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Modelling progression in HIV/AIDS antiretroviral intake stages in Akwa Ibom State using markov decision process and survival analysis

Abstract

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) continues to be a substantial public health concern, especially in areas with high rates of occurrence. In recent time, Antiretroviral Therapy (ART) has converted HIV/AIDS into a controllable chronic ailment. Prevalence among adults aged 15–69 years, Akwa Ibom State ranked among the highest HIV at 5.5%. Consequently, of this 5.5% (178,051 people), only 23% were on ART according to the United States Agency for International Development (USAID) in April 2019. On that note, this study becomes imperative to understand precisely the effect of the epidemic dynamics and the different treatments, and how such treatments may help Akwa Ibom State to find effective ways of reducing HIV prevalence in the state. This study sought to model the progression of the survival data from Akwa Ibom State for patients who are on ART using the Markov Decision Process and some Survival time's probability distributions to understand the survival rates of HIV-positive patients on treatment follow-up. Finally, the study compares the different methods used in monitoring the progression and survival rate of patients on treatment follow-up. The result from the Semi-Markov Chain shows that an average of 88% of HIV/AIDS infected persons rejuvenated from the weaker states of immunity to stronger states after several transitions and maintained a steady state probability after 240 months. Again, the application of survival analysis to study the trend of survival rates with right and left censored data has been very insightful. The Kaplan Meier method shows a higher percentage of incremental stepwise probability of survival with increasing time of ART intake. In addition, the Cox regression analysis simultaneously appraise the association between multiple covariates and survival outcome of patients. In the overall evaluation, the result reveals that all the parameters considered in this study are significant and contribute immensely to the survival of patients.

Keywords: antiretroviral therapy, disease progression, HIV/AIDS, semi-markov chain, survival analysis

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Introduction

According to World Health Organization (WHO),[1] the African Region carries a significant burden with 25.6 million reported cases of people with human immunodeficiency virus/acquired immunodeficiency syndrome HIV/AIDS with reports of 630,000 deaths attributed to HIV in the year 2022. The journey towards meeting the Joint United Nations Programme on HIV/AIDS (UNAIDS) targets and ending the AIDS epidemic in Nigeria was initially limited by the availability of reliable and actionable data Modjarad et al.[2] However, the Federal Ministry of Health, Nigeria[3] and UNAIDS[4] using the 2018 Nigeria HIV/AIDS Indicator and Impact Survey (NAIIS) presented more robust methods to provide incidence and prevalence data for Nigeria, with a clearer representation of Nigeria's HIV epidemic. In the result, NAIIS showed a 1.4% prevalence of HIV nationally, with an estimated 1.9 million Nigerians living with HIV. Prevalence among adults aged 15–69 years, Akwa Ibom State had the highest HIV at 5.5%.[5] According to the US President's Emergency Plan for AIDS Relief (PEPFAR),[6] of this 5.5% which translates to 178,051 people, only 23% were on antiretroviral therapy (ART). The Nigeria team used these findings to launch the Nigeria treatment surge plan which realigned PEPFAR programming and resources to rapidly increase access to ensure that high HIV burden states quickly attain treatment saturation. In addition, the United States Agency for International Development (USAID) launched the ART surge in Akwa Ibom State in April 2019 based on these epidemic dynamics. Consequently, it is essential to comprehend the sequence of patients' progression through different stages of ART intake in order to optimize treatment strategies, enhance patient outcomes, and provide valuable insights for public health policies.

Markov models provide a way of handling both costs and outcomes of the progression simultaneously in a simple and intuitive manner and as such, health care planning relies on a good understanding of disease prevalence, which requires an accurate knowledge of survival patterns. Monitoring the length of survival after diagnosis is, therefore, an important component of the surveillance of HIV/AIDS as it provides the basis for evaluating individual prognostic factors.[7,8] The survival of HIV/AIDS patients depends on a variety of factors including but not limited to the individual patient's demographic factors, serological baseline factors and presence of co-morbidity.[9] On the other hand, survival analysis entails methods that measure the risk of death or progression of a disease and provide predictions that can help clinicians to estimate trends in the patient outcomes.[10] These methods also allow health planners to predict the HIV/AIDS burden on the health system and to allocate health services resources appropriately. This study proposes using a Markov Decision Process (MDP) in conjunction with Survival Analysis to model the progression of HIV/AIDS patients on ART in Akwa Ibom State.

