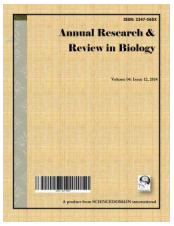

Annual Research & Review in Biology

31(3): 1-9, 2019; Article no.ARRB.34189
ISSN: 2347-565X, NLM ID: 101632869

Conditional Probabilities of AIDS Disease Transitions Using Semi-Markov Models

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Authors' contributions

This work was carried out in collaboration between both authors. The whole team jointly designed the study and developed the protocols. Author TFA wrote the first draft of the manuscript, while authors ATG reviewed the manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/ARRB/2019/v31i330049
Editor(s):
(1) Dr. David E. Martin, Martin Pharma Consulting, LLC, Shawnee, OK, USA.
(2) Dr. George Perry, Dean and Professor of Biology, University of Texas at San Antonio, USA.
Reviewers:
(1) Dr. Grienggrai Rajchakit, Maejo University, Thailand.
(2) Dr. Michael Rebhan, Novartis Institutes for Biomedical Research, Switzerland.
Complete Peer review History: http://www.sdiarticle3.com/review-history/34189

Original Research Article

Received 30 October 2017
Accepted 25 January 2018
Published 28 March 2019

ABSTRACT

Analyzing progression of diseases is vital to monitor patient's traversal over time through a disease. Clinical study settings present modeling challenges, as patients' disease trajectories are only partially observed, and patients' disease statuses are only assessed at clinic visit times. HIV disease is a continuum of progressive damage to the immune system from the time of infection to the manifestation of severe immunologic damage. We proposed a semi-Markov model and collected data at Yirgalem General Hospital. Our study found that for an HIV/AIDS patient the transition probability from a given state to the next worse state increases within the good states as time gets optimum and then decreases with increasing time during a follow up. In a specific state of the disease a patient will stay in that state with a non- zero probability in good states and a patient will transit to the next state either to the worst or to the good state with a non-zero probability. The probability of being in same state decreases over time. With the good or alive states, the probability of being in a better state is non-zero, but less than the probability of being in worst states. The survival probabilities are decreasing with increasing time. Therefore, we recommend that increased

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clinical care for patients on ART services should be strengthen and patients need to regularly check their CD4 T cell count in the appropriate day based on physician order to timely know and monitor their disease status to improve the survival probability and to reduce mortality.

Keywords: Immunology; HIV/AIDS; conditional probability; progression; Semi Markov.

1. INTRODUCTION

In the literature, most HIV/AIDS related studies focus on estimating HIV/AIDS epidemic, HIV infection, prevalence and incidence rates from a group of communities on hospital based data. Analyzing and presenting AIDS progression and estimating transition probability is vital for clinical care of patient's, for treatment management, decision making and monitoring patient traversal over time. It is also important to connect health state models with clinical care of patients by generating data on disease progression. This will enable physicians to administer and optimize the level of the therapies to patients.

Disease progression describes a change in disease status over time as function of disease process and treatment effects. During the past decades, epidemiologists have shown interest on Markov models for describing disease transmissions and progressions. In medicine, decision-making processes are increasingly relying on modeling technique to quantify a decision based on quantitative evidence. Markov models are used to blend the available evidence by describing the disease trajectories and treatment progress, as well as associated factors such as the treatment's effects on a patient's quality of life and the costs of therapy.

Disease progression models are represented by graphs. Nowadays, many different approaches have been developed to quantify the progression. Many diseases show different stages over time. These stages of diseases can be designated numerically to represent the disease process characterized as change of the status. This change can be described by mathematical expressions that best describe the evolution of the processes. The most preferable models used to express this evolution are transition probability models.

Transition probabilities between states of disease severity are mainly inferred indirectly from cross-sectional observations of prevalence of AIDS related data using the usual alive and death states but AIDS disease severities range beyond the two states (alive and death). In the literature, HIV/AIDS sicknesses are identified to four states, based on CD4 T cell counts of a patient and the final absorbing state (death) [1]. This paper uses these models to estimate the conditional probability of disease progression. We hope that this paper will help the consciousness of the importance of multi-state Markov models for HIV/AIDS disease progression. In this study, we define the states of the disease as a finite discrete state.

