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An Application of Homogenous Semi-Markov Model for Assessing HIV/AIDS Progression to ART Patients in Namibia

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

Background: The progression of HIV infection to AIDS and then to death can be considered a stochastic process. Disease progression can be broken down into a finite number of intermediate states, based on CD4 counts. The five states of the Markov process of HIV/AIDS progression are commonly defined as: S1: CD4 count > 500 cells/microliter; S2: 350 < CD4 count ≤ 500 cells/microliter; S3: 200 < CD4 count ≤ 350 cells/microliter; S4: CD4 count ≤ 200 cells/microliter; and D: Death.
Objectives: The objective of this study was to model the progression of HIV/AIDS disease of patients under ART follow-up in Namibia using homogenous semi-Markov processes, using the data obtained from Ministry of Health and Social Services.
Methods: A retrospective study design was used to obtain data on 2422 patients who were observed 11028 times. The semi-Markov model was employed to estimate the transition probabilities and transition intensity

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rate. Time Homogeneous Semi-Markov model was fitted to assess effectiveness of ART by comparing the forward transition and reverse transitions.

Results: As expected the probabilities of transiting from good states to worse states increased with time (from state 1 to state 3 and 4 after 6 months is 0.023 and 0.004, after 12 months is 0.059 and 0.010 respectively). As time increase the probabilities of remaining in the same state is decreasing (probabilities of remaining in state 1 after 6, 12 and 18 months is 0.804, 0.698 and 0.633). As expected the intensity indicates that the rate of transiting from good states to worst states is decreasing (the intensity of transiting from state 1 to 3 and 4 is $p<0.001$).

The strongest predictor of transition from state 1 to 2 is TDF/3TC/EFV, which has a hazard ratio of 1.338 (with p value of 0.002). Patients who were prescribed TDF/3TC/EFV, are over 1.338 times more likely to transit from state 1 to state 2 than patients who did not receive TDF/3TC/EFV. A hazard ratio of 0.678 for the predictor variable female shows that female were less likely to transit from state 2 to 3 than their male counterparts. The hazard ratios of females from a bad state to a better state are more than 1, which is an indication that females are less likely to respond to treatment compared to males.

Conclusions: HIV can progress to AIDS without delay if there is no intervention. Early ART initiation is crucial to reduce the probabilities of transiting from good states to worse states.

Keywords: Transition probabilities; transition intensity; hazard ratio; clinical states; log likelihood ratio.

1 Introduction

HIV/AIDS, is one of the leading causes of death in Namibia and worldwide. HIV/AIDS does not only have an enormous economic impact through lost productivity and medical care spending, but is also a major cause of disability and human suffering. It is important, therefore, to understand the natural history and etiology of HIV/AIDS [1]. Further, since many chronic diseases are caused or made worse by modifiable factors such as diet and lifestyle, understanding factors affecting disease progression is critical. For a number of chronic diseases, the progression is characterized by visits to clinically relevant and ordered states. Examination of the sequence of visited states and duration in each stage can enhance our understanding of the natural progression of the disease and how demographic and clinical factors may have an impact on disease progression [1].

The Human Immunodeficiency Virus (HIV) is a retrovirus that infects bodily fluids in humans and remains in the immune cells within these fluids. HIV targets these immune cells in order to replicate by damaging them in the process. This immune cells, CD4+ T-cells, play an important role in the body's immune system [2]. The CD4+ T-cells are the primary entry point for HIV into the host. The virus attaches itself to the CD4 receptor via its own surface protein when exposed to the CD4+ T-cells and makes use of the host cell to replicate itself and destroys it, impairing the functionality of the immune system. Within a few weeks of infection; there is a high level of replication in the blood that can exceed ten million viral particles per milliliter of blood [3].

