

MULTI-STATE MODELS OF HIV/AIDS BY HOMOGENEOUS SEMI-MARKOV PROCESS

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ABSTRACT

Multi-state stochastic models are useful tools for studying complex dynamics such as chronic diseases. The purpose of this study is to determine factors associated with the progression between different stages of the disease and to model the progression of HIV/AIDS disease of an individual patient under ART follow-up using semi-Markov processes. A sample of 1456 patients has been taken from a hospital record at Amhara Referral Hospitals, Amhara Region, Ethiopia, who have been under ART follow up from June 2006 to August 2013. The states of disease progression adopted in the multi-state model were defined based on of the following CD4 cell counts: ≥ 500 (SI); 200 to 499(SII); < 200 (SIII); and Death (D). The first three states are named as good. Female patients were 1.6 times more likely to move from state 2 to state 1 than those of male patients (adjusted HR = 1.60, CI = 1.02-2.49). Patients, who is not drug addicted, were 2.49 times more likely to move from state 3 to state 2 than those of drug addicted (adjusted HR = 2.67, CI = 1.52-4.68). Patients with tuberculosis were 2.67 times more likely to move from state 3 to state 4 than those with no tuberculosis (adjusted HR = 2.67, CI = 1.52-4.68). On the other hand, the probability of staying in same state until a given number of month decreases with increasing time. Multi-state modeling is a powerful approach for studying chronic diseases and estimating factors associated with transitions between each stage of progression. The major predictors of the intensity of transitions between different states of HIV/AIDS patients were gender, age, drug addicted and TB status. The dynamic nature of the AIDS progression is confirmed with particular findings that there is more likely to be in worse state than better one unless interventions are made.

Keywords: Disease Progression, Markov Chain, HIV/AIDS

1. INTRODUCTION

The rate of spread of the HIV/AIDS epidemic has reached a shocking level. The expansion of the epidemic has now become a burning issue globally and this is particularly so more important in developing countries. The disease being one without any cure is still account for economic, social and health crises in many developing countries. On a global scale, the HIV epidemic has stabilized, although with unacceptably high levels of new HIV infections and AIDS deaths. An estimated 34 million people worldwide were living with HIV in 2011 among which 23.5 million are living in sub-Saharan Africa. Ethiopia is one of the countries hardest

hit by HIV/AIDS epidemic. An estimated of 790,000 were living with HIV in 2011 (UNAIDS, 2013).

Most studies of AIDS have analyzed the factors associated with therapeutic failure, such as death, opportunistic disease, detect Viral Load (VL) or low levels of immunity, using semi parametric Cox models (Pradeep *et al.*, 2010; Muralidhar *et al.*, 2010; Keiser *et al.*, 2010; Koethe *et al.*, 2010; Neuhaus *et al.*, 2010). However, it is also important to consider chronicity and the relatively slow progression of the disease and to assess the multiple immune states resulting from the effect of the virus on the human immune system. The use of multi-state Markov models to analyze the factors associated with transitions between different states of

chronicity has been suggested for chronic diseases and the cost-effectiveness of various therapeutic regimes (Shih *et al.*, 2007; Pan *et al.*, 2007; Gil *et al.*, 2007).

Recent studies have shown that the predicted probability of patients that changing their status given his/her current status allows the measurements of medical scientific progresses due to the advances in the treatment of the HIV/AIDS (D'Amico *et al.*, 2009). Since the discovery of HIV/AIDS, numerous mathematical models Blasi and Manca (2004) have been developed to describe infectious disease transmission dynamics, understand the mechanisms of epidemic propagation, assess the impact of interventions on public health or forecast the future of epidemics. Among recent papers in biomedicine, Masala *et al.* (2014; Goshu and Dessie, 2013; Giuseppe *et al.*, 2007) analyzed HIV/AIDS dynamic evolution as defined by CD4 levels from a macroscopic point of view by means of homogeneous semi-Markov stochastic processes. Numerical analyses of the homogeneous semi-Markov process are dealt by Corradi *et al.* (2004; Janssen and Manca, 2001). Other more readings include (Davidov and Zelen, 2000; Viladent and Van Ackere, 2007; Satten and Sternberg, 1999; Baryarama *et al.*, 2005).

