.4)
	Catholic	6	1	5 (83.3)
Educational level	No education	74	12	62 (83.8)
	Primary	140	25	115 (82.1)
	Secondary & above	116	24	92 (79.3)
Employment status	Yes	88	16	72 (81.8)
	No	242	45	197 (81.4)
TB incidence	Yes	136	53	83 (61.0)
	No	194	8	186 (95.9)
HIV disclosure	Yes	198	32	166 (83.8)
	No	132	29	103(78.0)
Substance use	Yes	124	56	68 (54.8)
	No	206	5	201 (97.6)
Functional status	Working	228	26	202 (88.6)
	Ambulatory	98	31	67 (68.4)
	Bedridden	4	4	0 (.0)
Base line WHO clinical stage	Stage I	61	4	57 (93.4)
	Stage II	118	7	111 (94.1)
	Stage III	105	23	82 (78.1)
	Stage IV	46	27	19 (41.3)

The summary figures in Table 2 show that the mean age of the respondents was 35.57(median 35) years with oldest and youngest being 74 and 3 years old, respectively with standard deviation 12.968. The average CD4 count at the beginning of treatment was 270.68, with a minimum of 10, and a maximum of 1017. The average weight of the patients under study was 50.64kg with minimum weight of 7 kg and maximum of 90 kg with standard deviation of 12.893 kg.

The maximum survival time of AIDS patients in this study was 80 months and the minimum was 1 month with a mean survival time of 23.86 months and standard deviation of 19.997 months.

TABLE 2: Summary statistics of the continuous data/variables on HIV patients treated with HAART in Hawassa City Adare Hospital.

Variables	N	Minimum	Maximum	Mean	Median	Std Deviation
Age of patient	330	3	74	35.57	35	12.968
Baseline Weight	330	7	90	50.64	50	12.893
Baseline CD4 count	330	10	1017	270.68	290	121.218
Survival time	330	1.00	80	23.86	18	19.997

The estimates of the overall Kaplan-Meier survivor function presented in Figure 1 show that the majority of the deaths happened within few months after the start of HAART and it declined in the later months of follow up.

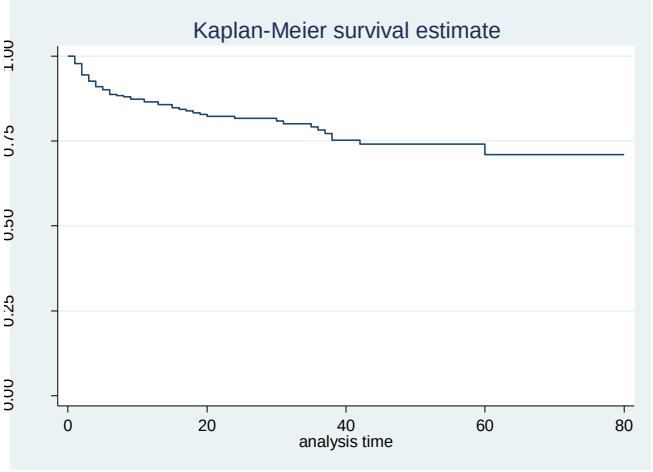


FIGURE 1: Plot of the overall estimate of Kaplan-Meier survivor function of HIV patients treated with HAART in Hawassa City Adare Hospital.

UNIVARIATE ANALYSIS

The log-rank test results presented in Table 3 show that marital status, religion, level of education, and employment status are not significant covariates for the survival of patients at 25% level of significance. However, sex, TB co-infection, HIV disclosure, substance use, functional status and WHO clinical stage had significant effect on the survival of the patients. Thus, those patients who were not using substance, had working functional status, were in WHO clinical stage I or II and had no TB co-infection had better survival experience.

TABLE 3: Kaplan-Meier Univariate Analysis for Categorical Covariates.