A few weeks after infection with HIV the CD4 count falls. Then the immune system begins to fight back. The CD4 count goes back up again, though not to as high as before HIV infection. Without ART, the CD4 count will gradually drop usually over several years. CD4+ T-cells provided the first reliable marker of disease progression as compared to other possible markers and it is one of the markers most closely correlated with the stage of HIV infection [4].

A vaccine would certainly be ideal for preventing infection by HIV and thus for avoiding AIDS the late stage of HIV infection, when immunity is severely impaired. For the immediate future, many scientists are concentrating on improving therapy. Few years ago, HIV infection was everyone's worst nightmare it was almost invariably a progressive, lethal disease that completely robbed its victims of dignity.

Although there are many factors that can help to keep a person with HIV infection well for many years, ultimately it becomes essential to take antiretroviral drugs in order to prolong a person's life and slow down the progression of HIV/AIDS. The antiretroviral therapy (ART) service has been available in Namibia's public sector since 2003, but its impact on survival and on HIV progression has not been well investigated. Successful implementation of such program needs scientific evidence, well studied research and routine hospital data in appropriate setting. In the public sector, ART is provided free of charge following a population-based model of

care with one primary first-line regimen and three alternate first-line regimens consisting of two nucleoside reverse transcriptase inhibitors (NRTI) combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI) [5].

Markov model is defined as a multi-state model where the multi-state model is defined as a model for a stochastic process $(X(t), t\epsilon T)$ with a finite space [6].

$$S = \{s_1, s_2, .., s_m\}. \quad (1)$$

The process starts in one of these states and moves successively from one state to another. Each move is called a step. If the process is currently in state (s_i), then it moves to state s_j at the next step with a probability denoted by p_{ij}, and this probability does not depend upon which states the chain was in before the current state, therefore it only matters where you are and where you want to go. The probabilities p_{ij}, are called transition probabilities. The process can remain in the state it is in, and this occurs with probability p_{ii}. An initial probability distribution, defined on S, specifies the starting state.

Continuous-time homogeneous Markov models have been used to model disease progression of HIV/AIDS patients. A study on the clinical indicators of the HIV disease progression, a 5-state Markov model was used [7, 8]. In 2014, a multistate model was used 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 [8]. In a study of HIV progression, an illness-death multistate model was used to estimate the effects of TB, age, mode of transmission, marital status, gender and ART [9]. In 2017, semi-Markov models were applied to HIV/AIDS disease progression and compared two sojourn time distributions, in Ethiopia [10]. Furthermore, in 2018, a 7-staged continuous-time Markov model was used to assess the disease progression of HIV/AIDS patients receiving ART from a clinic in Bela-Bela, South Africa [3].

In this study, a 4-staged continuous-time Markov model was used to assess the disease progression of HIV/AIDS patients receiving ART, in Namibia. The 4 stages are based on CD4 cell counts. The transition intensities, probabilities and the distribution functions associated with the times are the basic building blocks of the Markov processes [11]. For a continuous-time Markov model, transitions can occur at any (real-valued) time instant. Models with and without covariates are fitted and compared using the likelihood ratio test.

2 Materials and Methods

2.1 Study area, design and data collection

A retrospective study design was used to obtain data on 2422 patients who were observed 11028 times. This retrospective cohort study was conducted in Namibia, from January 2008- January 2012 to December 2017. The data was obtained from the Ministry of Health and Social Services. The data included the following variables: age, gender, stage of HIV infection at diagnosis, date of HIV infection and duration on ART. All registered patients with determined HIV infection and who measured their CD4 count for at least once constituted the study, irrespective of age, gender, stage of disease and date of diagnosis. Pre-processing of data was done and fields with spelling error, other irregularities and irrelevancies like outliers were corrected or removed.

At treatment commencement (t = 0), 657(27.13%) patients started ART in state 1, 683(28.19%) patients started ART in state 2, 677(27.95%) patients started ART in state 3 and 405(16.72%) patients started ART in state 4. Fig. 1 shows all the immunological states a HIV infected patient can go into. All the states are inter-related.

