A MODEL FOR ASSESSING THE PROGRESS AND PREDICTING THE EFFICACY OF ANTIRETROVIRAL THERAPY (ART)

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Abstract: The Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS) is posing a challenge as it has become drug resistant in some patients. Consequently, treatment failure and spread of drug resistant HIV/AIDS results. This compromises the effectiveness of the limited therapeutic options like the antiretroviral therapy (ART). It therefore becomes necessary to assess the future progress as well as predict the efficacy of ART treatment. To this end, a Markov chain model for this assessment and prediction of treatment efficacy was formulated using the CD4 counts of a sample of 1,418 patients, receiving treatment every six (6) month at the HIV Counselling and Testing (HCT) unit of the general hospital Wukari, Taraba State. Taraba state is one of the states with high prevalence rate of HIV in North-eastern Nigeria. This methodology is considered appropriate as it can be applied in assessing and predicting treatment performance on a group of HIV patients or a cohort study. The progression of patients response to the therapy was assessed from one CD4 count state to another using a transition probability matrix. The efficacy of the therapy which is the maximum response of patients to treatment was evaluated using the long run (steady state) chances of patients in each CD4 count state and the mean recurrence time of each CD4 count state. The CD4 count states adopted in the study are; CD4 cell counts ≥ 500 cells/μL (state 1), CD4 cell counts in the range of 200 - 499 cell/μL (state 2) and CD4 cell count < 200 cells/μL (state 3) representing the Good, Moderate and Poor health states of patents respectively. The model predicts that at the long run, there is a 40, 44 and 16% chance that a patient will attain a Good, Moderate and Poor health state, respectively, with respective mean recurrence time of 1.24, 1.13 and 3.21 years. The study concludes that the difference in the chances of the health state of patients might be due to antiretroviral drug resistance among other factors. The authors recommend that these factors should be identified and considered when administering ART to ensure very high chances of the Good and Moderate health states.

Keywords: HIV, CD4, ART, Model

Introduction

The Human immunodeficiency syndrome (HIV) causes acquired immunodeficiency syndrome (AIDS) by destroying CD4 and T cells. Primarily, HIV infests and kills CD4+T lymphocytes, which function as regulators and amplifiers of the immune response. In the absence of effective antiretroviral therapy, the hall mark decrease in CD4+T lymphocytes during AIDS results in a weakened immune system, impairing the body's ability to fight infections (Alimonti *et al*., 2003). The Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS) is considered to be the greatest development challenge in the world. According to UNAIDS (2004), 36.1 million people worldwide are estimated to be living with HIV/AIDS. It is estimated that 70% (25.3 million) of all HIV/AIDS cases worldwide are in sub-Saharan Africa (UNAIDS, 2006).

The first case of the HIV/AIDS epidemic was reported in Nigeria in 1986 (Kanki and Adeyi, 2006). In 2010, UNGASS estimated that 3.6% of the population in Nigeria is living with HIV/AIDS while approximately 220,000 people died of AIDS in 2009 in Nigeria UNAIDS, 2010).

Taraba state has one of the highest HIV/AIDS prevalence rate in North Eastern Nigeria. The prevalence rate of the disease in Taraba state ranged from 7.0 to 5.2% (Fidelis, 2007). Going by the 5.2% prevalence rate in the state as at 2008, it could be estimated that about 127,167 people were living with the virus in the state. As at 2007, only 2,541 infected persons in the state were known to be placed on the antiretroviral therapy (ART) programme in the state (Oruonye, 2011).

The HIV infection progressively weakens the immune system as reflected by the reduction in the CD4 cell counts; thus making the patients vulnerable to various opportunistic infections (Grover *et al*., 2013). The antiretroviral drugs used in the Antiretroviral Therapy (ART) work by crippling the enzymes that are crucial in the replication of HIV. The CD4 cell count has been an important factor in the clinical investigation of HIV patients as well as prognostic marker for assessing HIV progression. Apart from being a leading marker of disease progression, CD4 counts have been used as an indicator of ART initiation and disease progression, deciding when to commence therapy, staging the disease, determining treatment failure, and defining the risk for mother-to-child transmission.

