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Modelling of HIV/AIDS Disease Progression Using Homogeneous Semi-Markov Processes

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Abstract

The aim of this paper is to model the HIV/AIDS Disease Progression Using Homogeneous Semi-Markov process and to predict the probability of transition from one state to another and the length of stay that has been spent by a person with the Human Immunodeficiency Virus (HIV) infection. The result showed that conditional probability for a patient to stay in state SI, SII, SIII and SIV for at least 4 years are 0.289, 0.097, 0.679 and 0.569 respectively. Also, the probabilities of leaving state i ∈ {SI, SII, SIII, SIV} is lowest in SI and highest in SIII. The average time was considered and it was found out that the average time of visit per patient in State I was 10.35. A patient entering the model in State II is expected to visit the hospital for 11032 times which on the average is 19.08 visit per patient, a patient entering the model in State III is expected to visit the hospital for 11001 times which on the average is 4.05 visit per patient and a patient entering the model in State IV is expected to visit the hospital for 11016 times which on the average is 4.93 visit per patient.

Keywords: ART, CD4, Equilibrium, HIV/AIDS

1.0 Introduction

The human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) has become an epidemic since it was first identified in 1981 [1]. In December 2010, it was estimated that 33 million people worldwide were living with HIV/AIDS and the number of deaths caused by HIV/AIDS were over 35 million (UN Joint Programme on HIV/AIDS). In the United States, the number of people who were living with HIV/AIDS was estimated to be 1.2 million by the end of 2009, and it is estimated that about 50 000 new cases occur annually [2]. African Americans represent approximately 14% of the US population, but accounted for an estimated 44% of new HIV infections in 2009 and 46% of people living with HIV infection in 2008. In 2009, the estimated rate of new HIV infections among African American men was six and a half times as high as that of Caucasian men. In the same year, the estimated rate of new HIV infections among African American women was 15 times that of Caucasian women [3]. The disease called HIV is one of the leading causes of death in Nigeria and the African continental. This disease not only has economic impact through lost productivity and medical care's spending, but also a major cause of disability and human suffering. It is important, therefore, to understand the natural history of these diseases. The natural evolution of HIV infection usually starts with a latency phase. This phase can last for several years. The main characteristic of HIV infection is the gradual depletion of a particular class of lymphocytes named CD4+ (also called "helper lymphocytes"). These lymphocytes play an essential part in the body's immune response to infections. The depletion of CD4+ then causes a weakening of the immune response, which leads to opportunistic infections of significant seriousness. Besides, the presence of plasma viremia is linked to a possible worsening of the disease.

The disease evolves through successive stages [4], which can be defined according to CD4+ lymphocyte count, viral load and constitutional symptoms [5]. The final stage of the disease [6] is represented by full blown AIDS.

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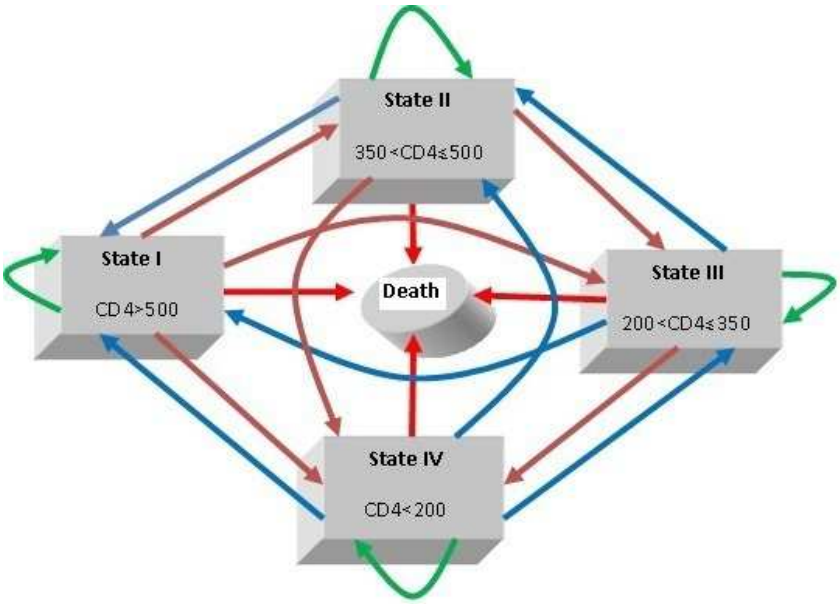


Figure 1: HIV Multi-state Model with 4 immunological states and 20 transitions. The red arrows show the progression of a patient to a worse state, blue arrows show recovery of a patient to a better state and green arrows show a patient remaining in the same state

Many mathematical models have been applied in this area of research such as Markov chain process, Non homogenous semi markov chain and Homogenous semi markov process. The Application to Credit Risk using Non Homogenous Semi markov process was modelled in [7],while Masala et al [8] modelled the Survival probabilities for HIV infected patients through Non Homogenous Semi markov processes. This intends to introduce features of non homogeneous semi-Markov models after determining the transition probabilities and the waiting time distributions in each state of the disease. The models try to solve the evolution equations of the process and also estimate the interval transition probabilities of HIV infected patients and compare them with respect to certain categories, such as gender, age group or type of antiretroviral therapy.