2.2 Modelling homogenous semi-markov processes

Markov chains and semi-Markov processes are very important classes of stochastic processes with many applications in science, engineering and beyond. A Markov chain is a stochastic process, but it differs from a general stochastic process in that a Markov chain must be "memory-less". A Markov chain is a mathematical system that experiences transitions from one state to another according to certain probabilistic rules. The

defining characteristic of a Markov chain is that the probability of transitioning to any particular state is dependent solely on the current state [12].

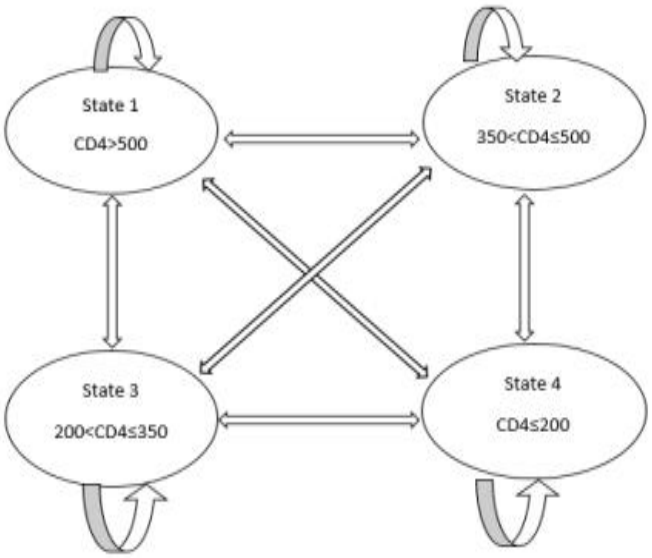

Fig. 1. Immunological state a HIV infected patient can go into

Homogeneous semi-Markov processes (HSMP) were introduced in the 1950s, independently by Levy and Smith, with the objective of generalizing Markov processes [13,14]. In a Markov process environment, the waiting time distribution functions in each state must be exponential, whereas in a semi Markov process environment these distributions can be of any type. This study will deal with semi-Markov stochastic models applied in a clinical field.These processes turn out to be a very efficient tool for predicting the dynamic evolution of human immunodeficiency virus (HIV) infection. This approach has the following advantages with respect to traditional epidemiological models [16]:

- We can consider an arbitrary number of states, linked to the seriousness of the infection;
- All transitions between states are allowed;
- We can consider the randomness of the evolution between all states, as well as the stochastic time spent in each state before a transition occurs;
- Model parameters are directly estimated from raw data;
- All the states are interrelated, therefore any improvements are also considered;
- A large number of disease states can be considered;
- Finally, conclusions consist in certain interval transition probabilities obtained by solving the evolution equations of the process.

A semi-Markov process is a process that makes transitions from state to state like a Markov process, however the amount of time spent in each state before a transition to the next state occurs is an arbitrary random variable that depends on the next state the process will enter [17]. In Giuseppe et al., homogenous semi-Markov process (HSMP) model was defined as follows [18]:

Let $X_n : \Omega \to S$ be a stochastic process with state space $S = \{S_1, S_2, \dots, S_m\}$ and $T_n : \Omega \to \mathbb{R}$ be the time of the n^{th} transition, with Ω domain of the process and $\mathbb{R}$ set of real numbers. Here the time is a random variable. The kernel $Q = [Q_{ij}]$ associated with the process and the transition probability P_{ij} of the embedded Markov chain is defined as follows:

$$Q_{ij}(t) = P[T_{n+1} = j, T_{n+1} - T_n \leq t | X_n = i] \tag{2.3.1}$$

$$P_{ij} = \lim_{t\to\infty} Q_{ij}(t) \tag{2.3.2}$$

Define the probability that the process will leave a state i in a time t as

$$H_i(t) = P[T_{n+1} - T_n \leq t | X_n = i] = \sum_{j=1}^{m} Q_{ij}(t) \tag{2.3.3}$$

