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Predicting AIDS disease progression using longitudinal CD4 count among adult HIV/AIDS patients in Southwest Ethiopia: Application of semi-markov process

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ABSTRACT

Mortality among HIV-infected individuals is much higher as the CD4 cell count declines. There is evidence that the CD4 cell count is a strong predictor of the subsequent risk of AIDS or death in HIV-infected patients. There is limited information regarding the application of statistical models to predict AIDS diseases progression using longitudinal CD4 counts. This study applied a semi-markov process to predict AIDS disease progression and death using longitudinal CD4 count measurements. A five-year retrospective study was conducted in Jimma University Specialized Hospital, Southwest Ethiopia. A total of 456 HIV-infected adult patients were enrolled in this study from 2005 to 2010. CD4 cell counts were measured every 6 months among HIV-infected study participants using FACS Count Machine (Becton Dickinson, San Jose, California, USA). CD4 count was classified as: state I (CD4 > 500 cells/mm^3), state II (350 cells/mm^3 < CD4 < 500 cells/mm^3), state III (200 cells/mm^3 < CD4 < 350 cells/mm^3) and state IV (CD4 <=200cells/mm^3) in order to estimate the transition probabilities from one state to another using a semi-markov chain concept. The last absorbing state is 'death'. Discrete Time Homogeneous Semi Markov (DTHSM) model was used to predict the evolution of CD4 count in time. The number of death observed from the state I, II, III, and IV was 3, 4, 15, and 40 respectively during the study period. The probability of dying was increased from the worse transition states. The probability of being found in state I after started the treatment at any other working state is higher. Reliability plot revealed that the probability of surviving 200 month, from state I, state II, state III and state IV, estimated as 0.71, 0.68, 0.63 and 0.58 respectively. The probability of remaining at the starting CD4 count state was decreased when time increased, patients from the state I has higher probability to remain in the ART starting state. The survival probability of a patient depends on the seriousness of a disease that measured by CD4 cell count. Attention should be given for patients with lower CD4 count to reduce mortality. Including risk factors which accelerate or deaccelerate the transition of patients in different state should be considered in the future researches.

Keywords: ART, CD4, HIV/AIDS, Semi-markov, Stochastic.

1. INTRODUCTION

The Human Immunodeficiency Virus (HIV) causes Acquired Immunodeficiency Syndrome (AIDS) by reducing a person's ability to fight infection. HIV attacks an immune cell called the CD4 cell which is the number of CD4 cells per microliter (µl) of blood. CD4 count is used to stage the patient's disease, determine the risk of opportunistic illnesses, assess prognosis, and guide decisions about the urgency of starting antiretroviral therapy (ART) [1]. Moreover, it is important biomarker in providing information about the progression of AIDS disease among HIV/AIDS

infected people who are following the ART treatment [2].

CD4 count often measured repeatedly over follow-up period in the ART treatment services [3]. The available data on such markers are usually characterized by unequal numbers of unevenly spaced observations for each individual [4]. Hence, describing the evolution of CD4 cell counts over time for patients on ART follow-up treatment useful to show the progression of AIDS disease.

Enormous mathematical models have been developed to describe the immunological marker response since HIV introduced for the first time. From the literature, many researchers have employed deterministic models to study HIV/AIDS disease progression using the CD4 count measurements, ignoring the stochastic effect and concept [2]. Some of studies conducted longitudinal analysis in modelling CD4 count, in Sub-Saharan Africa. A recent study reported that the pattern of increment in CD4 count is linear [5]. Other study in Ethiopia established that children CD4 count was increased when time increased after they started the ART treatment. However, observing the evolution of CD4 count in time by categorizing in different stage (state) is lacking [6]. Hence, this study aimed to predict the evolution of CD4 count in time using a stochastic model, discrete time semi-markov chain model, on longitudinal data from south west Ethiopia.