Semi markov model was applied in [9] to study theprogression of HIV/AIDS disease stages and discovered 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. This means that there are some periods of time when such probability is highest for a patient to transit to a worse state of the disease. Moreover, the probability of dying decreases with increasing CD4 counts over time. For an HIV/AIDS patient in a specific state of the disease, the probability of being in same state decreases over time.

A multi-state homogeneous semi-markov process was applied in [10] to model HIV/AIDS patients using the major predictors of the intensity of transitions between different states of HIV/AIDS patients as gender, age, drug addicted and Tuberculosis (TB) status and discovered that the probability of staying in same state until a given number of month decreases with increasing time. 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 and discovered. In this paper homogeneous semi-Markov (HSM) models is proposed as a tool for predicting the probability of transition from one state to another state, and the length of stay that has been spent by a person with the Human Immunodeficiency Virus (HIV) infection.

2.0 Material and Methods

Homogeneous semi-Markov process (HSMP) was introduced in the 1950s, independently in [11] and [12], with the objective of generalizing Markov processes. 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.

The homogenous semi markov processes can be of any distribution with mean μ_i in that state, before making transition. If the time spent in state 'i' is 't' then the transition will be into state 'j' with $P_{ij(x),i,j\geq 0}$. This method assume the sample paths are continuously observed and it is often a situation where the study individuals' states are observed only at discrete time points with no information about the types and times of events between observation times [13]

In SMP environment, two random variables run together. J_n $n\in$N with finite state space

$E = \{1,\ldots,m\}$ represents the state at the n-th transition. T_n, $n \in$N with state space equal to N represents the time of the nth transition, $J_n : \Omega \rightarrow \mathbf{E}$ $\mathbf{T_n}: \Omega \rightarrow N$

where J_n represents the state at the nth transition and T_n represents the chronological time of the nth transition. We denote $\{N(t),\ t \geq 0\}$ the counting process by $N(t)$ which is associated with the point process T_n, $n \in$N. In the health care environment, the elements of E represent all the possible stages in which the disease may show level of seriousness. T_n, represents the time of the n-th transition.

Suppose that the processes (J_n, T_n) are homogeneous Markov renewal processes. The kernels $Q = [Q_{ij}(t)]$: the probability that the process will be in state 'j' at an interval of times less than or equal to 't' given that the process was already in state 'i' associated to the homogeneous processes is defined in the following way:

$$Q_{ij}(t) = P[J_{n+1} = j, T_{n+1} - T_n \leq t / J_n = i, J_{n-1}, T_{n-1}, \dots, J_1, T_1, J_0, T_0] \dots \quad (1)$$

$$= P[J_{n+1} = J, T_{n+1} - T_n \leq t / J_n = i]$$ And it results: $P_{ij} = \lim_{t \to \infty} Q_{ij}(t); i, j \in E, t \in N$,

where respectively **P** = $[p_{ij}]$ is the transition matrix of the embedded homogeneous Markov chain of the process.

The matrices $Q(t)$ are defined as $Q(t) = F(t) \times P(t)$ ("element by element" product).

In the discrete environment, it is necessary to define also the following probabilities:

$$b_{ij}(t) = P[J_{n+1} = J, T_{n+1} - T_n = t / J_n = i] \dots \quad (2)$$

The matrices $b_{ij}(t)$: probability that the process will be in state 'j' at an interval of times equal to't' given that the process was already in state 'i' is given by:

$$b_{ij}(t) = \begin{cases} 0 \ if \ t = 0 \\ Q_{ij}(t) - Q_{ij}(t-1) \ if \ t > 0 \end{cases} \dots \quad (3)$$

Now it is necessary to introduce the probability that the processes will leave state i in a time t

i.e : $H_i(t) = P[T_{n+1} - T_n \leq t / J_n = i] = \sum_{j=1}^{m} Q_{ij}(t)$

We then obtain the matrices $H(t)$ in the following way:

$$H_{ij}(t) = \begin{cases} 0 \ if \ i \neq j \\ \sum_{k=1}^{m} Q_{ij}(t) \ if \ i = j \end{cases} \dots \quad (4)$$

The distribution functions of the waiting time in each state i, given that the state successively occupied is known, is as follows:

$$F_{ij}(t) = [T_{n+1} - T_n \leq t / J_{n+1} = j, J_n = i] = \begin{cases} \frac{Q_{ij}(t)}{P_{ij}} & if \ P_{ij} \neq 0 \\ 1 & if \ P_{ij} = 0 \end{cases} \quad (5)$$

The matrices $F(t)$ are square matrix (m denotes the number of states) and they must be evaluated for t =1,...,k using the distributions previously determined.