The distribution of waiting time in each state i, is given that the state j is subsequently occupied is

$$G_{ij}(t) = P[T_{n+1} - T_n \leq t | X_n = i, X_{n+1} = j], \tag{2.3.4}$$

which can be computed as:

$$G_{ij}(t) = \begin{cases} \frac{Q_{ij(t)}}{P_{ij}}, & if P_{ij} \neq 0 \\ 1, & if P_{ij} = 0 \end{cases} \tag{2.3.5}$$

For any homogenous semi-Markov process $\{X(t), t \geq 0\}$, the transition probabilities are given by (2.3.6) for which the solution should be obtained using the progression (2.3.7).

$$\emptyset_{(ij)}(t) = P[X(t) = j | X(0) = i], \tag{2.3.6}$$

$$\emptyset_{ij}(t) = (1 - H_i(t))\delta_{ij} + \sum_{l=1}^{m} \int_0^t Q_{il}(\tau)\phi_{lj}(t-\tau)\, d\tau \tag{2.3.7}$$

Here δ_{ij} represents the kronecker delta δ.

The variables involved are the following:

m= number of states of HSMP, which is 4 in this case.
T = number of periods to be examined for the transient analysis of HSMP.
P = matrix of order m of the embedded Markov chain in HSMP.
G^T = square lower-triangular block matrix order T +1 whose blocks are of order m.
Q^T = kernel of SMP.
Φ^T = block vector of order T + 1 where the blocks are square matrices of order m.
D^T = block vector of order T + 1 where the blocks are the diagonal square matrix of order m.
V^T = square lower-triangular block matrix order T + 1 whose blocks are of order m.
S^T = block vector of order T+1 the block which are the diagonal square matrix of order *m*. The diagonal element of each block *t* are $s_{ii} = \sum_{j=1}^{m} Q_{ij}(t)$.

3 Results and Discussion

3.1 Descriptive statistics

The study used data from MoHSS, with 2422 HIV patients on anti-retroviral therapy (ART) who were observed 11028 times. 7489 (67.9%) were females and 785 (32.41%) were males , 657(27.13%) patients started ART in state 1, 683(28.19%) patients started ART in state 2, 677(27.95%) patients started ART in state 3 and 405(16.72%) patients started ART in state 4, at treatment commencement (t = 0). Data analysis was done in *msm* (multi-state model) developed by [17], the "R package *msm*", contains numerous functions for fitting continuous-time Markov to longitudinal data. The msm package provides several numerical outputs such as transition intensity and transition probabilities

Table 1 shows that the highest observation were recorded in the age category of 25-49. The highest observed prescribed ART regimen in state 1 and 3 is TDF/3TC/NVP, the highest in state 2 is AZT/3TC/EFV and the highest in state 4 is AZT/3TC/LPV

Table 1. Descriptive statistics (counts and percentage (%))

Variable	State, n=11028(%)				Total (n)
	1	2	3	4	
Age					
<25	135 (50.0)	62 (23.0)	41(15.2)	32(11.9)	270
25-49	3985(40.3)	2928(29.6)	2135(21.6)	837(8.5)	9885
=>50	253(29.0)	240(27.5)	241(27.6)	139(15.9)	873
Sex					
Male	887(25.1)	1105(31.2)	1037(29.3)	510(1404)	3539
Female	3486(46.5)	2125(28.4)	1380(18.4)	498(6.6)	7489
Prescribed ART regimen					
AZT/3TC/EFV	537(43.2)	316(25.4)	247(19.9)	142(11.4)	1242
AZT/3TC/LPV	1302(37.8)	1057(30.7)	796(23.1)	290(8.4)	3445
TDF/3FTC/EFV	545(36.1)	389(25.8)	387(25.7)	187(12.4)	1508
TDF/FTC/EFV	557(41.7)	381(28.5)	291(21.8)	108(8.1)	1337
TDF/3TC/NVP	1421(40.9)	1081(31.1)	694(20.0)	279(8.0)	3475
Others	11(52.4)	6(28.6)	2(9.5)	2(9.5)	21