Variables	Test	Chi-square	Degrees of freedom	p value
Marital status	Log Rank	1.767	4	.778
Religion	Log Rank	.991	3	.803
Level of education	Log Rank	.356	2	.837
Employment status	Log Rank	.012	1	.914
Sex	Log Rank	1.752	1	.186
TB incidence	Log Rank	62.803	1	<.001
HIV disclosure	Log Rank	1.512	1	.219
Substance use	Log Rank	101.432	1	.000
Functional status	Log Rank	40.625	2	.000
Baseline WHO	Log Rank	54.655	3	.000

The 20% level of significance was used as a screening criterion for initial variable selection and the univariate Cox regression analysis results presented in Table 4 show that the covariates, age, weight and CD4 count were significant. Thus, these covariates together with the variables found significant in the Kaplan-Meier survival analysis were used as candidate covariates for the multivariable Cox regression model.

TABLE 4: Univariate Analysis for Continuous Variables Using Cox Regression.

Variable	B	SE	Wald	Df	p value	HR	95% CI for HR
Age	.061	.010	37.001	1	< .001	1.063	(1.043, 1.085)
Weight	-.013	.009	2.062	1	.151	.987	(0.969, 1.005)
Baseline CD4	-.014	.001	98.900	1	<.001	.987	(0.984, 0.989)

SE: Standard error, Df: Degrees of freedom, HR: Hazard Ratio.

MULTIVARIABLE COX PROPORTIONAL HAZARD MODEL

Nine variables were selected for the multivariable Cox proportional hazard model analysis.

The multivariable Cox regression model fit results in Table 5 show that only five variables are significant out of the nine variables found significant in the univariate analysis.

The results revealed that age of the patient, incidence of TB, substance use, base line weight and base line CD4 count are statistically significant predictors of the survival of patients. For all the five covariates which were found significant in the multivariable Cox regression model, the values of the Wald statistic were significant at 0.05 level of significance.

TABLE 5: Multivariable Cox Regression Model.

Variables	DF	Coef.	Error	Wald	Sig.	HR	95% CI for HR
Age	1	0.037	0.011	13.814	0.001	1.038	1.016 1.06
Sex							
Female	1	0.095	0.304	0.074	0.732	1.099	0.639 1.890
Male	0					1	
TB status							
No	1	- 1.117	0.440	4.490	0.011	0.327	0.138 0.775
Yes	0					1	
HIV disclosure							
No	1	0.056	0.307	0.110	0.848	1.057	0.599 1.867
Yes	0					1	
Substance use							
No	1	-2.312	0.051	19.926	<0.001	0.099	0.036 0.274
Yes	0					1	
Functional status							
Ambulatory	1	0.069	0.323	0.982	0.818	1.072	0 .594 1.936
Bedridden	1	0.519	1.055	1.146	0.408	1.681	0.491 5.754
Working	0					1	
Weight	1	-0.048	0.016	8.062	0.005	0.953	0.921 0.986
B_WHO							
I	1						
II	1	-1.080	0.231	1.328	0.112	0.339	0.090 1.287
III	1	-0.003	0.586	0.542	0.996	0.997	0.315 3.153
IV	0	-0.448	0.388	1.549	0.460	0.639	0.194 2.099
						1	
B_CD4	1	-0.008	0.002	20.242	<0.001	0.992	0.990 0.995

B_WHO: baseline WHO, B_ CD4: baseline CD4, DF: Degrees of freedom, HR: Hazard Ratio

After controlling the effects of all other covariates in the model, the hazard rate of infected patients increased by 3.8% for every one year increase in age (aHR=1.038). The hazard rate of TB negative patients was lower by 67.3% than TB positive patient (aHR=0.327).

The hazard rate of those patients who did not use substance was 90.1% lower than that for patients who used substances (aHR=0.099). In the same way, every one kilogram increase in baseline weight decreased the hazard rate of the infected patients by 4.7% (aHR=0.953).

Finally, base line CD4 counts have also a significant effect on the survival of the patients. A unit increase in baseline CD4 count decreased the hazard rate of patients by 0.8% (aHR=0.992).

3.4. Evolution of HIV/AIDS Disease

The frequencies of the transitions among the states of degree of seriousness of HIV disease are presented in Table 6 below.

TABLE 6: Transition frequencies matrix of those followed-up at Hawassa City Adare Hospital, 2008-2014.