3.0 Data

The data for this study were patients under the follow up of Antiretroviral Therapy (ART) at the Lagos State University Teaching Hospital (LASUTH), Ikeja from 2008 to 2014. There was 6600HIV/AIDS consultation (CD4 counts) in the hospital within the period under study. The study considered selected HIV infected patients under ART regardless of their treatment category during the study period. Transition between states occurs after a visit to the doctor which can be seen as the check to decide in which state a person is. This gives naturally an example where virtual transition is possible, i.e., the individual has neither become sufficiently better or worse to change state. The states are defined as:

SI: CD4 count > 500 cells/microliter.

SII: 350 < CD4 count ≤ 500 cells/microliter.

SIII: 200 < CD4 count ≤ 350 cells/microliter.

SIV: CD4 count ≤ 200 cells/microliter.

Frequencies and estimated transition probabilities of between the states are summarized from the data and displayed in Table 1& 2.

4.0 Results

Table 1: Frequencies of the transitions of the states of the process from 2007 to 2014

States	SI	SII	SIII	SIV
SI	654	261	99	51
SII	150	209	163	56
SIII	129	477	1490	627
SIV	136	279	525	1294

Table 2: Probabilities of the transitions of the states of the process

States	SI	SII	SIII	SIV
SI	0.614	0.245	0.093	0.048
SII	0.260	0.362	0.282	0.097
SIII	0.047	0.175	0.547	0.230
SIV	0.061	0.125	0.235	0.579

5.0 Discussion

Firstly, transitions within the “good" sates are considered. The probability that an HIV/AIDS patient who is currently in a given state i ∈ {SI, SII, SIII, SIV} will be in the subsequent “worse” is displayed in Figure 2. Such progressions are from state i ∈ {SI, SII, SIII, and SIV}. It is interesting to find out that, within the good states, the transition probability from state I to the next worse state decreases with time, while in state III to the next worse state increases with time; gets optimum at a time and then decreases with increasing time, same for state II while the transition probability of recovery from state IV to the next good state increases.

Secondly, transitions within the “good" states are considered. The conditional probability that an HIV/AIDS patient who is currently in a given state i ∈ {SI, SII, SIII} will be in worse state after t years is displayed in Figure 3. Such progressions are from SI to SII, SII to SIII and SIII to SIV. Moreover, the transition probability from SII to SIII is the lowest as compared to the others. It is interesting to find out that, within the good states, the transition probability from a given state to the next worse state increases with time.

Thirdly, Figure 4 shows the probability of waiting time. The conditional probability that a patient stays in state SI, SII, SIII and SIV for at least 4 years are as follows 0.289, 0.097, 0.679 and 0.569. It reduces in SII but increases with the increasing seriousness of the disease in SI, SIII and SIV. Also, within the good states, it is more likely for a patient to stay a little longer in a worse state than in a better one before moving to the absorbing state.

Fourthly, Figure 5 shows the probabilities of leaving state i ∈ {SI, SII, SIII, SIV}, which is lowest in SI and SII but fairly high in SIV and highest in SIII.

Finally, Figure 6 displayed the plot of the progression of HIV/AIDS diseases at different stages, over the period under study (seven years) in order to determine whether a point of equilibrium can be established among the four stages under consideration. A point of equilibrium exist in the progression of HIV/AIDS patient among stages I, III & IV between 2008 and 2009 while stage II displayed a relatively steady pattern.