Note: n is number of times patients has been observed. TDF=tenofovir, AZT=azidothymidine, FTC=emtricitabine, EFV=efavirenz, 3TC=lamivudine, NVP=nevirapine, OTHER=abacavi (ABC) and stavudine (D4T)

3.2 Model formulation

Formulation of the continuous homogeneous semi Markov model is done by considering transition probabilities over narrow interval of time Δt. In this study $\Delta t = ½$ months making it appropriate to assume that transition rates over these intervals are constant [3]. These transition rates, also known as transition intensities, are the essential concept in continuous semi- Markov processes. They can take values greater than 1, unlike transition probabilities.

At any time $t + \Delta t$, the state of an HIV-infected individual is defined based on the CD4 cell count level as follow: S1: CD4 count > 500 cells/microliter; S2: 350 < CD4 count ≤ 500 cells/microliter; S3: 200 < CD4 count ≤ 350 cells/microliter and S4: CD4 count ≤ 200 cells/microliter. Based on these four states, progression of HIV/AIDS disease is defined by the state diagram, Fig. 1. The arrows in the diagram show possible transitions between the four states defined above. As HIV progresses in an individual's body, there is a likelihood of an individual being in the same state in consecutive visit times.

3.3 Clinical progression of HIV/AIDS disease

This study considered that an infected patient can move among the immunological marker stages related to CD4 count. Patient who started treatment under any state has a likelihood to reach any other state. If there is an improvement on CD4 count, the patient has a recovery from the initial state and can transit to a better state. The transition of the patient in different state occurs at any time. Table 2 summarizes transition counts that took place for the whole period of the study.

Table 2. Transition counts

From	To			
	State 1	State 2	State 3	State 4
State 1	**1**	**2**	**3**	**4**
State 2	2547	616	99	26
State 3	917	1193	414	35
State 4	211	666	928	161

Table 2 shows that, transition counts from state *i* to *j* are higher for all the values in which *i=j*. In the followed up period, 3288, 2559, 1966 and 793 transitions had already been from state 1, 2, 3, and 4, respectively. Twenty six patients transited to state 4 from state 1 while 41 left state 4 to state 1. The time homogeneous model was

fitted to the data to assess the effectiveness of the treatment by comparing the forward transition and the reverse transitions.

Table 3 shows the estimated transition probability, patient from state 1, 2 and 3 transit to state 4 with probability $p<0.001$, $p<0.001$ and 0.018, respectively. Patients show improvement from state 4 to; state 3, state2 and state 1 with probability of 0.060, 0.002 and $p<0.001$, respectively. Patients show improvement from state 3 to 2, from state 3 to 1 and from state 2 to 1 with probability of 0.070, 0.003 and 0.071, respectively.

Table 3. Estimated transition probability matrix

From	To			
	State 1	**State 2**	**State 3**	**State 4**
State 1	0.958	0.040	$p<0.001$	$p<0.001$
State 2	0.071	0.887	0.041	$p<0.001$
State 3	0.003	0.070	0.909	0.018
State 4	$p<0.001$	0.002	0.060	0.937

The solution of the evolution equation is presented for specific month in Table 4. It represents the probability that an HIV positive patient being at time 0 in state *i* will be after *t* months, in the state *j*. Table 4, indicate the probability of a patient starting from state *i* at time zero, will do a transition after month *t* to state *j*. The conditional probability of a patient starting from state 4 at time zero, and transiting to state 3, 2 and 1 after 2 years is 0.328, 0.227 and 0.162 respectively. A patient being in state 4 at time zero, stay in same state after 2 years with probability 0.288. The probabilities of direct transition from state 1 to state 2, state 2 to state 3 and state 3 to state 4 after 4 years are estimated to be 0.284, 0.172 and 0.077 respectively. As t increases, the probability of the patient transiting to a next worse state is increasing while the probability to remain in the same state is decreasing.