Two major classification systems currently are in use; the U.S Centre for Disease Control and Prevention (CDC) Classification System and the World Health Organization (WHO) Clinical Staging and Disease Classification System. The U.S. Centre for Disease Control and Prevention staging system used the CD4 count as a tool to stage HIV into categories A,B and C. This is based on whether the CD4 count is ≥500 cells/mm^3, between 200-499 cells/mm^3 and <200 cells/mm^3, respectively. It defines AIDS as all HIV – positive patients with CD4 count <200 cells/mm^3 or CD4% <14%. On the contrary, WHO staging is based on clinical findings and does not require CD4 count in order to accommodate for resource constrained setting where CD4 count testing may not be available. This study adopts the CDC staging system.

The Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS) is posing a challenge as it has become drug resistant in some patients. Consequently, treatment failure and spread of drug resistant HIV results. This compromises the effectiveness of the limited therapeutic options like the antiretroviral therapy (ART) (WHO, 2018). It therefore becomes necessary to assess the progress of HIV patients response to ART treatment. A strong advocate of this is Lee *et al.* (2014) who stated that forecasting the progression of HIV/AIDS spreads plays an important role in controlling disease transmission and alleviating health disparities. According to them, the projection of the future epidemic can

help optimize resource allocation and design efficient, economical, timely health policies targeting the high risk population and high prevalence areas.

Over the years, a number of approaches and models have been used by different researchers to explain the dynamics of HIV/AIDS infection as well as the impact of the antiretroviral therapy. A preliminary study of the transition dynamics of the human immunodeficiency virus (HIV) is one of such works (Anderson *et al*., 1986) while a work on the modelling of medical treatment of HIV/AIDS infection using Markov decision processes is another (Andrew *et al*., 2005). A multistate Markov model based on CD4 count for HIV/AIDS patients on antiretroviral therapy which aimed at assessing the impact of the therapy is also a work in this vein (Grover *et al*., 2013). The authors estimated the mean sojourn time and total length of stay before absorption, and also examined the effects of explanatory variables (that is, age, sex, mode of transmission) on the rates of transition using Cox's proportional hazard model. They stated that the implication of their findings is that it might be prudent on the part of treatment and care providers to target early therapeutic interventions to slow the progression of a person living with HIV/AIDS (PLWHA) towards immune deterioration; thereby, contributing towards some gain in life years and somewhat increased quality of life due to the reduced chances of opportunistic infections.

A research on the determination of the life expectancy of HIV/AIDS patients in Anambra State using stationary and smoothed non-stationary Markov chain models is another research in this line of study that is worth mentioning (Nwosu, 2015). The impact of antiretroviral therapy on the epidemic of HIV (Williams *et al*., 2011) is another work in this regard.

Another research work on Markov chain modelling analysis of HIV/AIDS progression: a race-based forecast in the United States (Lee *et al*., 2014) investigated the most vulnerable racial minority population (the African Americans) in the United States and the second least affected (the Caucasians) in order to predict the trends of the epidemic. The results reveal discrepancy in HIV infection, AIDS diagnosis and deaths due to HIV/AIDS among the African Americans and the Caucasians races. They stated that there is need for interventions focusing on HIV/AIDS prevention and management, optimum resource allocation and development of ANTIAIDS campaigns to reduce the infection rate.

The effects of Highly Active Antiretroviral Therapy (HAART) of stavudine, lamivudine and nevirapine on the CD4 lymphocyte count of HIV-infected Africans (Erhabor *et al*., 2006) was studied. In this work, changes in CD4 counts in the HAART treated subjects and the untreated controls were assessed based on starting baseline CD4 count; <200, $200-350$ and >350 cells/ μ L. They were able to conclude that it is important to access the CD4 lymphocyte count of HIV infected patients before the initiation of HAART, which is used as a prognostic maker in predicting the initial response to HAART and in determining the optimal time to initiate therapy.