State	I	II	III	IV	V
I	7	1	2	0	0
II	20	15	4	1	1
III	60	41	39	16	12
IV	13	13	19	18	48

The above transition frequency matrix shows the transition of HIV/AIDS patients from one state to another. When this data were collected, there were two CD4 cell counts. The first one was the baseline CD4 cell count at the start of ART and the second one was the current (time of data collection for this study) CD4 cell count. Patients were classified on the basis of their CD4 count as state I (CD4 count >500), state II ($350 < \text{CD4 count} \leq 500$), state III ($200 < \text{CD4 count} \leq 350$), state IV (CD4 count$\leq$200) and an absorbing state V (death). Thus, each patient was classified into one of the five stages, SI, SII, SIII, SIV or death.

The Figure, 7 in cell (1, 1) of Table 6, indicates that 7 patients were in stage I (SI) when they started ART and were in the same state (SI) during the time of data collection. Similarly, the figure in cell (SI, SII) indicates that 1 patient was in state one at the start of ART but was in state two during the data collection period. Likewise, 60 patients were in state three at the start of ART but they were in state one during the data collection period. Conversely, 48 patients were in state four when they started ART but were not there during the data collection period because of the fact that they were dead. The remaining figures in the table can be described in a similar way.

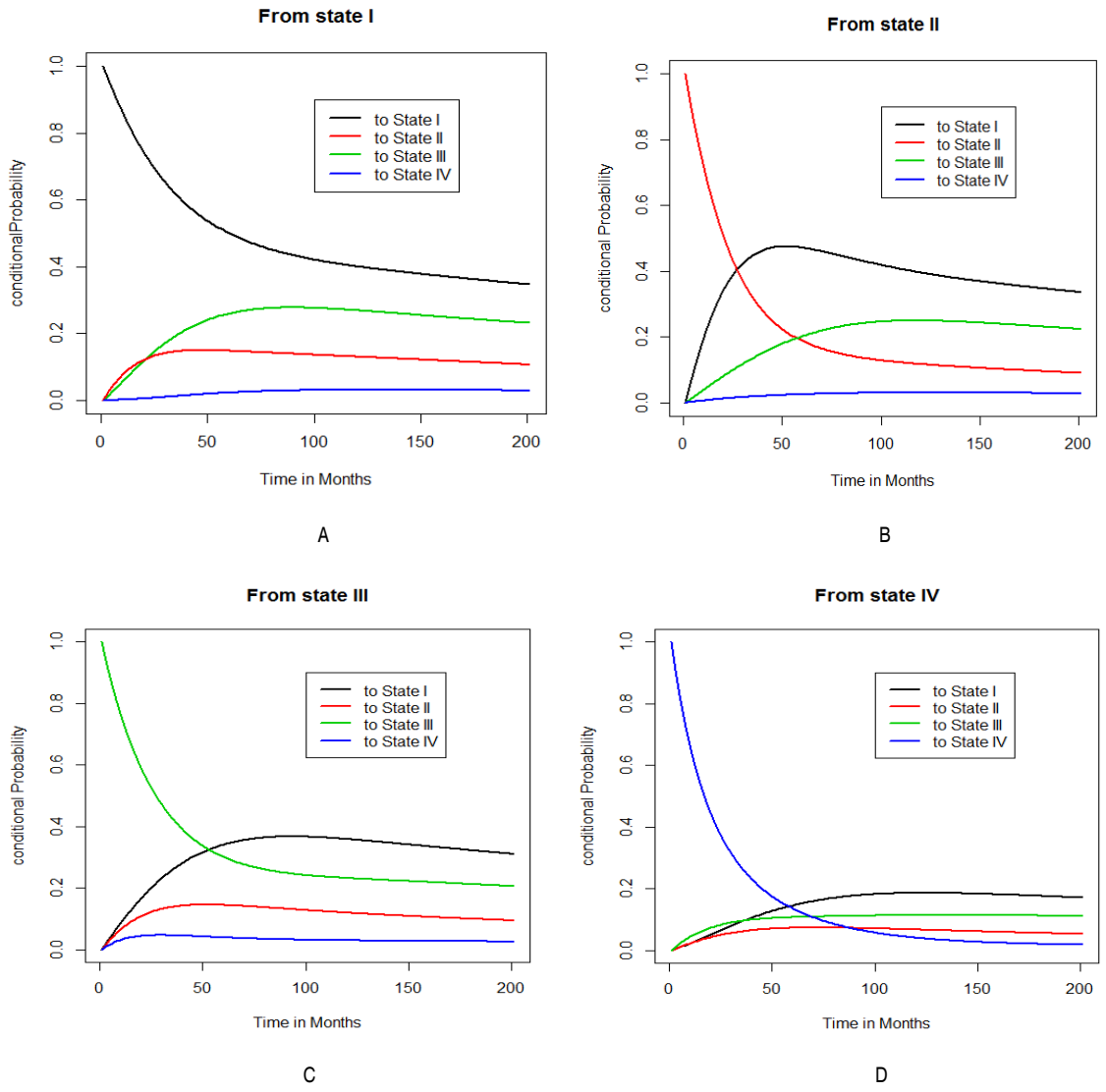
The estimates of transition probability matrix are also presented in Table 7.