Table 4. The solution of the evolution equation for month *t*

Transition	t=6	t=12	t=18	t=24	t=30	t=36	t=42	t=48
1→1	0.804	0.698	0.633	0.592	0.563	0.543	0.528	0.518
1→2	0.168	0.233	0.260	0.273	0.278	0.281	0.283	0.284
1→3	0.023	0.059	0.089	0.118	0.128	0.139	0.148	0.154
1→4	0.004	0.010	0.017	0.024	0.030	0.036	0.040	0.044
2→1	0.292	0.405	0.451	0.471	0.479	0.484	0.486	0.486
2→2	0.547	0.387	0.328	0.304	0.293	0.289	0.287	0.286
2→3	0.150	0.183	0.184	0.180	0.177	0.174	0.173	0.172
2→4	0.011	0.026	0.037	0.045	0.049	0.053	0.054	0.056
3→1	0.065	0.168	0.254	0.318	0.363	0.396	0.419	0.436
3→2	0.255	0.309	0.311	0.303	0.295	0.29	0.288	0.286
3→3	0.606	0.425	0.332	0.279	0.247	0.225	0.211	0.201
3→4	0.007	0.098	0.103	0.283	0.094	0.088	0.082	0.077
4→1	0.008	0.045	0.100	0.162	0.220	0.272	0.317	0.353
4→2	0.054	0.130	0.189	0.227	0.251	0.264	0.272	0.277
4→3	0.246	0.327	0.341	0.328	0.306	0.283	0.262	0.243
4→4	0.069	0.497	0.369	0.288	0.222	0.179	0.149	0.127

Table 5 shows the transition intensity matrix. The estimated intensity indicates that the rate of transiting from good states to the worst state is decreasing. The elements in each row of the transition intensity matrix (Table 5) sum to zero and off diagonal elements non-negative and the elements in diagonal must be negative for all *i* equal to *j*. This implies that subjects in those states remain in their respective state while the off diagonals are rates at which subjects move to other states.

3.4 Hazard ratios of covariates on transition intensities

In this section the hazard ratios for each of the covariates; gender, age and prescribed ART regimen are estimated. The results show that the strongest predictor of transition from state 1 to 2 is TDF/3TC/EFV, which

has a hazard ratio of 1.338. This means that patients who were prescribed TDF/3TC/EFV, this means that patients who received TDF/3TC/EFV were over 1.338 times more likely to transit from state 1 to state 2 than patients who did not receive TDF/3TC/EFV. The strongest predictor of immune deterioration from a CD4 level between 200 and 350 to a CD4 level less than or equal to 200 (3 to 4) is sex, with a hazard ratio of 2.074. This means that sex is the major cause of further immune deterioration when the immune system is too weak. A hazard ratio of 0.854 for the predictor variable female shows that female were less likely to transit from state 2 to 3 than their male counterparts.

Table 5. Transition intensity matrix

From	To			
	State 1	**State 2**	**State 3**	**State 4**
State 1	-0.044	0.044	p<0.001	p<0.001
State 2	0.076	-0.122	0.045	p<0.001
State 3	p<0.001	0.078	-0.097	0.019
State 4	p<0.001	p<0.001	0.064	-0.064

The hazard ratios of females from a bad state to a better state are more than 1, which is an indication that females are less likely to respond to treatment compared to males. For states which do not have intensity (i.e. (1→3)) the underlying model specifies that the patient must have passed through state 2 in between, rather than jumping straight from 1 to 3 [19]. Table 6 shows the hazard ratio for covariates.