Goshu and Dessie in [2] studied HIV/AIDS disease progression and define the states of the disease as finite discrete states. Weltan in [3] described how states can be used from partially observed data and takes a Bayesian approach to estimate Markov transition rate and probability parameters. Semi-Markov and hidden semi-Markov models for disease progression are dealt with numerous researchers during the past decades. Other studies on AIDS disease progressions included in many researchers [4-9] and [10]. Comprehensive introductions in semi-Markov models are given by D'Amico et al. [11] while Levy [12] introduced the semi-Markovian process briefly. Semi-Markov models for disease progressions has been studied in recent decades by Goshu and Dessie [2] and Dessie [13].

Nowadays, Markov models are frequently used to assess disease progression. The parameters in Markov model can be estimated by observing the time it takes to stay in any state before making a transition to another state. However, in clinical recorded data only shows the starting state and the end state some years later as [3] described.

In medical sciences, researchers recognize a pattern of AIDS disease from the histories of disease markers and symptoms observed. Unrecognizing its past disease stages and future adverse events may increase the patient's risk of dying from the particular disease. Depending on the evaluation type, transition probabilities and type of treatment therapies should take into account the trend and the variability of the disease stages. It is necessary to assess the pattern of HIV/AIDS disease progression, the evaluation of disease stages and transition

probabilities of different follow-up times to improve quality of life of patients and reduce cost of therapies. Therefore, the main aim of this study is to apply appropriate statistical methods to monitor HIV/AIDS disease progression and exploiting the available complex information that enhance patients living and health conditions.

2. STATISTICAL MODEL AND DATA

2.1 Description of the HIV/AIDS Patient's Data

The data for this study were obtained from Yirgalem General Hospital. Yirgalem General Hospital is located 300 km South of Addis Ababa at Yirgalem town of Sidama zone, the Southern Nation's Nationalities Peoples Region. There are HIV-exposed patients under the ART follow-up at the hospital between 2006 and 2015. We adopted a simple random sampling procedure to collect the data. The following sample size determination formula of Cochran [14] is used:

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

where $Z_{a/2}$ is the value of a standardized normally distributed variable at which the upper area under the curve is a/2, where a is significance level. For a= 0.05, $Z_{a/2}$ =1.96. The term p represents proportion of death among HIV/AIDS patients. The value of P used here is obtained from the previous comparable study conducted by Goshu and Dessie (2013) on data taken from Felege-Hiwot Referral Hospital which is p = 0.134. The degree of precision d selected for this study is taken to be 0.03. With total number of N = 1570 HIV/AIDS patients at the Yirgalem General Hospital, the sample size for this study is estimated to be 375 patients.

Referring to the [1] immunological classification of HIV/AIDS infected patients, we have five states, where the first four states are the good states (transient states) and the last state is bad state or death state or absorbing state. The states are defined as follows.

SI: CD4 T cells count $\leq$500 x 10^6 T cells/L
SII: 350 x$_{10^6}$ T cells/L $\leq$ CD4 T cells count < 500 x 10^6 T cells/L
SIII: 200 x 10^6 T cells/L $\leq$ CD4 T cells count < 350 x 10^6 T cells /L
SIV: CD4 T cells count $\leq$200 x 10^6 T cells/L
D: Death.

We assume the good states (state I, state II, state III and state IV) communicate with each other, and they also communicate with the absorbing state which is death.

2.2 Homogeneous Semi-Markov Process

A semi-Markov model is a statistical model with same structure as a Markov model except that the sojourn time distribution is flexible in semi-Markov. These models are useful tools to predict the clinical progression of a disease [15]. It is used for computing the probability of a patient being in one of the possible stages of the disease for a certain time and the probability that the subject might survive for a time t. The most important property of semi-Markov processes is they enable to consider both the randomness in different states in which the infection can evolve and the randomness of the time spent in each state.