2. MATERIALS AND METHODS

2.1 Study design and settings

A five-year retrospective cohort study was conducted at Jimma University Specialized Hospital (JUSH), Southwest Ethiopia from 2005 to 2010. JUSH is found in Jimma town, which is 350 KM away from Addis Ababa in the Southwest direction. JUSH is one of the oldest public hospitals in the country. It was established in 1930 E.C during the Italian occupation for the service of their soldiers. It became the only teaching and referral hospital in the South western part of the country. It provides services for approximately 9,000 inpatient and 80,000 outpatient attendances in a year.

2.2 Data

Data were collected from ART electronic data base and from the review of patient charts. Data were collected by a dedicated nurse who works at the ART clinic of JUSH under supervision of principal investigators. CD4 cell count of patients was recorded longitudinally, each patient CD4 count was observed during the study period. The study was aimed to identify also the determinant factors to AIDS related death during the ART follow-up. The predictive factors are reported for other paper. However, to apply the semi-markov application, we are only used the CD4 count measurements from the data set. Successive CD4 count measurements had been with at least 6 months interval. Then the CD4 count of patients was classified as the following based on the worse of the disease: state I (CD4 > 500 cells/mm^3), state II (350 – 500 cells/mm^3), state III (200 – 350 cells/mm3) and state IV (< 201 cells/mm3). There is additional state which is 'death'.

2.3 Stochastic model

In this study, homogeneous semi-markov stochastic model was adopted for predicting the progression of AIDS disease using longitudinal CD4 count measurements.

Semi-markov supposes that the probability of a patient goes to from one state to another is not depend on the past states where a patient was, but depends on the current state. Moreover, probability that a patient jump from one state to another is depends on the elapsed time in the current state. This model resulted the probability of remaining or leaving the current state, survival probability and death rate probability at time t later. The working states (state I, II, III and IV) and bad (absorbing) state (death) transition was plotted in Figure 1.

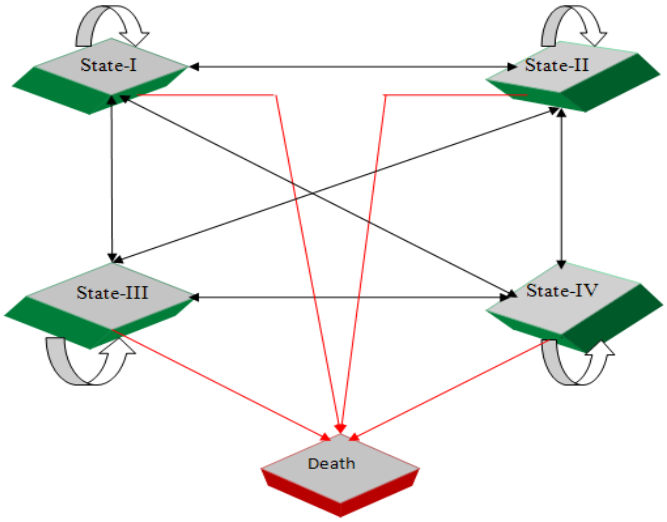


Figure 1: The CD4 count measurement classified states transition including the absorbing state 'death'

2.4 Discrete Time Homogeneous Semi-Markov Process (DTHSMP)

Let *I={1,2,……,m}* be the state space and let *{Ω,Є,P}* be a probability space. Let us define two random variables:

$J_n : \Omega \rightarrow E \qquad T_n : \Omega \rightarrow N$

Where:

J_n, $n \in N$ represents the state at the n^{th} transition

T_n $n \in N$ represents the time of the n^{th} transition

we supose that $T_0=0$ and $0 < T_1 < T_2 <.....< T_n < T_{n+1}$ <……

The process (J_n, T_n) is a discrete time homogeneous Markov renewal process. The associated homogeneous semi-Markov Kerbel Q is defined by [7]:

$$Q = [Q_{ij}(t) = [P(J_{n+1} = j, T_{n+1} - T_n \leq t | J_n = i)] \quad i, j \epsilon I, t \epsilon N$$