Problem statement/justification

Most times, in modelling waiting times distributions, researchers do not consider fulfilling the basic components involved while using Markov Decision Process. In other instance, while using the survival modelling techniques, decisions are made without considering/test for proportionality of the models. In this study, emphasis is on the progression of a HIV/AIDS patient after taking the ART and the time it takes to make a record change using the Clusters of Differentiation 4 (CD4) counts. This will be achieved using the basic components of MDP to be fulfilled in addition to testing for proportionality of the survival models before an informed decision(s) is/are made.

Objectives of the study

The main aim of this study is to model and analyze the measure of progression of survival time distribution of people living with HIV/AIDS on ART use and to determine factors influencing survival of people living with HIV/AIDS on treatment follow up using Markov Decision Process and some Survival modelling techniques.

The specific objectives include:

i **Develop a model:** Construct a comprehensive model using MDP and Survival Analysis to depict the progression of patients through different stages of ART.

ii **Understand progression:** Examine the likelihood of transitioning between various stages of ART to identify the factors that impact the advancement and survival of patients as well as characterize the risk factors that affect HIV/AIDS patients' survival in the shorter to medium survival times.

iii **Optimize model strategies:** Utilize the model by comparative analysis to make informed decisions regarding the most effective technique strategies in order to improve patient outcomes.

iv **Policy formulation:** Provide valuable insights to researchers, policymakers and government to enhance ART programmes in Akwa Ibom State.

Literature review

Homogenous semi-Markov process (HSMP) was initiated in the 1950s.[11] Some recent and impactful studies on the semi-Markov processes include Corradi et al.,[12] Giuseppe et al.,[13] Goshu and Dessie,[10] Ofori et al.,[7] and Ofori et al.[14] Markov models have a long history of use in health-care service decision-making, including clinical and epidemiological applications, however, health economist have also delved into the use of Markov models in economic-evaluation studies.[15,16] According to the authors, these models are more appealing to use due to their simplicity, computational ease, accuracy and broad applicability in presentation of clinical problems. In what follows, Karnon used the Markov models traditionally to evaluate the cost-effectiveness of competing health-care technologies that require the description of patient pathways over extended time horizons. According to Gray et al.,[17] these models are most powerful when a decision problem involves risk that is continuous over time, considering that the timing of events is important and when events may happen more than once. Picking up the challenges, the authors observed that representing such clinical settings with conventional decision trees is difficult as the tree will be too "jungly" and may require unrealistic simplifying assumptions. Hence, in a health-care context, Markov decision models are mostly suited in modelling the progression of chronic disease or situations where events are likely to recur over time. On that note, the assertion by Mullins and Weisman, that Markov models incorporate a multi-stage decision process give rise to its wide usage.

The markov decision analysis model

Markov decision model remains an alternative to standard decision-analytic formulation and addresses the limitations of decision trees and as such is widely used in economic evaluations. These models have been adopted to replace the decision tree completely or can be grafted onto standard decision analysis as an equivalent to the utility structure. Markov models are based on a series of states that a patient occupies at a given point in time and the model assumes that the patient is always in one of a finite number of states of health referred to as Markov states. In each case, the states are defined with reference to clinical characteristics such as stages of disease severity, HIV/AIDs clinical stages etc. and economically important events that occur to patients over time.[10,14,16,18,19] The states are mutually exclusive and a patient is assumed to be in a single state during a cycle.