A detailed theoretical description of the model is presented in 16. They have been applied in a number of scientific fields including, engineering applications (systems reliability), finance, insurance, actuarial and demographic sciences. Homogeneous semi-Markov process (HSMP) is defined based on two random variables running simultaneously.

$$X_n : \Omega \to S \; T_n : \Omega \to N+ \qquad (1)$$

Where X_n has state space S= $\{S_1, S_2, S_3, \ldots S_m\}$ represents the state at the nth transition. In the health care environment, the elements of **S** represent all the possible stages in which the disease may show level of seriousness and T_n with state space equal to N+ represents the time of the nth transition. In this way, we cannot only consider the randomness of the states but also the randomness of the time elapsed in each state as explained in Giuseppe et al. [15]. The kernel $Q = \lfloor Q_{ij} \rfloor$ associated with the process is defined as follows.

$$\begin{aligned} Q_{ij}(t) &= P(X_{n+1} = j, T_{n+1} - T_n \leq t \mid X_0, X_1, \ldots X_{n-1}, X_n = i, T_0, \ldots, T_n) \\ &= P(X_{n+1} = j, T_{n+1} - T_n \leq t \mid X_n = i) \end{aligned} \qquad (2)$$

$P_{ij} = \lim_{t\to\infty} Q_{ij}(t)$ is the transition matrix of the embedded Markov chain in the process.

Furthermore, it is necessary to introduce the probability that the process will leave state i in time t as

$$H_i(t) = P(T_{n+1} - T_n \le t \mid X_n = i) = \sum_{j=1}^{m} Q_{ij}(t)$$

It is now possible to define the distribution function of the waiting time in each state i given that the state subsequently occupied is known,

$$G_{ij}(t) = P(T_{n+1} - T_n \le t \mid X_n = i, X_{n+1} = j) \qquad (3)$$

The related probabilities can be:

$$G_{ij}(t) = \begin{cases} \dfrac{Q_{ij}(t)}{P_{ij}} & if\ P_{ij} \neq 0 \\ 1 & if\ P_{ij} = 0 \end{cases} \qquad (4)$$

Now it is possible to define homogenous semi-Markov process $Z = (Z, t \in n)$ representing the state occupied by the process. The transition probabilities are defined in the following way:

$$\phi_{ij} = \left(Z_{(t)} = j \mid Z_{(0)} = i\right) \qquad (5)$$

These are obtained by means of the following evolution equations:

$$\phi_{ij}^{h}(kh) = d_{ij}^{k}(kh) + \sum_{l=1}^{m}\sum_{\tau=1}^{k} V_{ij}^{\tau}(\tau h)\,\phi_{ij}^{K}((k-\tau)h) \qquad (6)$$

Where h represents the discretization step

$$d_{ij}^{k}(kh) = \begin{cases} 0 & if\ i \neq j \\ 1 - H_{ij}^{k}(kh) & if\ i = j \end{cases}$$

$$V_{ij}^{k}(kh) = \begin{cases} 0 & if\ k = 0 \\ \phi_{ij}^{k}(kh) - \phi_{ij}^{K}((k-\tau)h) & if\ K > 0 \end{cases}$$

If h= 1 the above evolution model can be rewritten as:

$$\phi_{ij}(k) = d_{ij}^{k}(k) + \sum_{l=1}^{m}\sum_{\tau=1}^{k} V_{ij}^{\tau}(\tau)\,\phi_{ij}^{K}(k-\tau) \qquad (7)$$

The long run proportion of time in state j is

$$\phi_j = \frac{j\phi_j}{\sum_i i\phi_i}$$

The proportion of time the process in state i and will next enter j is equal to $\frac{\phi_i \phi_j t_i}{\mu_i}$ where t_i conditional expected time and μ_i expected time in state i.

For solving the above evolution equation [17,20] proposed the following algorithm. Given m, T, **P**, and **G**, the algorithm numerically solves the linear systems for the unknown matrix Φ. The variables involved are the following.

m= number of states of the process.

T = number of periods to be examined for the transient analysis.

P = matrix of order m of the embedded Markov process.

G$^{\mathbf{T}}$= square lower-triangular block matrix of order T+1 whose blocks are of order m.

Q$^{\mathbf{T}}$= represents the kernel of the Markov process.

Φ^T = block vector of order T+1 the block of which are square matrices of order m.