The transition matrix of the embedded Markov chain of the process **P** is defined as:

$$P = [P_{ij}] = \left[\lim_{t \to \infty} Q_{ij}(t)\right]; \quad i, j \epsilon I, t \in N$$

The probability that the process will leave the state *i* before or at a time *t* is:

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

$$H_i(t) = \sum_{j=1}^{m} Q_{ij}(t)$$

Matrix B is defined as follows

$$B = [B_{ij}(t)] = [P(J_n = j, T_{n+1} - T_n = t | J_n = i)]$$

$$B_{ij} = \begin{cases} Q_{ij}(0) = 0 & if\ t = 0 \\ Q_{ij}(t) - Q_{ij}(t-1) & if\ t = 1,2, \ldots \ldots, \end{cases}$$

The discrete time conditional distribution functions of the waiting times given the present and the next states while the state successively occupied, are given by:

$$F = F_{ij}(t)] = [P(T_{n+1} - T_n \leq t \,|\, J_n = i, J_{n+1} = j]$$

The related probabilities can be obtained by means of the following formula:

$$F_{ij}(t) = \begin{cases} Q_{ij}(t) \Big/ P_{ij} & if\ P_{ij} \neq 0 \\ U_1(t) & if\ P_{ij} = 0 \end{cases}$$

Where $U_1(t) = 1, \forall t$

The chain $X = (X_n)$ $n \in N$ is the sojourn time (Figure 2) in state J_{n-1} before the n^{th} jump. Thus, for all $n \in N$, we have $X_n = T_n - T_{n-1}$.

Now, we can introduce the discrete time semi-Markov process Z= (Z (t), t ∈ N) where $Z(t) = J_{N(t)}$, $N(t) = \max\{n:T_n \leq t\}$ representing the state occupied by the Process at time t.

For i,j=1,2,……,m, the discrete time homogeneous semi-Markov (DTHSMP) transition probability are defined in the following way:

$$\phi_{ij}(t) = P(Z_t = j | Z_0 = i)$$

They are obtained by solving the following evolution equations [7]:

$$\phi_{ij}(t) = \delta_{ij}(1 - H_i(t)) + \sum_{\beta=1}^{m} \sum_{v=1}^{t} b_{i\beta}(v) \phi_{\beta j}(t - v)$$

Where, δ_{ij} represents the Kronecker symbol, $\phi_{ij}(t)$ represents the probability that a system is in the state i will be in the state j after a time t. The algorithm to solve the evolution equation and homogenous semi-markov chain is found in detail [7].

2.5 Ethical considerations

Ethical approval was obtained from ethic committee of Jimma University, college of Health Sciences, Ethiopia. Letter of permission to collect data was obtained from JUSH administration office. Any information regarding study subjects had a number on it instead of their name and kept confidential.

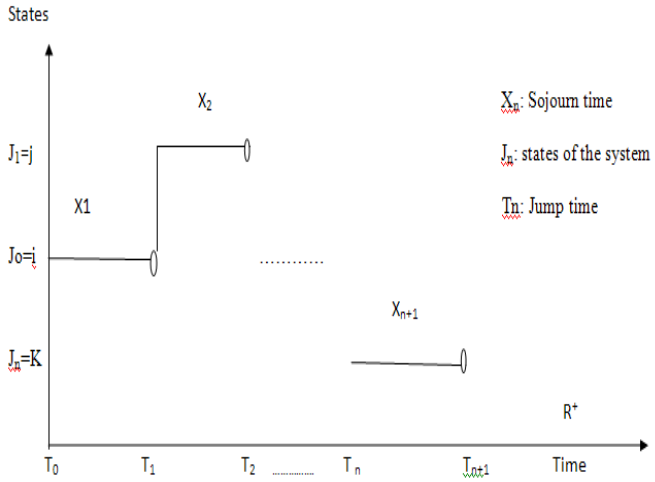


Figure 2: A Typical Sample Path of Semi-Markov Process.