The probability of a patient occupying a given state expressed over a series of discrete time periods is called Markov cycles. Briggs and Sculpher [16] revealed that the cycle length is chosen to represent a clinically meaningful time interval and varies depending on the disease and the intervention being evaluated, ranging from one week, one month, one year etc. The authors also posited that all events are represented as transitions from one state to another and the likelihood of moving from one health state to another is called a transition probability. Transitions are assumed to take place for each cycle of the model. The transition probabilities may be constant or vary within a model. States of Markov models from which it is impossible to leave are known as 'absorbing states'; the most common example of an absorbing state in medical decision-making is death.[15,16]

The markovian property

The choice of a Markov model rests on two overall assumptions which include the Markov property and stationary assumption. The first assumption (Markov property) states that Markov models have no intrinsic property to memorize the history of the previous events to determine transitions. Therefore, the probability of moving out of a state is not dependent on the states a patient may have experienced before entering that state.[15,16,20] This is the 'memoryless' feature of Markov models, which is often referred to as the 'Markovian assumption'. This implies that individuals starting in a given state can be modeled in the same manner and that the route to arriving in a state or the time spent in a state has no influence on subsequent parameters. However, the Markovian assumption is not followed strictly in medical problems.[15] It may be possible to address it by characterizing the progressive part of the disease as tunnel states and use time dependent probabilities.[10] The stationary assumption states that parameters are time homogeneous and do not vary from one cycle to another.

Survival analysis

Survival analysis is a statistical method for data analysis where the outcome variable of interest is the time to the occurrence of an event.[21] Survival analysis could also be referred to as "time to event analysis", "transition data analysis" or "event history analysis". It is the analysis of the duration for the occurrence or non-occurrence of an event during the risk period and an individual can only be eligible to experience an event if there was a period during which they were at 'risk' of experiencing the event. Wooldridge[22] summarizes that, in survival analysis, the interest is therefore on how various treatments or demographic characteristics affect survival times.

Consequently, in medical science, time to event can be time until recurrence in a cancer study, time until change in drug regimens, time to death, or time until infection. However, some respondents may not experience a transition before the end of the observation period. These respondents are treated as right-censored observations. Censoring and truncation mechanisms can lead to incomplete observation of time. A censored observation is one whose value is incomplete due to factors that are random for each subject. A truncated observation is incomplete due to a selection process inherent in the study.[21]

Nakhaee and Law, and Assefa & Wencheko[8] observed that Survival analysis entails methods that measure the risk of death or progression of a disease and provide predictions that can help clinicians to estimate trends in the patient outcomes. These methods also allow health planners to predict the HIV/AIDS burden on the health system and to allocate health services resources appropriately. Health care planning relies on a good understanding of disease prevalence, which requires an accurate knowledge of survival patterns. Monitoring the length of survival after diagnosis is, therefore, an important component of the surveillance of HIV/AIDS as it provides the basis for evaluating individual prognostic factors. The survival of HIV/AIDS patients depends on a variety of factors including but not limited to the individual patient's demographic factors, serological baseline factors and presence of co-morbidities. Survival analysis models fall in three main categories which include non-parametric, semi-parametric and parametric. In this study emphasis will be on the first-two categories.

Nonparametric models

These models make no assumption about the shape of the hazard function or about how the covariates affect the hazard function. The hazard function is instead estimated based on the empirical data, showing change over time. The effect of covariate variables is shown only by stratifying the data into groups (by gender) to plot and contrast separate hazard functions for each group. Nonparametric models are neither able to handle continuous data nor multivariate analysis and control for other explanatory variables. Kaplan-Meier survival analysis is the primary example of the nonparametric approach to event history analysis.

Semi-parametric models

These models also make no assumption about the shape of the hazard function in relation to time but do make strong assumptions about how covariates affect the hazard function. Specifically, they assume that hazard rates are proportional between groups over time. While estimates of the shape of the hazard function may be derived empirically, these estimates are data-driven and may be considered over fitted, with the result that semi-parametric models are not considered appropriate for testing hypotheses about time dependence. According to Cleves, Semi-parametric analysis is a combination of separate binary-outcome analysis, one per failure time while the parametric analysis is a combination of several analyses at all possible failure times. These models are able to support multivariate analysis and when no covariates are considered, semi-parametric analysis such as Cox regression and non-parametric analysis produce identical estimates. Hence, semi-parametric models are often the method of choice in event history analysis. However, if no failures occur over a particular interval, such periods are considered informative and non-informative in parametric and semi-parametric analysis respectively. Cox regression, is the primary example of the semi-parametric approach to event history analysis.