In this study, the author proposes homogeneous Markov process to study the evolution of HIV/AIDS. The homogeneous approach considered is a piecewise Markov process, with the transition intensity functions being step functions. The author is interested in determining factors associated with the progression between different stages of the disease. Several researchers have studied Markov processes with covariates and a procedure to obtain the parameters in a model with covariates has been reported (Maciulis *et al.*, 2009; Gentlemann *et al.*, 1985; Mathieu *et al.*, 2007; Pérez-Ocón *et al.*, 2001). The author also present the results of modelling of the waiting time of HIV/AIDS so as to predict the future waiting time of a patient. This is: The conditional probability of staying in the starting state until month t .

2. MATERIALS AND METHODS

2.1. Ethics Statement

This investigation was conducted according to the principles expressed in the Declaration of Bahir Dar University, Ethiopia. It was approved by the research ethics committee at the University of Bahir Dar and all participants who agreed to participate in this study signed a consent form.

2.2. Data and Model Descriptions

The target population for this study was patients under the follow up of ART at Amhara Referral Hospitals, Amhara Region, Ethiopia from June 2006 to August 2013. Multistage sampling was used to select study subjects. First, all the Referral Hospitals in the Amhara Region were stratified in to Western and Eastern area. The calculated sample size was proportionally allocated to Eastern ($n = 482$) and Western ($n = 874$) areas respectively. The sampling frame consists of 65000 HIV/AIDS patients who have visited the hospitals since the initiation of ART. The study may consider all HIV infected patients under ART whose age is ≥ 15 years regardless of their treatment category during the study period in Amhara Referral Hospitals, Amhara Region, Ethiopia.

The states of disease progression adopted in the multi-state model were defined based on the following CD4 cell counts as in Oliveira *et al.* (2013; Giuseppe *et al.*, 2007): ≥ 500 cells/mm³(SI); 350 to 499 cells/mm³(SII); <350 cells/mm³(SIII); and death(D). The death state is considered to be an absorbing state-meaning that once a patient is in the death state she/he will never be in the others states and rather stays there forever. The time elapse between state transitions was determined using the difference (in months) between the dates of CD4 tests.

In **Fig. 1** the graph model is pictured. It shows all the immunological states a HIV infected patient can go into. All the states apart from than Death are inter-related and also improvements are considered. It is also possible that an examination will show that the patient's state has not changed.

2.3. Modelling Semi-Markov Processes

2.3.1. The Transition-Specific Semi-Markov Model

A semi-Markov process is a stochastic process, $\{X(t): t \geq 0\}$, where an embedded Markov chain governs the state to state transitions of the process while a separate probabilistic mechanism determines the time spent in each state. It is assumed that the transition probabilities depend on the current state and the time spent in each state depends upon the current and next state. Several authors have discussed the use of Markov processes techniques in health. The author cites only some of them, i.e., (Jackson *et al.*, 2003; D'Amico *et al.*, 2005; Foucher *et al.*, 2005; Barbu and Limnios, 2009).

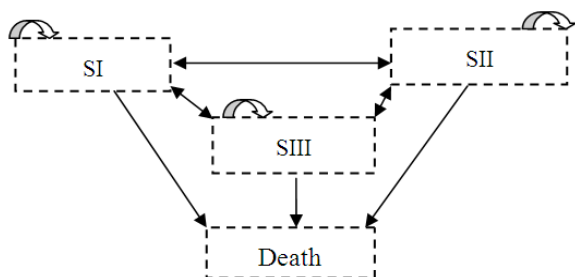


Fig. 1. Communication between the states of the process

In this part, Homogeneous Semi-Markov model are described by using the notation of Foucher *et al.* (2005).

On a complete probability space the author define two random variables. $X_n: \Omega \rightarrow S$ be the stochastic process with state space $S = \{S_1, S_2, \dots, S_m\}$ and $T_n: \Omega \rightarrow \mathcal{R}$ be the time of the n^{th} transition, with Ω domain of the process and \mathcal{R} set real numbers.