D$^{\mathbf{T}}$ = block vector of order T+1 the block of which are the diagonal square matrix of order m.

V$^{\mathbf{T}}$= square lower-triangular block matrix of order T+1whose blocks are of order m.

S$^{\mathbf{T}}$= block vector of order T+1 the block of which are the diagonal square matrix of order m. The diagonal element of each block at time t is given by $s_{ii} = \sum_{j=1}^{m} Q_{ij}(t)$

The algorithm is:
The algorithm is:
(a) *Read m, T, P, G*
(b) *Construct* $\boldsymbol{Q}^T, \mathbf{V}^T, \boldsymbol{D}^T$

$V_{(0)} = I;\ Q_{(0)} = 0;\ S_{(0)} = I;\ D_{(0)} = I;$
$for\ t = 1\ to\ T$
$Q_{(t)} = P * G_{(t)}$
$for\ i = 1\ to\ m$
$s_{ii(t)} = Q_{i.}(t) \bullet 1$
$end\ \ for$
$V_{(t)} = Q_{(t)} - Q_{(t-1)}$
$D_{(t)} = D_{(0)} - S_{(t)}$
$end\ \ for$

(c) $Given\ \Phi_{(0)} = D_{(0)}$, $Solve\ for\ \Phi^{(T)}$
$for\ t = 1\ to\ T$
$\Phi_{(t)} = D_{(t)}$

$for\ s = 1\ \ to\ t$

$\Phi_{(t)} = \Phi_{(t)} + V_{(s)} \bullet \Phi_{(t-1)}$

$end\ \ for$

$end\ \ for$

(d) *Return the results*

Note: In the algorithm, the symbol • represents row column matrix product while * represents element by element product.

3. RESULTS

The primary aim of this study is to model the progression of HIV/AIDS and survival probability of a patient using semi-Markov models. Semi-Markov models explicitly define distributions of waiting times, giving an extension of continuous time and homogeneous Markov models based implicitly on exponential distributions. The data analyzed in this study were collected at Yirgalem General Hospital between September 2008 to August 2015, of fixed time points while the transition between the states of the diseased could occur at any time. Frequencies and estimated transition probabilities are summarized and displayed in Table 1.

Each patient was followed throughout the study period on the change in the status of the disease while using ART. Among 365 patients, 69 (18.904%) patients died. We observed a very high transition from state SII to state SI, which is 240 transitions and followed by 183 transitions from state SIII to state SII. The transition probabilities and mean waiting times can be of interest also when data on transitions and sojourn times are available. Estimation of transition probabilities as discussed here follows the same lines after obtaining estimates for Q and for its variance. The solution for the transition probabilities at time t using the algorithm are obtained with m=5 states, T=204 months, transition probability matrix P as given in transition frequency of Table 1.

First, we plotted the Conditional probability that a patient will be in state i at time t months given that she/he is currently in state j is depicted in Fig. 1. Fig. 1(a) expresses the progression from state SI to state SII, state SII to state SIII and state SIII to state SIV of a specific HIV/AIDS patient in these states of the disease using exponential waiting time distribution. This is the transition within the good states. In this figure we observed a parabolic curve with optimal/peak (45, 0.158) from state SI to state SII, (24,0.054) state SII to state SIII and (48,0.158) state SIII to state SIV in the time probability axis. These peaks indicate there is a time at which a patient at highest risk of being to progress to the next worst state. Moreover, the transition probability from state SII to state SIII is the lowest as compared to the others. This result shows out that, within the good states, the transition probability from a given state to the next immediate worst state increases with time gets optimum at a time and then decreases with increasing time while considering the exponential waiting time distribution.

In Fig. 1 (b) transition to the death states are computed. The estimated probability of dying before 204 months is 0.396 for a patient who is in the first stage, 0.404 for one who is in the second stage, 0.4298 for one who is in the third stage and 0.5057 for one who is in the fourth stage of the disease. The probability of dying will increase by 8.5 percent for a specific HIV/AIDS patient in state three compared to an HIV/AIDS patient in state one. Similarly, the probability of dying will increase by 27.7 percent for a specific HIV/AIDS patient in state four compared to an HIV/AIDS patient in state one. This can be interpreted as the probability that an HIV/AIDS patient with any one of the good states will be in death state is increasing with time.