Materials and Methods

Data description and transformation

The data for this work is the CD4 counts of a sample of 1,418 patients, receiving treatment every six (6) month at the HIV Counselling and Testing (HCT) unit of the general hospital Wukari, Taraba State, Nigeria. The CD4 cell counts of the 1,418 HIV/AIDS patients was carefully organized to reflect the transition among the states defined has; less than 200 cells/ μ L, between 200-499 cells/ μ L, and equal or greater than 500 cells/ μ L. These states were referred to as states I, II, and III representing the Good, Moderate and Poor health states of patients, respectively. This is captured in a table of transition counts as well as a transition probability matrix (Tables 1 and 2).

Some mathematical details of the Markov Chain Model

Markov Chain

If a stochastic process $\{X_t, t \geq 0\}$ is such that at any given time t_n, when the current state X_{t_n} and all previous states $X_{t_1}, X_{t_2}, \ldots, X_{t_{n-1}}$ of the process are known, the probabilities of the future states $X_{t_j}\,(j \geq n)$ depends only on the current state X_{t_n} and do not depend only on the earlier states X_{t_1}, $X_{t_2}, \ldots, X_{t_{n-1}}$. Then the process is said to exhibit Markov dependence. The set of all possible values of t is called the parameter space and the set of all possible values of X_{t_n} is called the state space.

A Markov chain is a stochastic process in which given a set of ordered time points $\{t_1 < t_2 < \ldots < t_n\}$, and for any possible sequence of states $X_{t_1}, X_{t_2}, \ldots, X_{t_{n+1}}$

$$P(X_{t_{n+1}} = x_{t_{n+1}} \setminus X_{t_1} = x_{t_1}, X_{t_2} = x_{t_2}, \ldots X_{t_n} = x_{t_n}) = P(X_{t_{n+1}} = x_{t_{n+1}} \setminus X_{t_n} = x_{t_n}) \quad 1$$

(Ugwuowo, 2009)

Transition probability matrix

Every Markov chain has associated with it transition probabilities; the probabilities of moving from one state of the chain to another (Udom 2010). Transition probabilities are usually based on frequency distribution of the number of transitions from one state to another in the system under consideration (using historic data). The frequencies are converted to estimates of the probabilities by dividing each row by its total.

Consider a finite Markov chain with n possible states, $x_1, x_2, \ldots, x_n$ Let p_{ij} be the conditional probability that the process will be in state x_j given that it was in state x_i at the preceding observation time. The transition probability matrix of the Markov Chain is defined to be the nxn matrix P with elements P_{ij}. These elements P_{ij} are also called stationary probabilities.

Thus

$$P = \begin{pmatrix} p_{11} & p_{12} & \cdots & p_{1n} \\ p_{21} & p_{22} & \cdots & p_{2n} \\ \cdots & \cdots & \cdots & \cdots \\ p_{n1} & p_{n2} & \cdots & p_{nn} \end{pmatrix}$$

These elements P_{ij} are also called stationary probabilities. They are defined as

$$P(X_n = j \setminus X_{n-1} = i) = p_{ij} \quad 2$$

N-step transition probability matrix

For any value of n ($n = 2,3...$), the nth power p^n of the matrix P in above which specify the probability p_{ij}^n that the chain will move from any state x_i to any state x_j in n-step is called the n-step probability matrix. The matrix P in 3.4 is called the one-step transition probability matrix (Udom, 2010).

Steady state probabilities of a Markov Chain

Consider a Markov Chain with r-states and the row vector

$$\pi = (\pi_1 \quad \pi_2 \quad ... \quad \pi_r)$$

such that

(i) $\pi_i \geq 0$ (ii) $\sum_{i=1} \pi_i = 1$ (iii) $\pi_j = \lim_{n \to \infty} p_{ij}^n$

where p_{ij} is as defined in 2.3.2 then $(\pi_1 \quad \pi_2 \quad ... \quad \pi_r)$ is called the steady state vector of the Markov Chain. This means that as $n \to \infty$, the probability that the chain will transit from state x_i to a state x_j is independent of the initial state x_i. π can be obtained by solving the relation

$$\pi = \pi P$$

Assessing the progress and predicting the efficacy of ART using Markov chain.

The three CD4 count states (I, II and III) in 2.1 above defines a three-state Markov chain for modeling the progress and predicting efficacy of ART. Initially the process may be in any of the three states and thereafter transit to the other state. The probability of this transition is what is known as the transition probability.