TABLE 7: Transition matrix of the embedded Markov chain (estimates).

State	I	II	III	IV	V
I	0.700	0.100	0.200	0.00	0.00
II	0.488	0.366	0.098	0.024	0.024
III	0.357	0.244	0.232	0.095	0.071
IV	0.117	0.117	0.171	0.162	0.432
V	0.000	0.000	0.000	0.000	1.000

The transition matrix in Table 7 shows the probability of moving or transiting from one state to other states. For instance, the probability of staying in state I is 0.7, the probability of transiting to state II from state I is 0.1, probability of transiting to state III from state I is 0.2 and the probability of transiting to state V (Death) from state IV is 0.432.

Figure 2 provides the graphical representation of the communication between the states. It shows all possible immunological states an HIV/AIDS patient may undergo. The first four states are defined to be "good" states or "working" states and the last one is taken as death state.



A: Conditional probabilities of being in state $i \in \{SI, SII, SIII, SIV\}$ after t months given the starting state is *one*;
B: Conditional probabilities of being in State $i \in \{SI, SII, SIII, SIV\}$ after t months given the starting state is *two*;
C: Conditional probabilities of being in state $i \in \{SI, SII, SIII, SIV\}$ after t months given the starting state is *three*;
D: Conditional probabilities of being in state $i \in \{SI, SII, SIII, SIV\}$ after t months given the starting state is four.

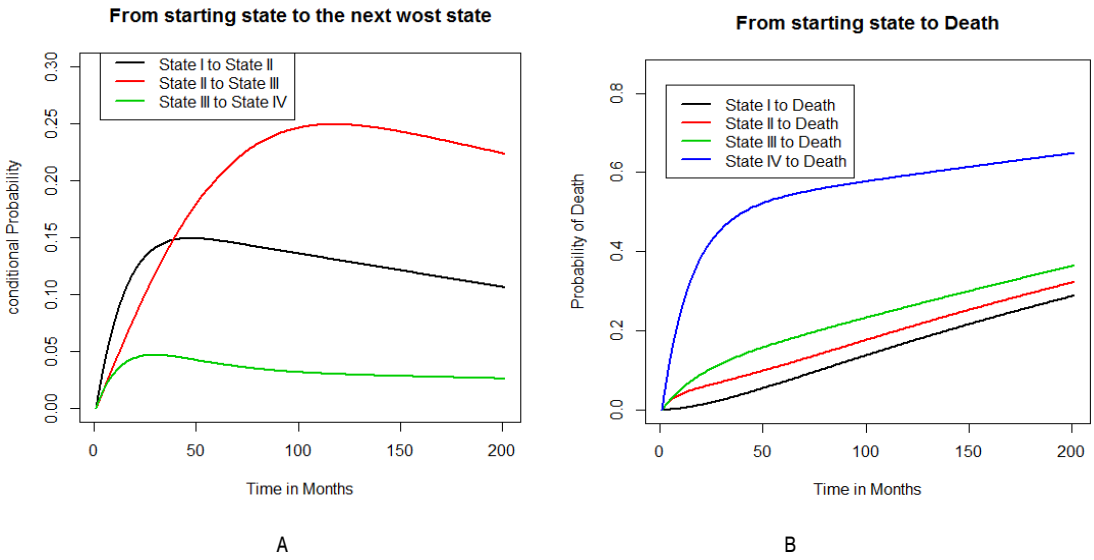
FIGURE 2: Conditional probabilities versus time.