3. RESULTS AND DISCUSSION

Of 456 individuals, 312 (68.4) are female and 144 (31.6%) are male. During the study period 66 (14.5%) of individuals are died due to HIV/AIDS related death. The baseline CD4 count showed that 200 (69.3) of individuals had less than 200cells/mm^{3}CD4 count. The median age of adults at the ART initiation in JUSH was 30 years (Inter quartile range: 23-37 years). The estimated mean survival time was 53.9 month (95% CI: 52 - 55.7) during the study period. This study has taken a CD4 count of adult patients which was measured for at least 6 times during the study period. In the followed up period, the number of death observed from the state I, II, III, and IV was 3, 4, 15, and 40 respectively. The number of death from state IV that the patient CD4 count declined below 200 cells/mm^3, was high compared to others (Table 1). The transition frequency matrix of the embedded Markov chain formed by the possible states of the process is shown in Table 1. The estimated death from the state I, II, III, and IV was 2.3%, 2.2%, 5.5 % and 8.9% respectively (Table 2). Estimates of the transition probabilities from state I, II and III to state IV is shown 5.5%, 8% and 6.7% respectively. Patients showed improvement from state IV to III, state III to IV and state II to I were 22%, 18.8% and 21% respectively.

The probability of adult HIV positive patient to be in state j after time t from state *i* at time 0 presented in Table 3. Of patients who were started ART on state IV, 26% transited on state III, 29 % transited on state II, 26% transited on state I, 7% dead and 23% of them remained in state IV, after 2 years. The probability of the patient entering to worst next state was increasing while the probability to remain in the starting state is decrease. After 5 years, the probability of death from sate I, II, III, and IV estimated as 0.05, 0.068, 0.107 and 0.17 respectively.

Table 1: Transition Frequency Matrix for HIV Positive Adult Patients at Jimma University Specialized Hospital ART center (Year: 2005-2010).

State	S-I	S-II	S-III	S-IV	Death
S-I	96	12	10	7	3
S-II	37	104	17	14	4
S-III	66	51	120	18	15
S-IV	50	75	100	184	40

Table 2: Estimates of the Transition Probability Matrix of the Embedded Markov Chain (At JUSH ART center, during 2005-2010)

State	S-I	S-II	S-III	S-IV	Death
S-I	0.7500	0.2000	0.0781	0.0547	0.0234
S-II	0.2102	0.5909	0.0966	0.0795	0.0227
S-III	0.2444	0.1889	0.4444	0.0667	0.0556
S-IV	0.1114	0.1670	0.2227	0.4098	0.0891

Table 3: The Solution of the Evolution Equation for Month t

	Estimates			
Transition	month = 24	month = 48	month = 60	month=84
1 → 1	0.67785	0.62422	0.59853	0.54769
1 → 2	0.21692	0.22997	0.23532	0.24456
1 → 3	0.06139	0.07028	0.07374	0.07914
1 → 4	0.03091	0.03928	0.04175	0.04503
1 → Death	0.01292	0.03624	0.05064	0.08357
2 → 1	0.23391	0.37208	0.41068	0.44697
2 → 2	0.60582	0.42689	0.37315	0.30653
2 → 3	0.08674	0.09806	0.09663	0.09097
2 → 4	0.05553	0.05290	0.05084	0.04722
2 → Death	0.05005	0.05005	0.06867	0.10828
3 → 1	0.33028	0.41186	0.43009	0.43957
3 → 2	0.29592	0.28531	0.27221	0.24953
3 → 3	0.28189	0.16875	0.14228	0.11278
3 → 4	0.05614	0.05099	0.04837	0.04456
3 → Death	0.03575	0.14237	0.10703	0.15355
4→ 1	0.25755	0.34847	0.37217	0.39114
4 → 2	0.28991	0.27764	0.26272	0.23632
4 → 3	0.14500	0.11516	0.10392	0.08868
4 → 4	0.23526	0.11635	0.08893	0.06015
4 → Death	0.07226	0.14237	0.17225	0.22369