Let $\{X_t, t \in T\}$ be a Markov chain with index set T and state space S. Particularly for this work, since $S = \{I, II, III\}$ then $\{X_t, t \in T\}$ is a three-state Markov chain as earlier mentioned. The most common of this is its first order which is defined as

$$P(X_{n+1} = j \setminus X_0 = i_0, X_1 = i_1 ..., X_n = i_n) = P(X_{n+1} = j \setminus X_n = i_n) \quad 3$$

for all $i_0, i_1, ..., i_n \in S)$

We assume in this work that the chance of the process entering a future CD4 count state only depend on the immediate past CD4 count state. It does not depend on all the previous or past CD4 count states. This is the well known Markov property and it holds for order one Markov chains. The probability of transitions is estimated from data using relative frequencies. These frequencies are transition frequencies from each CD4 count state to another CD4 count state. The n-step transition probabilities (P^n), where n =1st, 2nd, 3rd,..., nth six month, is used for a six- month period assessment of the progress of the ART until steady state. Simply put, the n-step transition probability matrix (P^n),, holds the chances of patients response to ART over a six month interval (1st , 2nd , 3rd ,..., nth six month) as they move from one CD4 count state to the other. We envisage that this can be used to periodically and holistically assess the progress of patients response to ART.

The steady state probabilities for the first order Markov chain model are determined by solving the equations:

$$(\pi_1, \pi_2, \pi_3) = (\pi_1, \pi_2, \pi_3)P \quad 4$$

$$\pi_1 + \pi_2 + \pi_3 = 1 \quad 5$$

Where $\pi_1 =$ steady state probability of a good health state,

$\pi_2 =$ steady state probability of a moderate health state and

$\pi_3 =$ steady state probability of a poor health state

The mean recurrence time for a good, moderate and poor health states are computed as the reciprocals of π_1, π_2 and π_3 respectively.

As earlier mentioned, the efficacy of a treatment or therapy is a measure of maximum response of patients to treatment. In the terminology of Markov chains, we interpret this as the long run response of patients to treatment. Hence in predicting the efficacy of the ART, we make use of the long run or steady state probabilities of patients health states. These enable us to forecast the long run (steady state) chances of patients in each CD4 count state as well as their respective mean recurrence times.

Results and Discussion

Assessing the progress of patients response to ART

As earlier mentioned, the CD4 cell counts of the 1,418 HIV/AIDS patients was carefully organized to reflect the transition among the states I, II, and III representing the Good, Moderate and Poor health states of patients, respectively. This is captured in Table 1.

Table 1: CD4 transition counts of the HIV/AIDS patients

	I	II	III	Total
I	683	405	150	1238
II	704	1001	231	1936
III	133	569	378	1080
Total				**4254**

The initial transition probability matrix (P^1) was obtained from Table 1 by dividing the elements of each row by their respective row totals. This is captured in the matrix below and represented in Fig. 1 by a transition diagram. This matrix captures the initial probabilities that a patient will transits from one health state to another in the first six month of the therapy. The diagonal elements of the matrix show that there are respectively 55, 52 and 35% chance that a patient will maintain the Good, Moderate and Poor health state. The off diagonal elements show the respective chances of a patient transiting between the health states. This provides progress information on patients response to the ART in the first six month.

$$P^1 = \begin{array}{c} \\ I \\ II \\ III \end{array} \begin{array}{c} \begin{array}{ccc} I & II & III \end{array} \\ \begin{bmatrix} 0.551696 & 0.327140 & 0.121163 \\ 0.363636 & 0.517045 & 0.119318 \\ 0.123148 & 0.526852 & 0.350000 \end{bmatrix} \end{array}$$