Moreover, a patient who is in the fourth state has the highest probability of dying after any given t months, while that of one who is in the first state is the lowest probability throughout the time.

The conditional probability of a patient making changes in disease states given his/her current status is computed and displayed in Fig. 2. It shows the conditional probabilities of being in next state j after a month t given the starting state i.

Table 1. The transition probability matrix computed from the progression data

State	I	II	III	IV	D
I	171 (0.438462)	169 (0.433333)	32 (0.082051)	7 (0.017949)	11 (0.028205)
II	240 (0.495868)	76 (0.157025)	132 (0.272727)	22 (0.045455)	14 (0.028926)
III	59 (0.166667)	183 (0.516949)	52 (0.146893)	41 (0.115819)	19 (0.053672)
IV	12 (0.079470)	30 (0.198675)	77 (0.509934)	7 (0.046358)	25 (0.165563)

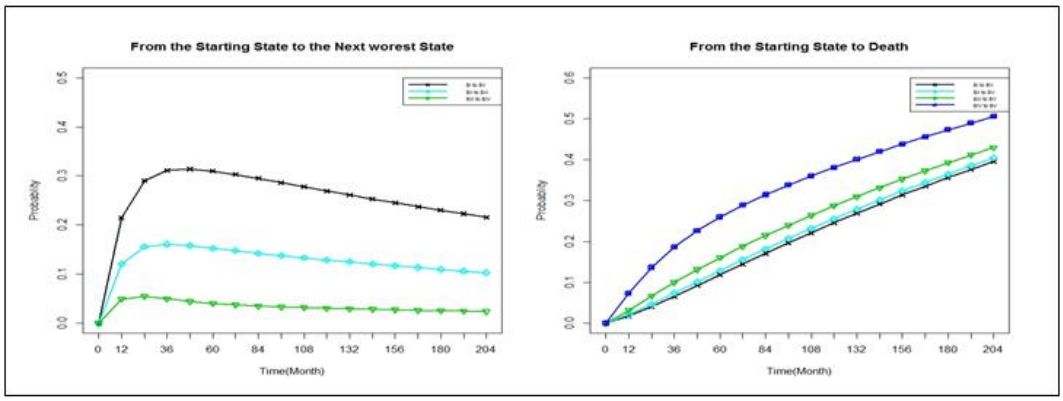

Fig. 1a. Conditional probability that a patient will be in state $j,\ j \in \{SII, SIII, SIV\}$ after t Months given that she/he is currently in state $i \in \{SI, SII, SII\}$