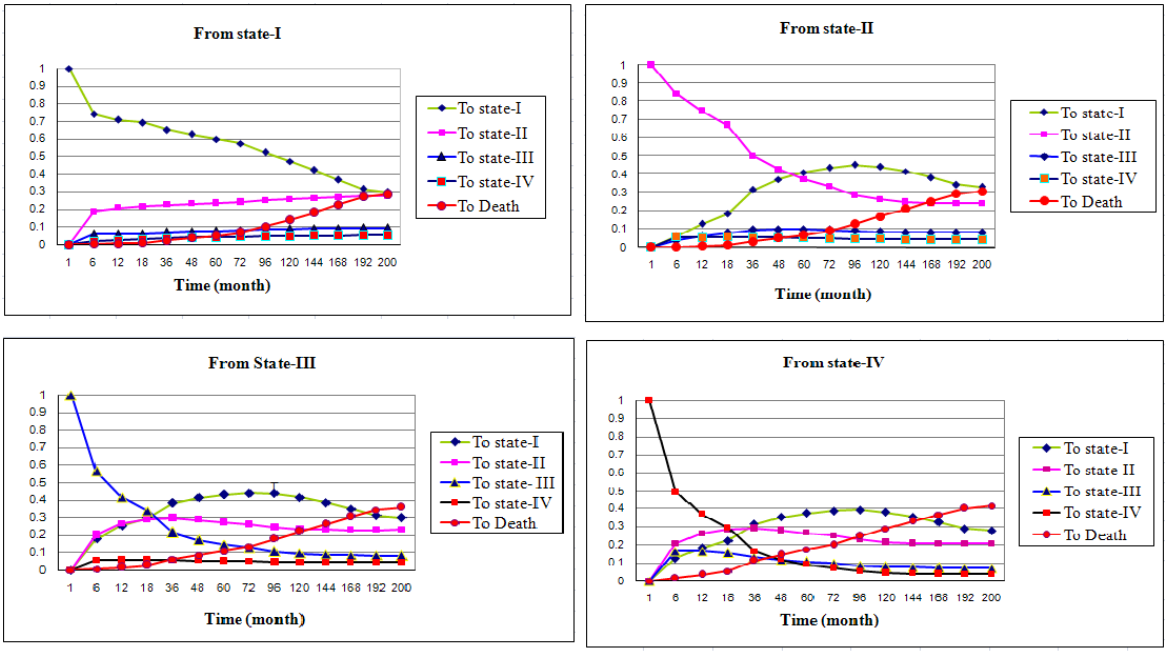
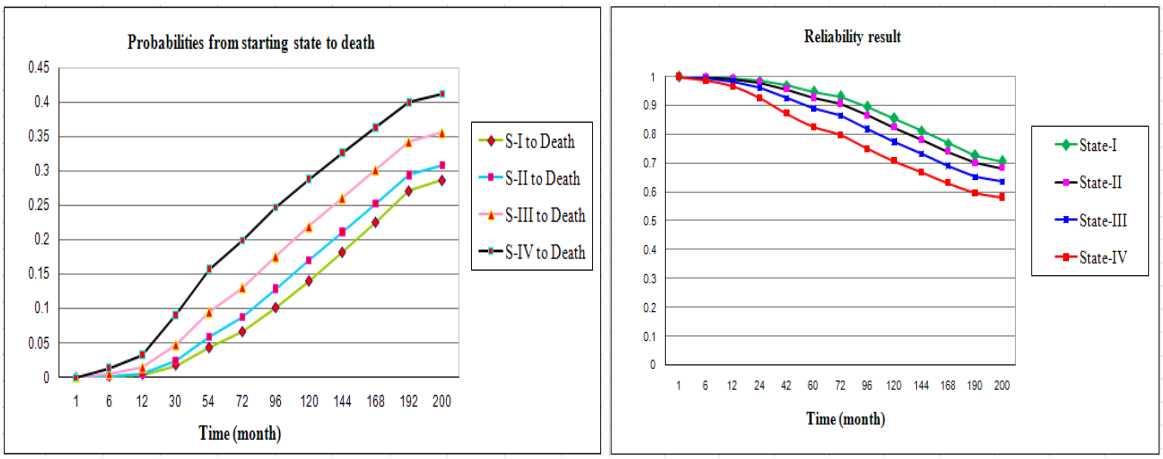