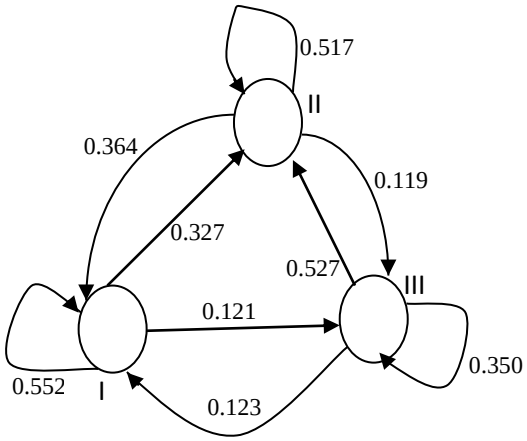

Fig. 1: Transition Diagram of patients between health states

For the other six months interval appointments, the N-step transition probability matrix was used. These were obtained by finding powers of the initial transition probability matrix (P^1). The result of these is displayed in Table 2 for P^2, P^3 …, P^{11} showing the chances of patients transition between the health states at the 2^{nd} , 3^{rd} ,…, 11^{th} six months interval appointments. P^{11} captures the steady state situation of patients response to the therapy. The diagonal elements of each matrix, shows the chance that a patient will maintain the Good, Moderate and Poor health state, while the off diagonal elements show the respective chances of a patient transiting between the health states (Table 2).

Table 2: N–step transition probability values

		Transition Probability Actual State		
Nth - Six Months Interval appointment	**Previous State**	**I**	**II**	**III**
2nd	**I**	0.438615	0.413330	0.148055
	II	0.403753	0.449030	0.147217
	III	0.302774	0.497130	0.200096
3rd	**I**	0.410778	0.435144	0.154078
	II	0.404426	0.441759	0.153815
	III	0.372698	0.461474	0.165828
4th	**I**	0.404094	0.440493	0.155414
	II	0.402963	0.441697	0.155340
	III	0.394103	0.447846	0.158052
5th	**I**	0.402515	0.441776	0.155709
	II	0.402320	0.441990	0.155689
	III	0.400001	0.443701	0.156298
6th	**I**	0.402147	0.442079	0.155774
	II	0.402115	0.442116	0.155769
	III	0.401532	0.442563	0.155905
7th	**I**	0.402062	0.442150	0.155788
	II	0.402057	0.442156	0.155787
	III	0.401915	0.442268	0.155817
8th	**I**	0.402043	0.442166	0.155791
	II	0.402042	0.442167	0.155791
	III	0.402008	0.442194	0.155798
9th	**I**	0.402038	0.442170	0.155792
	II	0.402038	0.442170	0.155792
	III	0.402030	0.442176	0.155793
10th	**I**	0.402037	0.442171	0.155792
	II	0.402037	0.442171	0.155792
	III	0.402036	0.442172	0.155792
11th	**I**	0.402037	0.442171	0.155792
	II	0.402037	0.442171	0.155792
	III	0.402037	0.442171	0.155792

Figures 2 - 4 were obtained from table 2 to better explain the progress of patients response to the therapy. Fig. 2 shows the transition probabilities from states I, II, III to state I. Here after the second appointment (the second six month period), the probability that a patient's health will remain in state I is 0.438615 (43%) chance. While the chances that it will transit from states II and state III to state I are 0.403753 (40%) and 0.302774 (30%), respectively. This shows a decreased chance of the patients health improving from the Moderate and Poor health states to the Good health in the second appointment. These chances continue to decrease over the rest of the appointments and become constant at the 11^{th} appointment. The steady state value is 0.402, explaining a 40% chance that a patient will attain the Good health state at the long run.