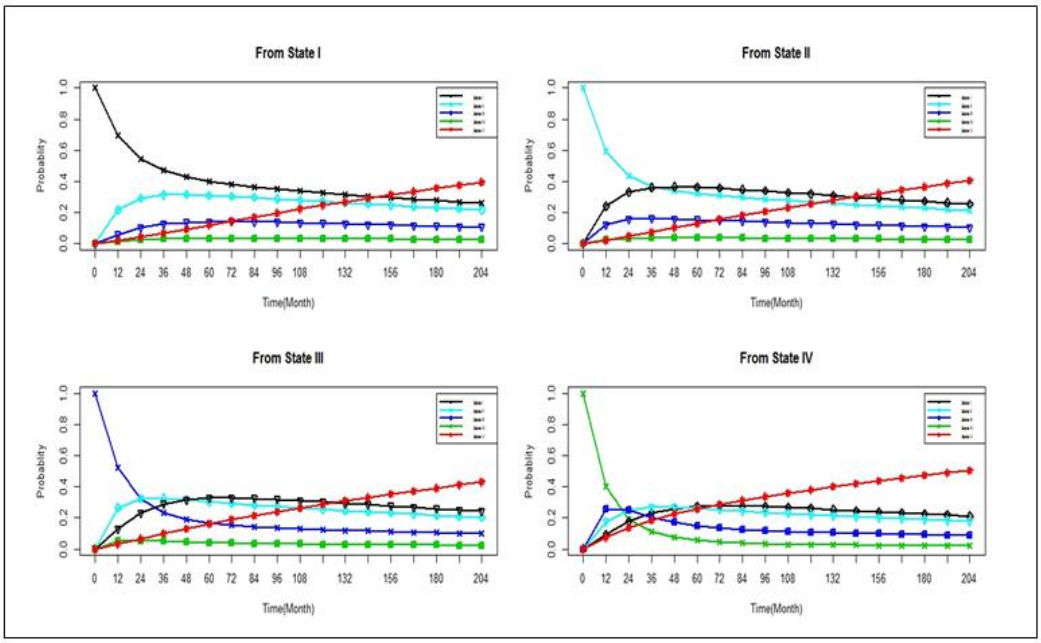

Fig. 2. The conditional probability of patient making changes in disease states given his/her current status using exponential waiting time distribution

The probability of a patient to stay in a given state for at least 24 months' decreases with increasing time. For instance, the probability of staying in state one for 24 months is 0.545 for state one, 0.433 for state two, 0.321 for state three and 0.187 for state four. In good states an HIV/AIDS patient in a specific state of the disease will stay in that state with a non-zero probability.

In Fig. 3 we computed the probability of staying in the same state. It is also interesting to find out that the conditional probability of staying in the same state until a given number of month decreases with increasing the time for both waiting time distributions. This shows patients change states with a non-zero probability after some time t given that he/she was at some state at time t initially. This result indicates that the probability of being in the same state for an HIV/AIDS patient in a specific state of the disease decreases over time. The results show that probability of being in a better state is non-zero for good states, but less than the probability of being in the next worst states.

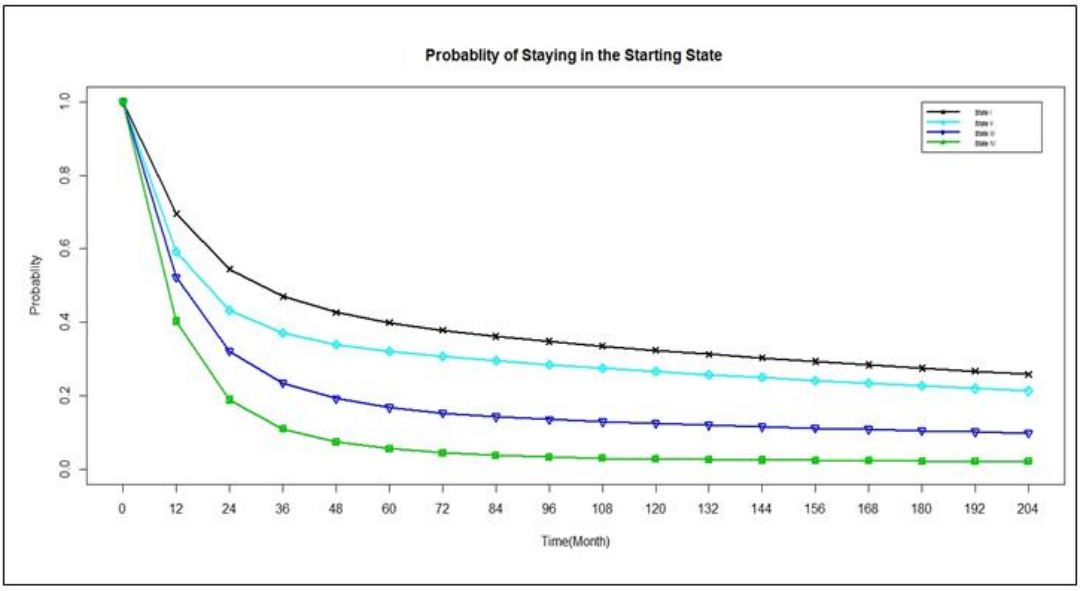

Fig. 3. The probability that a patient stays in some state of disease for at least t months through the study period