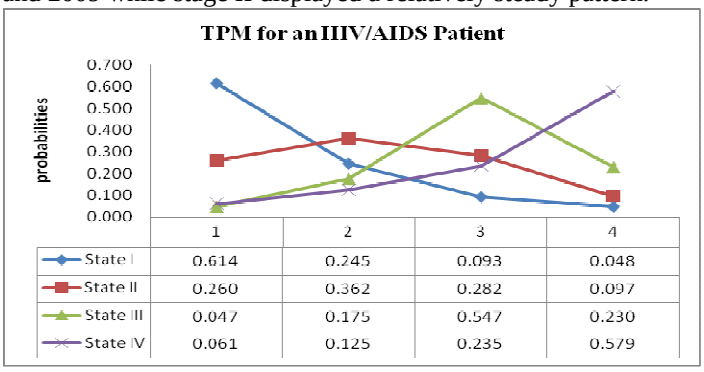
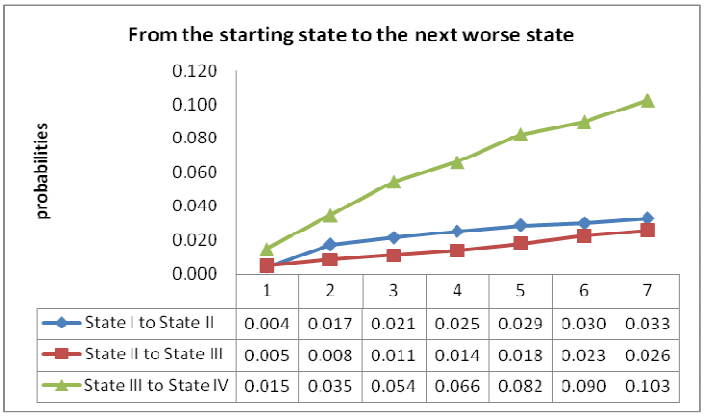
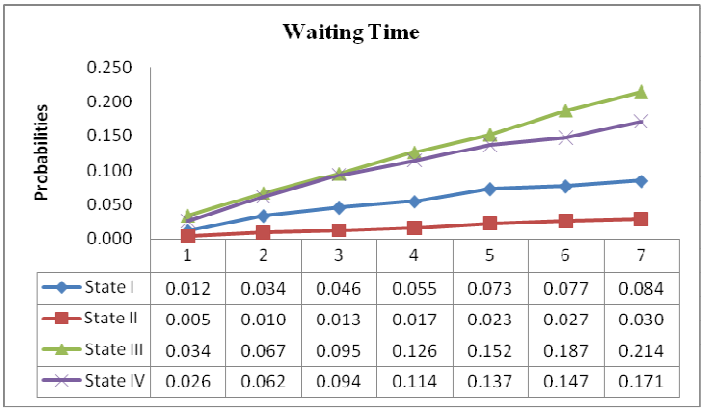


Figure 2: Transitional probabilities that a patient will be in state j given that she/he is currently in state i ∈ {SI, SII, SIII, IV} j ∈ {SI, SII, SIII, SIV} within the period of 7 years.



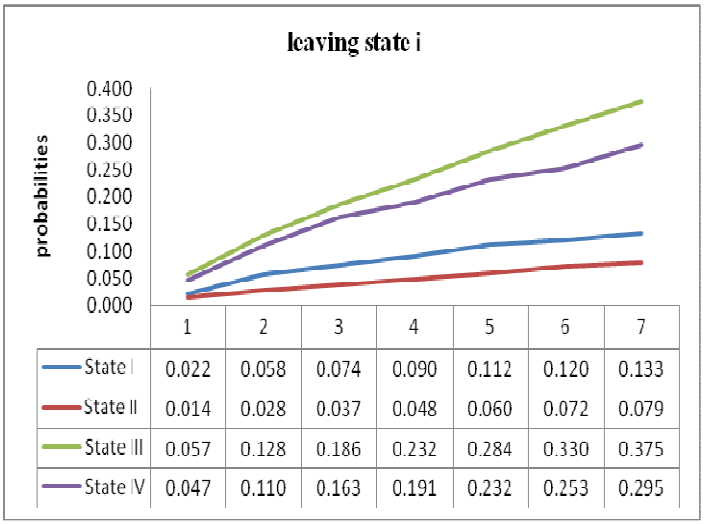
	1	2	3	4	5	6	7
State I to State II	0.004	0.017	0.021	0.025	0.029	0.030	0.033
State II to State III	0.005	0.008	0.011	0.014	0.018	0.023	0.026
State III to State IV	0.015	0.035	0.054	0.066	0.082	0.090	0.103

Figure 3: Conditional probabilities that a patient will be in state j after years given that she/he is currently in state i ∈ {SI, SII, SIII} j ∈ {SII, SIII, SIV} within the period of seven years.