Figure 3: Conditional probabilities from one transit to any given state.

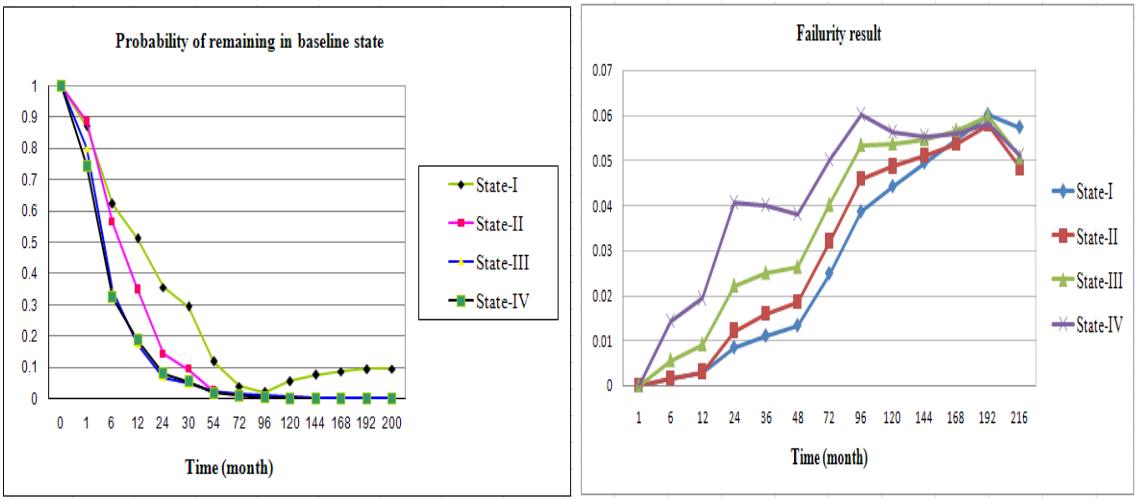


A B

Figure 4: Conditional Probability: A) conditional probability of a patient going to death time t later, from starting stage $j \in \{I, II, III, IV\}$ at time zero. B) Probability of a patient survival up to month t from stage $i \in \{I, II, III, IV\}$ at time zero.

The probability that a patient starting from stage $i \in \{I, II, III, IV\}$ at time 0 will do a transition after month t to stage $j \in \{I, II, III, IV\}$ is plotted in Figure 3. The probability of remaining in its stage is high compared to others till 168 months. The conditional probability that a patient who was started ART in state IV will die 200 months later was computed as 0.4. Moreover, state I seem transient state for a patient who started with any working state. In other word, the probability of turn to state I from other state was high compared to other transient state.

The conditional probability that the death of a patient occurs time t later, given that a patient started the ART treatment with any working state was plotted in Figure 4A. The probability of death among patients who were started the ART in state 4 was higher. The reliability result presents the probability that a patient has survived without death in the period [0, t]. The reliability result is plotted in Figure 4B. The curve represents the survival probability of patients who were started the treatment at any state. The conditional probability patients survive until 120 months, given that a patient from stage I, stage II, stage III and stage IV at time zero, estimated as 0.85, 0.82, 0.77 and 0.71 respectively.