PREDICTION OF HIV/AIDS DISEASE PROGRESSION FOR AN INDIVIDUAL PATIENT

The graphical representation of the conditional probability of individuals changing their status given their current status is also displayed in Figure 2. The figure displays the probabilities of patients being in state $i \in \{SI, SII, SIII, SIV\}$ after t months given that they entered in state $i \in \{SI, SII, SIII, SIV\}$ at time 0. For instance, an AIDS patient who is in the second stage of the disease will be in the third stage of the disease after 60 months with probability 0.1940 (Figure 2B). Similarly, the probability is 0.30 for an AIDS patient who is in the third stage of the disease to be in the first stage of the disease after 50 months (see Figure 2C). Like-

wise, an AIDS patient who is in the fourth stage of the disease transits to the second stage of the disease, after 100 months with probability 0.01 (Figure 2D).

The conditional probability of being in the next worse state after t months *given* that the starting state was I, $i \in \{SI, SII, SIII\}$ is plotted in Figure 3A.



A B

A: Conditional probabilities of being in the next worse state after t months given starting state *i;*
B: Conditional probabilities of being in the death state after t months given the starting state *i.*

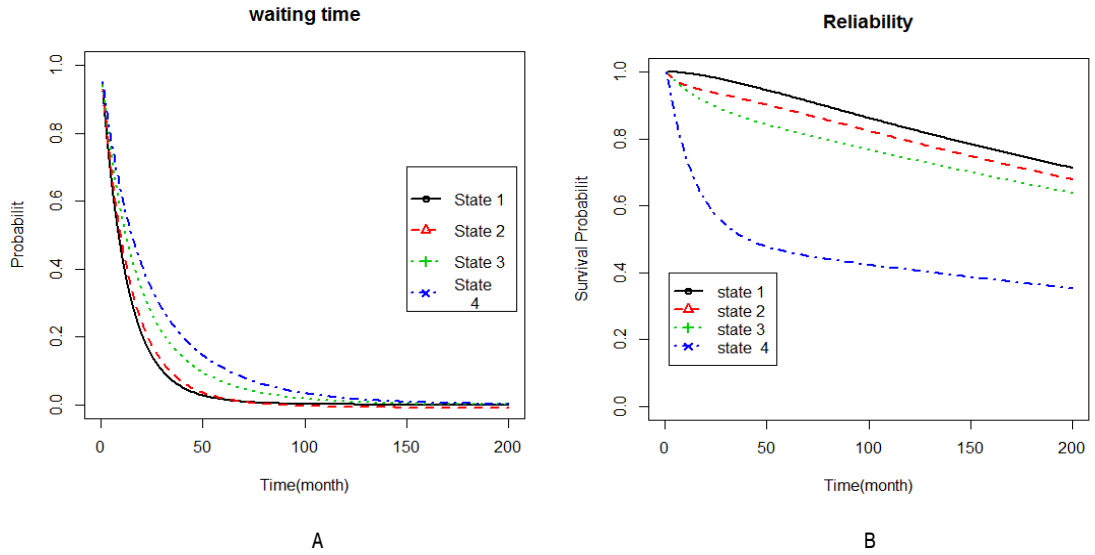
FIGURE 3: Conditional probabilities versus time.

In the time/months-probability plot of the conditional probability of being in the second stage of the disease given that a patient was in the first stage of the disease against time (in months), the pick was at about (48, 0.14). Similarly, the pick in the plot of time (in months) against the conditional probability of being in the third stage of the disease, given that the patient was in the first stage of the disease was at about (100, 0.24).Likewise, the pick was at about (25, 0.04) for the plot of time against the conditional probability of being in the third stage of the disease given that the patient was in the first stage of the disease (see Figure 3A).