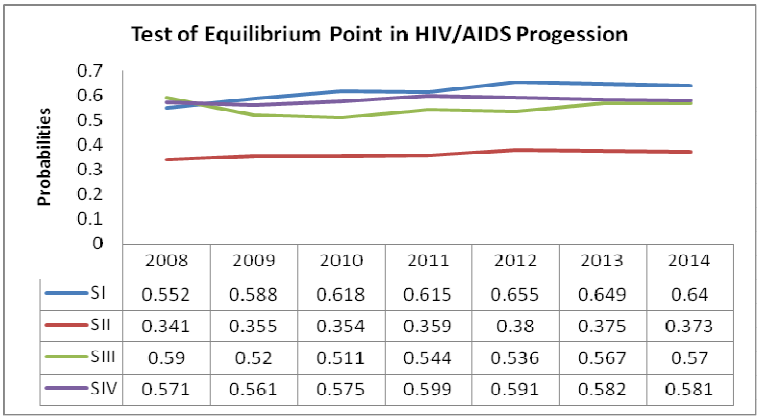
	1	2	3	4	5	6	7
State I	0.012	0.034	0.046	0.055	0.073	0.077	0.084
State II	0.005	0.010	0.013	0.017	0.023	0.027	0.030
State III	0.034	0.067	0.095	0.126	0.152	0.187	0.214
State IV	0.026	0.062	0.094	0.114	0.137	0.147	0.171

Figure 4: The probability that a patient stays in same state of disease for 7 years.



	1	2	3	4	5	6	7
State I	0.022	0.058	0.074	0.090	0.112	0.120	0.133
State II	0.014	0.028	0.037	0.048	0.060	0.072	0.079
State III	0.057	0.128	0.186	0.232	0.284	0.330	0.375
State IV	0.047	0.110	0.163	0.191	0.232	0.253	0.295

Figure 5: The probability that a patient leaves state i of the disease to state j for 7 years.



	2008	2009	2010	2011	2012	2013	2014
SI	0.552	0.588	0.618	0.615	0.655	0.649	0.64
SII	0.341	0.355	0.354	0.359	0.38	0.375	0.373
SIII	0.59	0.52	0.511	0.544	0.536	0.567	0.57
SIV	0.571	0.561	0.575	0.599	0.591	0.582	0.581

Figure 6: Graphical representation of the progression rate of HIV/AIDS patients

6.0 Determination of Expected Number of Visit

Considering a patient who enters the system in state i and after a visit for medical check-up obtains his average visit time in state j before leaving that state. The average number of times that a patient resides in transient states before absorption, starting from state I, estimated from the fundamental (N) matrix according to [14, 15] is given by $N = (I - A)^{-I}$ where I is an identity matrix and A is the square matrix of the transient probabilities; which is estimated below:

$$A = \begin{pmatrix} 2477 & 2420 & 3420 & 2702 \\ 2477 & 2422 & 3422 & 2710 \\ 2469 & 2414 & 3414 & 2703 \\ 2473 & 2418 & 3418 & 2708 \end{pmatrix} \quad (6)$$

In the matrix (6) above, if a patient enters the model in state I, with a CD 4 count of ≥5 00 cells/mm^3, He/ She is expected to stay in the state for 2477 times, be in state II for 2420 times, be in state III for 3420 times and be in state IV in 2702 times. After all this visits to the transient states, the patients are expected to move to the death state.

$$\sum_{j}^{4}(1 - A)_{ij}^{-1} = \begin{pmatrix} 11025 \\ 11032 \\ 11001 \\ 11016 \end{pmatrix} \quad (7)$$

In matrix (7), it is expected that all patient entering the model in state I will visit the hospital for 11025 times from entering the model in state I which on average is 10.35 visit per patient, a patient entering the model in State II is expected to visit the hospital for 11032 times which on the average is 19.08 visit per patient, a patient entering the model in State III is expected to visit the hospital for 11001 times which on the average is 4.05 visit per patient and finally a patient entering the model in State IV is expected to visit the hospital for 11016 times which on the average is 4.93 visit per patient.

7.0 Conclusion

This paper considered a homogeneous semi-Markov processes approach modelled Human Immunodeficiency Virus Infection, as defined by CD4+ levels and viral load, has been presented. The results obtained from the model revealed that the transition probability from SII to SIII is the lowest compared to the others. It is interesting to find out that, within the good states, the transition probability from a given state to the next worse state increases with time. Furthermore, the Figure 4 result of semi-Markov predicts the probability of waiting time of a patient stays in state SI, SII, SIII and SIV for at least 4years are 0.289, 0.097, 0.679 and 0.569 respectively. Finally, average time of visit per patient is 10.35. A patient entering the model in State II is expected to visit the hospital for 11032 times which on the average is 19.08 visit per patient, a patient entering the model in State III is expected to visit the hospital for 11001 times which on the average is 4.05 visit per patient and a patient entering the model in State IV is expected to visit the hospital for 11016 times which on the average is 4.93 visit per patient

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