4. DISCUSSION

This study intended to model the progression of HIV/AIDS and survival probability of a patient using Semi-Markov Model. Accordingly, different probability plots produced from the observed data obtained from Yirgalem General Hospital during the follow-up year (between 2008 and 2015 follow up period) in every six months at known and fixed time points. In figure 2 (a)) we observed a parabolic curve with optimal/peak points in the time probability axis plotted using the exponential waiting time distribution. These results also agree with the results of several authors [2,13,18] and [19]. A study conducted by Masala et al. [9] adopted a non-homogeneous semi-Markov model for estimating interval transition probabilities for HIV/AIDS disease progression. These probabilities are fundamental in order to perform predictions concerning the clinical evolution of patients. Their findings suggested that a follow-up time is fundamental importance for the disease process. This result suggests that timely follow up of their disease states will enable patients to actively monitor their survival and will help physicians to for early diagnosis and appropriate individual therapy. The results support the idea of Goshu and Dessie [2] and Dinberu et al. [19].

Goshu and Dessie [2] in studied disease progression modeling using semi-Markov model from data collected from Felege-Hiwot referral hospital during 2005-2009. This finding are is in line with their studies in many ways. First, the pattern of disease progression is similar with our study in such a way that the probability of dying from an HIV/AIDS disease is 18.4 percent in the current cohort while it is about 13 percent in Goshu and Dessie [2]. Second, the conditional probability of moving to the next worse state has similar patterns with Goshu and Dessie [2] study. Third, we compute the conditional probability of being in next worst state after a month t given the starting state as similar with their studies. We see that there is similar pattern again while transiting into the next worst state. From this result, we observed that the probabilities are relatively higher for this study as compared to Goshu and Dessie [2]. This might be because of the increased access to modern therapies currently being investigated as compared with the time of their study. The results revealed that within the good states, the transition probability from a given state to the next worse state increases with time gets optimum at a time and then decreases with increasing time while considering exponential waiting time distribution. This might be because of the fact that patients will initially carefully follow their initial status and be able to effectively consider and consult their physicians follow up their ART this might decrease their probability to die and perhaps they might lose the follow up and this will intern

increase the probability of dying. The study conducted by Goshu as in Goshu and Dessie [2] has cited the probability that an HIV/AIDS patient with any one of the good states will be in death state is increasing with time. Moreover, a patient who is in the fourth state has the highest probability of dying after any given t months, while that of one who is in the first state is the lowest probability throughout the time as stated in Dessie [18]. This is because of the fact that as time in the follow up goes or increases the likelihood that the patient will survive decreases, as his/her CD4 cell counts decline over time because of the virus, affects the immunity of the patient and frequently enters to the next highest worst states and then to death.

In general, this study suggests that, the survival probability of an HIV/AIDS patient depends on his/her current state of the disease thus lowering the CD4 counts will highly increase the survival probability and decrease the risk of transitioning from the worse health state or death state, which is similar with what was noted in Goshu and Dessie [2] an Dessie [13]. Thus, this finding suggests increased clinical care for patients on ART should be strengthened and patients need to regularly check their CD4 count in the appropriate day based on physician order to timely know their disease stage to improve survival probability and reduce mortality.

5. CONCLUSIONS

This study intended to model the progression of HIV/AIDS and survival probability of a patient in Yirgalem General Hospital during 2008-2015. The data analyzed in this study was collected at Yirgalem General Hospital during September 2008 to August 2015 follow-up period in every six months at known and fixed time points but the transition between levels of the state space could occur at any time. The semi-Markov model is used to model the progression and the following conclusions are drawn from this study.

For an HIV/AIDS patient, the transition probability from a given state to the next worse state increases within the good states as time gets optimum then decreases with increasing the time during a follow up. For a specific patient in the study the probability of dying increases as patient's state changes to the next higher states. This is because as the patients state increases to the next higher/ bad state the CD4 count of the subsequent patient decrease. Thus, the immunity of the patient also fails. The study found that for an HIV/AIDS patient in a specific state of the disease the patient will stay in that state with a non- zero probability in good states, further indicates that a patient will transit to the next state either to the worst or to the good state with a non-zero probability. Thus, an HIV/AIDS patient in a specific state of the disease the probability of being in the same state decreases over time. With the good or alive states, the results show that probability of being in a better state is non-zero but less than the probability of being in worst states. The survival probabilities are all decreasing with increasing time. Thus, we recommend that increased clinical care for patients on ART should be strengthened and patients need to regularly check their CD4 count in the appropriate day based on physician order to timely know their disease stage to improve survival probability and reduce mortality.