In the same way, a graph of the conditional probabilities that patients in starting state $i \in \{SI, SII, SIII, SIV\}$ will die after t months is plotted in Figure 3B. The plot of the conditional probability of dying after t months given the starting status against time reveal interesting results that coincide with the usual instructions of physicians to their patients. Among the patients who were in the different states, patients in state one had the lowest conditional probability of dying throughout time *t*. This graph reveals that the probability that a patient in any one of the states {SI, SII, SIII, SIV} will die {D} is increasing with time. For a patient who was in the first stage, second stage, third stage and fourth stage of the disease, the probability of dying after 200 months was 0.22, 0.24 0.26 and 0.65 respectively.

The conditional probability of staying in the starting state up to t months is presented in Figure 4A. Among the patients in the different stages of the disease, patients in stage four had the highest conditional probability of staying at a starting state up to t months. The probability that an AIDS patient stays in the fourth stage of the disease up to 50 months was 0.18. On the other hand, the conditional probabilities of staying up to 50 month in state three, state two and state one were 0.16, 0.08 and 0.05 respectively. The conditional probability of staying in the starting state until a given number of months decreased with increasing of time.

Moreover, the survival probabilities up to t months given that a patient is currently in state $i \in \{SI, SII, SIII, SIV\}$ are presented in Figure 4B. The lowest curve indicates that the probability that an AIDS patient who is in the fourth stage of the disease will not die after 100 months is 0.4. Similarly, an AIDS patient who is in the third stage of the disease will not die after 140 months with probability 0.65. Likewise, the probability that an AIDS patient who is in the second stage of the disease will survive for at least 150 months is 0.65 and the probability is 0.08 for an AIDS patient who was in the first stage of the disease to stay alive for at least 100 months.



A: Conditional probabilities of staying in the starting state before leaving that state;
B: Probability of survival up to *t* months given the starting state.

FIGURE 4: Conditional probabilities of staying in the starting state before leaving that state and Probability of survival up to *t* months given the starting state.

DISCUSSION ON THE PREDICTIVE FACTORS OF SURVIVAL OF AIDS PATIENTS

This study attempted to identify the major factors that are significantly associated with the risk of mortality of AIDS patients under ART and also attempted to estimate and compare survival probabilities within a given time period of AIDS patients under ART. The results of our single variable analysis revealed that the survival time of a patient is significantly associated with age of the patient, sex, TB incidence, HIV disclosure, substance use, functional status, baseline weight, WHO clinical stage and baseline CD4 count.

The mortality rate of patients in the few months after ART initiation was high and it declined in the later months of follow up. Studies conducted in southern Ethiopia and Tanzania also revealed that the mortality rates were high within the first three months of follow up.[4,16,19] This may be attributable to the fact that most of the patients start HAART at the severe stage of the disease.

The Cox's proportional hazard model fitted using complete case analysis identified age of the patient, TB incidence, substance use, baseline weight and baseline CD4 count as predictors of the survival longevity of AIDS patients.

According to our finding, older patients were more likely to have greater risk of mortality as compared to younger patients. This result is similar to the result that older age was linked with increased rate of mortality and low quality of life and defaulting, which leads to mortality.[10] However a study in Tanzania showed that age is not significantly associated with mortality[4] contrary to our finding.

TB incidence is the leading cause of death in people living with HIV/AIDS. This study showed that TB increased the rate of mortality. Patients co-infected with TB had nearly 3 times higher risk of dying while on ART compared to non-infected. Studies from Baltimore, USA and mainland China have also revealed that TB is an independent predictor of mortality of patients on ART, after controlling for potential confounders, including CD4 cell count and viral load.[8] In the Baltimore study the hazard of AIDS related death was more for the person-time with TB compared with the person-time without the incident of TB. A cohort study in Abidjan, Ivory Coast also found out that TB is a risk factor for immunological and virological failure, which leads to severe morbidity and mortality in adult patients treated with ART.[9]