Table 6. Hazard ratio of covariates

State	Hazard ratio						
	age	**Sex:**	**Prescribed ART regimen**				
		Female* vs Male	**AZT/3TC/LPV**	**TDF/3TC/EFV**	**TDF/3TC/NVP**	**TDF/FTC/EFV**	**OTHER**
1→2	1.028	0.62	1.051	0.545	0.998	1.338	0.721
1→3							
1→4	0.927	0.838	0.841	0.494	1.684	1.002	0.302
2→1	1.007	1.415	0.726	0.574	0.877	0.999	0.716
2→3	1.043	0.854	0.935	0.974	0.864	1.089	0.632
2→4	0.403	0.885	1.277	0.749	1.409	1.063	0.633
3→1							
3→2	1.007	1.353	1.373	1.397	1.387	1.587	0.948
3→4	0.983	2.074	0.679	0.417	0.919	0.557	0.919
4→1							
4→2	0.397	1.511	1.645	0.611	1.684	1.407	0.869
4→3	0.949	2.065	1.539	0.733	1.302	1.636	0.681

Table 7. Model selection criterion

Model	-2 Log likelihood ratio test	df	p-value
Sex as a covariate	-131.088	9	1.00
Age as a covariate	-1721.034	9	1.00
Prescribed ART regimen as a covariate	78.106	45	0.002
All covariates	-546.99	63	1.00

3.5 Model comparison

A continuous-time semi-Markov model for the effects of covariates; age, sex and prescribed ART regimen is fitted as shown in Table 7. Identification of covariates that have a significant effect is done by entering each covariate one after the other and performing the likelihood ratio test in comparison to the model without covariates. A Likelihood ratio test is performed to compare the models that were fitted. The fitted time homogeneous model with prescribed ART regimen as a covariate has -2xLL = 78.106. The other fitted time

homogenous models have likelihoods less than -2 x LL= 78.106. Which represents a weakening of LRT. The value of the $LRT = -2log_e = \left(\frac{L_0(\theta)}{L_1(\theta)}\right)$ where $L_0(\theta)$ is the null model (without covariates) and $L_1(\theta)$ is the general model (with covariates).

4 Discussion

This study modeled the progression of HIV infection using longitudinally measured CD4 count for HIV positive patients initiated to ART. A continuous-time homogeneous semi-Markov model is fitted with and without covariates and comparison of these two models is done using the likelihood ratio test. Results shows that the model with prescribed ART regimen is the best model. The probability of a patient transiting from state 1, 2 and 3 to state 4 after 24 months is 0.024, 0.045 and 0.283 respectively. Patients shows improvement from state 4 to, state 1, state 2 and state 3 with probability of 0.162,0.227 and 0.328, this is in agreement with the results of Kashihalwa et al. [19]. Similar study conducted in Ethiopia has shown that probability of a patient to enter from stage IV to stage III, stage II and stage I in 2 year follow up period was 0.17, 0.9 and 0.2, respectively [20].

The hazard of covariates; sex, age and prescribed ART regimen are estimated. The results show that the strongest predictor of transition from state 1 to 2 is TDF/3TC/EFV, which has a hazard ratio of 1.338. As time increases the probability of remaining in the same state is decreasing, this is in agreement with the results of Seyoum et al., [21] and that of Goshu and Dessie 7, 8].

5 Conclusion

This study evaluated the progressions of HIV /AIDS infection using longitudinally measured CD4 count and its possible predictors via homogenous semi-Markov processes. Model with and without covariates have been compared using the LRT, the model with prescribed ART regimen exhibited the best fit. The study also found that the conditional probabilities of transiting to the next worst state as time increases is very small and the probabilities of remaining in the same state as time increase is increasing. Finally the evolution of CD4 count (HIV infection) is differing by patient's baseline demographic and clinical characteristics like sex, age, WHO stages and prescribed ART regimen.

Data Availability Statement

The datasets analyzed during the current study are not publicly available due to confidentiality but are available from the MoHSS.

Disclaimer

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Consent

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

Ethical Approval

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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Competing Interests

Authors have declared that no competing interests exist.

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