The kernel $Q = [Q_{ij}]$ associated with the process and the transition matrix P_{ij} of the embedded Markov chain is defined as follows Equation 1 and 2:

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

$$P_{ij} = \lim_{t \rightarrow \infty} Q_{ij}(t) \tag{2}$$

And it is necessary to introduce the probability that the process may leave state i in a time t as Equation 3:

$$H_i(t) = P[T_{n+1} - T_n \leq t | X_n = i] = \sum_{j=1}^m Q_{ij}(t) \tag{3}$$

Foucher *et al.* (2005) defines the density probability function, of the waiting time in state i before passing to state j as follow Equation 4:

$$f_{ij}(x, \theta_{ij}) = \lim_{h \rightarrow 0^+} \frac{P(x < T_{n+1} - T_n < x + h | X_{n+1} = j, X_n = i)}{h} \tag{4}$$

where, θ_{ij} is the parameter vector of the density probability function $f_{ij}(\cdot)$. The distribution and the value of parameters can vary between transitions. As usual in survival analysis, we deduce from $f_{ij}(x)$ the corresponding survival function and hazard function, respectively $S_{ij}(x)$ and $g_{ij}(x)$ Equation 5:

$$G_{ij}(x) = \lim_{h \rightarrow 0^+} \frac{P(x < T_{n+1} - T_n < x + h | T_{n+1} - T_n \geq x, X_{n+1} = j, X_n = i)}{h} \tag{5}$$

The hazard function of the semi-Markovian process corresponds to the probability of jumping towards state j , given that the process occupies state i for duration x Equation 6:

$$G_{ij}(x) = \frac{P_{ij} f_{ij}(x)}{S_i(x)} \text{ with } \begin{cases} i \neq j \\ i, j \in E \\ \lambda_{ii}(x) = -\sum_{j=i} \lambda_{ij}(x) \end{cases} \tag{6}$$

It is assumed that process spends some time in a given state and random time has distribution $G_{ij}(x)$, Weibull distribution: -The hazard function is defined as Equation 7:

$$G_{ij}(x) = \theta_{ij} \left(\frac{1}{\sigma_{ij}} \right)^{\theta_{ij}} x^{\theta_{ij}-1}, x \geq 0 \tag{7}$$

Foucher *et al.* (2005) also defines the hazard function with covariates as follow:-

$G_{ij}(x, z_{ij}) = G_{0,ij}(x) \exp(\beta_{ij}^T z_{ij})$, where $z_{ij} = (z_{ij}^1, z_{ij}^2, \dots, z_{ij}^{n_{ij}})$ the vector of n_{ij} covariates, specific to the transition $i \rightarrow j$. In the same paper, they proved that the Parameter estimations and likelihood methods Equation 8:

$$L = \prod_h \prod_{r=1}^m \{P_{X_{r-1}^h, X_r^h} f_{X_{r-1}^h, X_r^h}(T_h, r - T_{h, r-1}, Z_{X_{r-1}^h, X_r^h})\}^{\delta_{h,r}} \{S_{X_{r-1}^h}(T_h, r - T_{h, r-1}, Z_{X_{r-1}^h, X_r^h})\}^{1-\delta_{h,r}} \tag{8}$$

where, $\delta_{h,r}$ is equal to 1 if the transition r is observed for the individual h and 0 if censored.

2.3.2. Semi-Markov for Predicting the Probability of Waiting Time

After solving the evolution equations of the semi-Markov model, it is appropriate to give some concrete applications of these processes as models of evolution of the probability of waiting time of some system.

In this part, Numerical solution of the Homogeneous Semi-Markov model is described by using the notation of Giuseppe *et al.* (2007).