A B

Figure 5: A) Probability of remaining in the starting stage up to month t, B) The conditional probability that the failure of the patient occurs at month k, given that the patient has survived until specified previous month.

The probability that a patient will remain in the starting state for t months was shown in Figure 5A. The conditional probability that the death of the patient occurs at time k, given that the patient has survived until the fixed time C (C < K) was plotted in Figure 5B. As we have seen in the graph, the probabilities of death increased when time increased in the study population. And, the worse sate has higher probability than the preceded better state throughout time. The conditional probability that the death of a patient at six years, given that a patient survived up to four years, for state I, state II, state III and state IV, estimated as 0.024, 0.032, 0.04 and 0.05 respectively.

The HIV/AID evolution model considered in this study relates to a 'macroscopic' view of the disease process and it is based on the CD4 cell count measurement. In this study we considered that an infected patient can move among the following immunological states related to CD4 cell counts: state I (CD4 > 500 cells/mm^3), state II (350 – 500 cells/mm^3), state III (200 – 350 cells/mm3) and state IV (< 201 cells/mm3). And, patient death was considered as an absorbing state. Patient started the treatment at different CD4 count state, and, six measurements which was done with at least 6 month interval was considered for this analysis.

The semi-markov model is a useful tool to predict the clinical progression of a disease [8]. It computes mainly the probability of a patient being into one of the possible stages of the disease for a certain time, and the probability that the patient might survive for a time t [6]. The most important property of semi-markov processes is that they enable us to consider not only the randomness in the different states in which the infection can evolve into but also the randomness of the time spent in each state.

To investigate the evolution of HIV/AIDS in the cohort, 979 CD4 count observations were included. Of total observations, 3, 4, 15 and 40 deaths were occurred from patients who were started the ART treatment at the state I, II, III and IV, respectively. Comparable study in Italy [7], data refer to subjects selected from a series of 766 HIV positive people who were under follow-up for ART for 87 month, 6 patients death from stage I, 8 patients death from stage II, 31 patients accounted from each stage III and stage II.

In the cohort patients passed away from the state I, II, III, and IV during the study period were 2.3%, 2.2%, 5.5 % and 8.9% respectively. Higher death was reported among patients who were in the worst CD4 state at the start of the ART. High mortality among patients with lower CD4 count has been associated with immune reconstitution inflammatory syndrome and WHO clinical stage IV [9]. However, the probability of being in state I was higher among patients who were strted relatively at the worse state. This may be due to the treatment of ART. Effective treatment with antiretroviral (ARV) drugs can control the virus so that people with HIV can enjoy healthy and productive lives [10].

In this study the reliability result of a discrete-time semi-Markov process at time t shows the probability that a patient will survive without death in the period [0, t]. This result resemble survivorship function which calculates the probability of a subject be alive after a time period t but a little difference in the interpretation [12-13]. The conditional probability that no death within 120 month, given that a patient from stage I, stage II, stage III and stage IV at time zero, estimated as 0.85, 0.82, 0.77 and 0.71 respectively. Comparable result in Ethiopia (Zelalem, 2010) found that the conditional probability that no death within month 120, given that a patient from stage IV at time zero is 0.85. Patients who were started the ART treatment at better CD4 count state had a better survival experience. And, our study established also higher death probability was related to lower CD4 count in the study population. Patients who were starting ART in state IV has turned to state I after 5 years with probability 0.372 while the probability of a patient arrives in state IV from state I was 0.04. This means when time is gone

patients goes to a better state while they are under the follow-up of ART treatment. This study has a limitation: the future studies should incorporate covariates to explore the covariates which either accelerate or decelerate the transition of patients.

4. CONCLUSION

Discrete time semi-markov chain could explore the transition probability of patients in different CD4 count measurements. Having lower CD4 count at the start of the ART treatment resulted higher probability of death. To increase probability of survival patients are recommended to start the treatment at a better CD4 count, actual reduction of death probability could be achieved through timely ART treatment initiation.

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