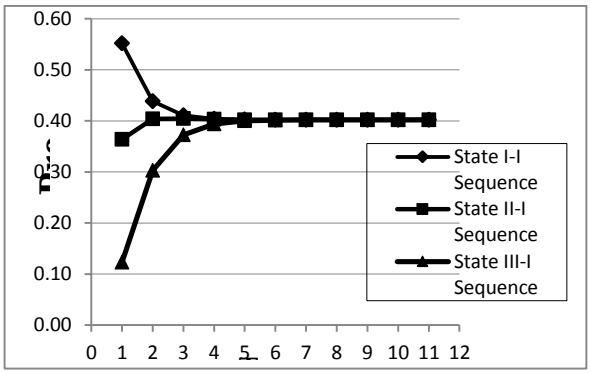

Fig. 2: Transition probabilities from states I, II, III to state I

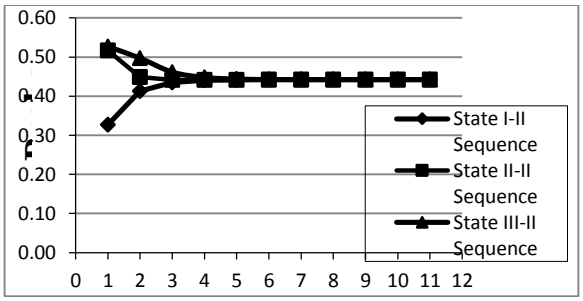

Fig. 3: Transition probabilities from states I, II, III to state II

Figure 3 shows the transition probabilities from states I, II, III to state II. In this case, the probability that a patient will remain in the Moderate health state is 0.449030 (45%) after the second appointment (the second six month period). The chance of transition from the Good and Poor health states to the Moderate health state are respectively 0.413330 and 0.497130. These chances continued to fluctuate over the rest of the appointments and became steady during the 11^{th} appointment at a value of 0.442171 (44%). This shows there is a 44% chance that a patient will attain the Moderate health state at the long run.

Figure 4 shows the transition probabilities from states I, II, III to state III. In this case, the probability that a patient will remain in the Poor health state is 0.200096 (20%) after the second appointment (the second six month period). The

chance of transition from the Good and Moderate health states to the Poor health state are respectively 0.148055 and 0.147217. These chances also continued to fluctuate over the rest of the appointments and became steady during the 11th appointment at a value of 0.155792 (16%). This shows there is a 16% chance that a patient will attain the Poor health state at the long run.

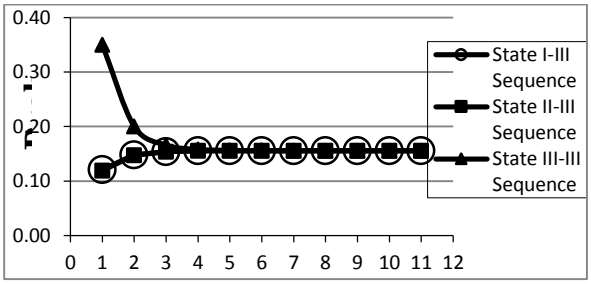

Fig. 4: Transition probabilities from states I, II, III to state III

Predicting the efficacy of the ART

The steady state or long run probabilities of patients being in the respective health state were obtained from the chances of these respective states on Table 2 during the 11th appointment. This is displayed in the matrix (P^{11}) below.

$$P^{11} = \begin{bmatrix} 0.402037 & 0.442171 & 0.155792 \\ 0.402037 & 0.442171 & 0.155792 \\ 0.402037 & 0.442171 & 0.155792 \end{bmatrix}$$

As earlier mentioned, this shows a 40, 44 and 16% chance that a patient will attain the Good, Moderate and Poor health states, respectively. The mean recurrence time (years) for each state was obtained by finding the reciprocal of their respective steady state probability. These were computed as 1.24, 1.13 and 3.21 years, respectively.

As earlier mentioned, the efficacy of a treatment or therapy is a measure of maximum response of patients to treatment. In this work this is interpreted as the long run response of patients to treatment. Therefore, in predicting the efficacy of the ART, we make use of the long run or steady state probabilities of patients health states. These enable us to forecast the long run (steady state) chances of patients being in each health state. Their respective mean recurrence time is also used to compliment this prediction. In this vein we state that the overall efficacy of the ART is such that a patient will attain a Good health state 40% of the time, a Moderate health state 44% of the time and a Poor health state 16% of the time, with mean recurrence times of 1.24, 1.13 and 3.21 years, respectively.

Conclusion and Recommendation

The following conclusions were drawn from the study:

(i) The health of the patients was assessed at each appointment to be transiting between any pair of the Good, Moderate and Poor health states at defined chances.

(ii) The overall efficacy of the ART is such that a patient will attain a Good health state 40% of the time, a Moderate health state 44% of the time and a Poor health state 16% of the time.

(iii) The mean recurrence times of the Good, Moderate and Poor health states are respectively 1.24, 1.13 and 3.21 years, respectively.

The paper, thus recommends that;

(a) The Markov chain model should be used in assessing the progress and predicting the efficacy of ART.

(b) The methodology of this work should be applied to a cohort study to further validate the results.

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