For any homogeneous semi-Markov process $\{X(t), t \geq 0\}$, the transition probabilities are given by (9) for which the solutions should be obtained using the progression (10):

$$\varphi_{ij}(t) = P[X(t) = j | X(0) = i] \tag{9}$$

$$\varphi_{ij}(t) = (1 - H_i(t))\delta_{ij} + \sum_{l=1}^m \int_0^t Q_{il}(\tau)\varphi_{ij}(t - \tau)d\tau \quad (10)$$

Here δ_{ij} represents the Kronecker delta. An approximate solution of (10) can be obtained using the general numerical integration formula given in Corradi *et al.* (2004). In the same paper, they proved that the numerical solution of the process converges to the discrete time HSMP described as an infinite countable linear system Equation 11:

$$\varphi_{ij}^h(kh) = d_{ij}^h(kh) + \sum_{l=1}^m \sum_{\tau=1}^k v_{ij}^h(\tau h)\varphi_{ij}^h((k - \tau)h) \quad (11)$$

where, h stands for the step measure of the approximation and:

$$d_{ij}^h(kh) = \begin{cases} 0 & \text{if } i \neq j \\ 1 - H_i^h(kh) & \text{if } i = j \end{cases} \quad (12)$$

$$v_{ij}^h(kh) = \begin{cases} 0 & \text{if } k \neq 0 \\ Q_{ij}^h(kh) - Q_{ij}^h((k - 1)h) & \text{if } i = j \end{cases}$$

In matrix form, Equation 12 becomes:

$$\Phi^h(kh) - \sum_{\tau=1}^k V(\tau h)\Phi^h((k - \tau)h) = D^h(kh) \quad (13)$$

The fact that the matrix $\Phi^h(kh)$ is stochastic is already proved in Corradi *et al.* (2004; Janssen and Manca, 2001). For solving the evolution Equation 13, Corradi *et al.* (2004) proposed the following algorithm with suggested matrix form Equation 14:

$$V^T \Phi^T = D^T \quad (14)$$

The variables involved are the following:

- m = number of states of SMP
- T = number of periods to be examined for the transient analysis of SMP
- P = matrix of order m of the embedded Markov chain in SMP
- G^T = square lower-triangular block matrix of order $T+1$ whose blocks are of order m
- Q^T = It represents the kernel of SMP
- Φ^T = block vector of order $T+1$ the block of which are square matrices of order m
- D^T = block vector of order $T+1$ the block of which are the diagonal square matrix of order m

- V^T = square lower-triangular block matrix of order $T+1$ whose blocks are of order m
- S^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 t are $s_{ii} = \sum_{j=1}^m Q_{ij}(t)$

Given an epoch T is fixed, matrices G^T and P , the algorithm solves the linear system (14) for the unknown matrix Φ^T by means of a purely iterative procedure. The algorithm is:

(0) Read the inputs: m, T, P, G^T

(1) Construct: Q^T, V^T, D^T

$$V_{(0)} = I; Q_{(0)} = 0; S_{(0)} = 0; D_{(0)} = I$$

for $t = 1$ to T

$$Q_{(t)} = P * G_{(t)}$$

for $i = 1$ to m

$$s_{ii}(t) = Q_{ij}^*(t) \bullet 1$$

end for

$$V_{(t)} = Q_{(t)} - Q_{(t-1)}$$

$$D_{(t)} = D_{(0)} - S_{(t)}$$

end for

(2) Given $\Phi_{(0)} = D_{(0)}$, solve for Φ^T

for $t = 1$ to T

$$\Phi_{(t)} = D_{(t)}$$

for $s = 1$ to t

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

end for

end for

(3) Print the results, Φ^T, Q^T

In the above (\bullet) represent the usual row column matrix product ($*$) stands for element by element product and ($\bullet 1$) is the m -component's sum vector.

In this study, a computer program for solving the evolution equations is developed in the R statistical software version 2.6.2.

3. RESULTS AND DISCUSSION

3.1. Descriptive Statistics

The study analyzed data obtained from 1456 AIDS patients during seven years of follow-up. Female represent about 58% of individuals and 42.5% of

transitions concerns patients over 40 years old. The proportion of a patients who is not drug addicted accounted a larger proportion in the sample (about 52.0%) compared to those of addicted patients (42.5%). The information presented above is summarized in **Table 1**.