ACKNOWLEDGMENTS

The authors would like to thank Yirgalem General Hospital administration for permitting us to use the data analyzed in this study. Our special appreciation goes to Hawassa and Arba Minch Universities for the financial supports for this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Centre for Disease Control (CDC). Revised Classification System for HIV Infection and Expanded Surveillance Case Dentition for AIDS among Adolescents and Adults, MMWR Recommendations and Reports. 1992;41(17):1-19.
2. Goshu AT, Dessie ZG. Modelling progression of HIV/AIDS disease stages using semi-Markov Processes. Journal of Data Science. 2013;11:269-280.
3. Welton NJ, Ades AE. Estimation of Markov chain transition probabilities and rates from fully and partially observed data. Uncertainty Propagation, Evidence Synthesis and Model Calibration. Medical Decision Making. 2003;25:633-645.
4. Joly P, Commenges D. A penalized likelihood approach for a progressive three state model with censored and truncated data. Application to AIDS. Biometrics. 1999;55:887-890.

5. Foucher Y, Mathieu E, Saint-Pierre P, Durand JF, Daures JP. A semi-Markov model based on generalized weibull distribution with an illustration for HIV disease. Biometrical Journal. 2005;47:825-833.
6. Mathieu E, Yohann F, Pierre D, Jean-Pierre D. Parametric and non homogeneous semi-markov process for HIV control. PNHSM Process for HIV Control; 2013.
7. Mandel M. Estimating disease progression using panel data. Biostatistics. 2010;10:1-13.
8. Fonteijn HM, Matthew JC, Marc M, Josephine B, Manja L, Sebastien O, Nick CF, Daniel C. An event-based disease progression model and its application to familial Alzheimer's disease. Springer-Verlag Berlin Heidelberg. 2011;6801:748-759.
9. Masala G, Cannas G, Micocci M. Survival probabilities for HIV infected patients through semi-Markov processes. Biometrical Letters. 2014;51(1):13 -36.
10. Titman AC, Sharples LD. Semi-Markov models with phase-type sojourn distributions: Biometrics 2010;66(3):742-752.
11. D'Amico G, Janssen J, Giuseppe D, Monica R. HIV progression through two different temporal scales. According to Non-Homogeneous Semi-Markov Models. Proceedings of the 13th International Conference on Applied Stochastic Models and Data Analysis. 2009;473-476.
12. Levy P. Processes semi-Markoviens. Proceedings of the International Congress of Mathematicians. The Netherlands. 1954;3:416-426.
13. Dessie ZG. Multi-state Models of HIV/AIDS by homogeneous semi-Markov process. American Journal of Biostatistics. 2014a;4:21-28.
14. Cochran WG. Sampling technique. John Wiley and Sons, New York; 1997.
15. Giuseppe D, D'Amico G, Girolamo A, Janssen J, Iacobelli S, Tinari N, Manca RA. Stochastic model for the HIV/AIDS dynamic progression. Mathematical Problems in Engineering. 2007;20:656-674.
16. Janssen J, Monica N. Numerical solution of non-homogenous semi-Markov processes in transient case. Methodology and Computing in Applied Probability. 2001;3:271-279.
17. Corradi G, Janssen R, Monica R. Numerical treatment of homogeneous semi-Markov processes in transient case a straight forward approach. Methodology and Computing in Applied Probability. 2004;6:233-246.
18. Dessie ZG. Modeling of HIV/AIDS dynamic evolution using non-homogeneous semi-Markov process. Springer Plus. 2014b;3(1):10-21.
19. Dinberu S, Sisay W, Kibrealem S, Mulualem T. Predicting AIDS Disease progression using longitudinal CD4 cell count among adult HIV/AIDS patients in Southwest Ethiopia. Application of semi-Markov Process. Int J Comput Bioinfo *in Silico* Model. 2016;5(2):808-814.
20. Janssen J, Manca R. Applied semi-Markov Processes. Springer, New York; 2006.

Peer-review history:
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