Among the findings of our study is that substance use is associated with the time to death of patients. Substance abuse was associated with mortality, non-adherence to medication and lower quality of life in many studies.[20] Baseline weight and baseline CD4 count determine one's resistance to different opportunistic diseases. Thus, the larger these values, the lower the danger of being at risk of death due to HIV. The outcomes of this study support this fact as the hazard rate of death risk are high for those with lower baseline weight and CD4 count. This result is comparable to the findings of studies in Uganda and Ethiopia which showed that baseline CD4 count and baseline weight are the most predictive factors of survival of AIDS patients.[14,15]

DISCUSSION ON HIV/AIDS DISEASE PROGRESSION

The HIV/AIDS progression model considered in this study relates to a microscopic view of the disease process and it is based on the CD4 counts. This study attempted to predict the proportion of individuals changing their status and the survival probability of AIDS patients. The results indicated that the probability that a patient dies after time t given his/her current status increased with increasing of time.

The conditional probability of being in the next worse state of the disease also did rise rapidly during the earlier time period, reached the peak and then declined slowly. Conversely, the conditional probability of dying for a patient in any state increased with increased time duration. However, the conditional probability of staying in the starting state until a given number of months decreased with increasing of time. These results confirm the results obtained in previous studies.[21,22]

The survival probability of an AIDS patient up to *t* months given his/her current status decreased with increased length of time but with increasing CD4 count, the survival probabilities up to *t* months increased. An AIDS patient who was in the first state of the disease had highest survival probability compared to patients in the second, third and fourth stages of the disease at a given time. On the other hand, an AIDS patient who is in the fourth state of the disease had the lowest survival probability compared to patients in the first, second and third stages of the disease at a given time. This result is similar to the results obtained in previous studies.[21,22]

CONCLUSION

The objectives of this study were to identify factors that affect the survival time of AIDS patients under ART and to investigate the progression of HIV among individual patients in Hawassa City Adare Hospital.

The Cox regression analysis revealed that baseline age, TB status, substance use, baseline weight and baseline CD4 cell count are the major factors that affect the survival of HIV/AIDS patients. As the age of a patient increases, the survival probability is decreasing. Patients, who used substances like alcohol, chat, and cigarette had higher hazard rate or lower survival rate than patients who did not use substance. Similarly, patients in poor health conditions such as TB positive patients and patients with small baseline CD4 count and small baseline weight were less likely to survive.

The results of this study also indicated that the survival probability of a patient is not statistically different among groups classified by sex, marital status, religion, educational level, employment status, HIV disclosure, functional status and baseline WHO.

From the homogeneous semi-Markov modeling of HIV/AIDS evaluation, the survival probability of a patient depends on his/her current state of the disease. In other words, with increasing CD4 count, the survival probability of a patient increases. Patients with low CD4 counts were more likely to die than patients with high CD4 counts at a given time.

The conditional probability of being in the next worst stage of the disease moved up rapidly in the initial times reaching at the peak and bending downward slowly. Thus, this study showed the disease progression of HIV/AIDS patients under ART treatment and confirmed that the ART treatment had clearly improved the survival of the patients. In general, the HIV patients on HAART tended to live longer and pre-ART clinical status of a patient has a significant influence on the ultimate survival of the patient.

To avoid many deaths, more attention should be given during the early phase of treatment of HIV/AIDS patients on HAART.

Ethical Clearance

Ethical clearance has been obtained from the institutional review board of Hawassa University.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept**: Ashenafi Kalayu; Design: Ashenafi Kalayu and Mekonnen Tadesse; **Control/Supervision**: Mekonnen Tadesse; **Data Collection and/or Processing**: Ashenafi Kalayu; **Analysis and/or Interpretation**: Ashenafi Kalayu and Mekonnen Tadesse; **Literature Review**: Ashenafi Kalayu and Mekonnen Tadesse; **Writing The Article**: Mekonnen Tadesse; **Critical Review**: Ashenafi Kalayu and Mekonnen Tadesse; **References and Fundings**: Ashenafi Kalayu.*

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