3.2. Multivariate Analysis

According to univariate strategies, 10 factors out of 72 possible (6 covariates * 12 transitions), were selected. Finally, the multivariate model uses the 8 regression parameters given in **Table 2**. Women tend to move quickly from state 2 to state 1. More precisely, Female patients were 1.6 times more likely to move from state 2 to state 1 than those of male patients (adjusted HR = 1.60, CI = 1.02-2.49). Similarly, The hazard of moving from state 3 to state 2 for female patients is about 23% higher than for male patients (adjusted HR = 1.23, CI = 1.01-1.48). Patients, who is not drug addicted, were 2.49 times more likely to move from state 3 to state 2 than those of drug addicted (adjusted HR = 2.67, CI = 1.52-4.68). Patients with tuberculosis were 2.67 times more likely to move from state 3 to state 4 than those with no tuberculosis (adjusted HR = 2.67, CI = 1.52-4.68). Similarly, patients with tuberculosis were 2.28 times more likely to move from state 2 to state 4 than those with no tuberculosis (adjusted HR = 2.28, CI = 1.29-3.99). The hazard of moving from state 3 to state 4 for a patients less than 40 years of old were about 2% lower than those of a patient greater than 40 years old (adjusted HR = 0.98, CI = 0.97-0.99). **Table 2** reveals this in detail.

3.3. Results of Semi-Markov for Predicting the Probability of Waiting Time

Table 3 and Fig. 2 shows that the result of semi-Markov for predicting the probability of waiting time. The conditional probability that a patient stays in state one, two and three for at least 30 months are 0.167, 0.186 and 0.199 respectively. It is increasing with increasing seriousness of the disease. Within the good states, it is more likely for a patient to stay in a worse state than in a better one. Of course, the death state is an absorbing state, i.e., once a patient enters the death state he/she stays in same state forever. It is also interesting to find out that the conditional probability of staying in same state until a given number of month decreases with increasing time. So there is a possibility of changing from one state to another which is a non-zero probability. **Table 3 and Fig. 2** reveal this in detail.

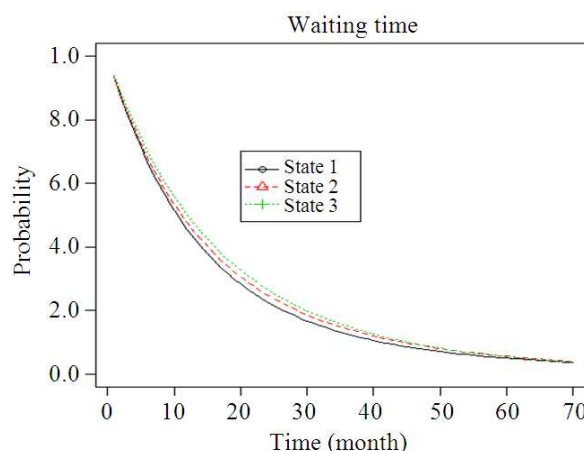


Fig. 2. The probability that a patient stays in same state of disease for at least t months

Table 1. Characteristics of 1456 patients diagnosed with AIDS under Antiretroviral Treatment (ART)

Variables	Frequency (%)
Sex [n (%)]	
Female	853(58.6)
Male	603(41.4)
Drug Addicted [n (%)]	
No	757(52.0)
Yes	619(42.5)
Age [n(%)]	
<40	922(63.3)
≥40	534(36.7)
Baseline Weight [n (%)]	
<60 kg	925(63.5)
≥60 kg	531(36.5)
TB Status [n (%)]	
Negative	1085(74.5)
Positive	371(25.5)
Baseline Immunological State [n (%)]	
SI: CD4≥500	348(23.9)
SII: (200<CD4<500)	549(37.7)
SIII: (CD4≤350)	559(38.4)
Transition between States [n (%)]	
1→1	152(10.4)
1→2	52(3.6)
1→3	116(8)
1→4	28(1.9)
2→1	206(14.1)
2→2	126(8.7)
2→3	167(11.5)
2→4	50(3.4)
3→1	97(6.7)
3→2	226(15.5)
3→3	157(10.8)
3→4	79(5.4)

Table 2. Multiple multi-state model in patients diagnosed with AIDS under ART, Amhara Referral Hospitals, Amhara Region, Ethiopia

Variables	Transition	Adjusted HR (95% CI for its HR)	Adjusted HR p-value
Sex			
Female Vs male*	2→1	1.60(1.02, 2.49)	0.040**
	3→2	1.23(1.01, 1.48)	0.047**
	3→4	0.54(0.34, 0.85)	0.008**
TB status			
Positive Vs negative*	3→4	2.67(1.52, 4.68)	0.001**
	2→4	2.28(1.29, 3.99)	0.004**
Drug addicted			
No Vs Yes*	3→2	2.49(1.48, 4.19)	0.001**
	3→4	0.96(0.97, 0.98)	0.019**
Age			
≤40 Vs >40*	3→4	0.98(0.97, 0.99)	0.000**

(*) Reference Category; (**) Hazard Ratio (HR) is a significant at $\alpha = 0.05$

Table 3. The probability that a patient stays in same state of disease for at least "T" months

States	T = 1	T = 5	T = 10	T = 15	T = 20	T = 25	T = 30	T = 35	T = 40	T = 50	T = 60	T = 70
State 1	0.933	0.712	0.515	0.378	0.283	0.216	0.167	0.132	0.105	0.071	0.050	0.036
State 2	0.936	0.725	0.534	0.401	0.306	0.237	0.186	0.149	0.120	0.080	0.056	0.039
State 3	0.941	0.742	0.558	0.424	0.326	0.254	0.199	0.157	0.125	0.081	0.054	0.037

3.4. Discussion

The Markov process framework developed by Kay (1986), continued by Gentlemann *et al.* (1985) and applied by Anderson *et al.* (1991; Foucher *et al.*, 2005; D'Amico *et al.*, 2009; Giuseppe *et al.*, 2007; Goshu and Dessie, 2013), for studying the effect of disease indicators on survival has been used in this study for constructing survival probabilities for different states of disease progression on HIV/AIDS, introducing non-homogeneity in time. The present paper is also to estimate transitions between states based on CD4 counts and to predict the probability of waiting time in the starting state until month t . The use of the multi-state model, as compared to the Cox regression, improved substantially the understanding of variation in risk factors related to the evolution of this chronic. Foucher *et al.* (2005) used multi-state models to estimate transitions between states based on VL and CD4 counts.

The most significant difference between studies that use multi-state models is the definition of the different states. Although CD4 count, VL and the incidence of opportunistic infections are used to assess AIDS progression from a clinical point of view, few studies have used these multiple variables. The high cost of the VL assays is a major obstacle to the adoption of this test, therefore restricting its availability compared to CD4 cell counts test. As a result, we found that gender, age, drug

addicted and TB status were predictors of the intensity of transitions between different states. This result is similar to the result obtained in previous study (Oliveira *et al.*, 2013; Foucher *et al.*, 2005).

The conditional probability of waiting time in the starting state until month t decreases with increasing of time; while with increasing CD4 count, the probability of waiting time in the starting state until month t decreases. Specifically, AIDS patient who is in the third state of the disease may have a highest waiting time until month t compared to the patients who is in the first and second stage of the disease with a given time. This result is similar to the result obtained in previous studies (Goshu and Dessie, 2013; Giuseppe *et al.*, 2007; Corradi *et al.*, 2004).

4. CONCLUSION

The semi-Markov process model is applied to capture the AIDS dynamic progression of a patient. The model considers the randomness of the time that a patient spends in a given state of the disease. The following can be concluded from this study.

When estimating survival in patients with chronic diseases, such as AIDS, that involve the transition between different states, it is fundamentally important to consider progression between the different degrees of chronic. AIDS multi-state modeling is capable of

identifying the factors associated with each transition between the degrees of chronic defined by CD4 count ranges. The multi-state model analysis showed that the major predictors of the intensity of transitions between different states of HIV/AIDS patients were gender, age, drug addicted and TB status.

Within the good states, it is more likely for a patient to stay in a worse state than in a better one at any time of the process. The death state is an absorbing state, i.e., once a patient is death state he/she stays in same state forever. The conditional probability of staying in same state until a given number of month decreases with increasing time. So there is a possibility of changing from one state to another with non-zero probability.

The dynamic nature of the AIDS progression is confirmed with particular findings that there is more likely to be in worse state than better one unless interventions are made. It is recommendable to keep up the ongoing ART treatment services in most effective ways with the careful considerations of recent disease status of patients.

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