In the progression, this study seeks to avail researchers, bio-statisticians and epidemiologists a better insight of the alternative methods that can be used in waiting time (survival) data analysis. These methods can be used either by themselves or as complementary tools to gain more insight into the risk factor dynamics at any given point of the patients' survival time.

Methodology

The scope of this study under theoretical pinning is categorized into proper data collection and befitting modelling techniques to ensure acceptable result. This is presented as follows:

i **Data collection:** Data is collected for this study through collaboration with stakeholders in the Hospitals, ART programs and patient surveys.

ii **Modeling techniques:** The Homogeneous Markov Chain and the survival analysis technique are used as the statistical tools used to develop the progression of model.

Data collection

Sources: Data used in this study is gathered from medical records of the University of Uyo Teaching Hospital, Akwa Ibom State, from 2013 to 2022 with the ART programs and patient surveys.

Data analysis

This section considers cleaning and preprocessing of data to handle missing values, outliers, and inconsistencies, exploratory analysis using descriptive statistics before application of the model and model validation to ensure accuracy and generalizability.

Markov decision process (MDP)

i **States:** The stages of ART intake are defined as states (e.g., initial diagnosis, different ART regimens, treatment adherence levels, and health outcomes).

ii **Transitions:** The probabilities of transitioning from one state to another based on historical data and patient characteristics are determined.

iii **Policy:** The decision policy to determine the best actions (e.g., treatment adjustments, adherence interventions) at each state to maximize long-term patient outcomes is achieved.

Progression of HIV/AIDs patients on ART drugs

According to World Health Organization (WHO),[1] the different stages of HIV/AIDS can be classified as:

Stage 1 (HIV infection): The CD4+ cell count is at least 500 cells per microliter

Stage 2 (HIV infection): The CD4+ cell count is 350 to 499 cells per microliter

Stage 3 (advanced HIV infection): The CD4+ cell count is 200 to 349 cells per microliter

Stage 4 (AIDS): The CD4+ cell count is less than 200 or the percent of CD4+ cells per microliter is less than 15% of all lymphocytes.

Consequently, the four states of the Markov process of the seriousness of HIV/AIDS sickness based on the CD4 counts of a patient[13] are defined as:

S_1 : CD4 count $\geq$ 500 cells/microliter

S_2 : 350 $\leq$ CD4 count < 500 cells/microliter

S_3 : 200 ≤ CD4 count < 350 cells/microliter

S_4 : CD4 count < 200 cells/microliter (AIDs)

D: Death.

Among the states of the semi-Markov process, the death state D 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 state D is categorized as "bad" and the others S_1, S_2, S_3 and S_4 as "good" states. As defined earlier, S_1 represents a good state, indicating a strong immunity of the HIV/AIDS infected person. The immunity of the infected person weakens as the CD4 count reduces in stages S_1 gradually to S_4. Hence, the higher the CD4 count, the stronger the immunity of the patient. Frequencies and estimated transition probabilities of between the states are summarized from the data and displayed in Table 1. The solutions for the transition probabilities $P_{ij}(t)$, where $P_{ij}(t)$ is the transition probability of an HIV/AIDS infected person transiting from i^{th} state to j^{th} state of health at time 't' using the algorithm are obtained with m = 5 states, T = 240 months, transition probability matrix P as given in Table 1 is as follows:

Description of table 1

Table 1 is a non-symmetrical transition matrix that describes the probabilities of HIV/AIDS infected person transiting from one state of health to another based on the CD4 count. The matrix has three diagonals, namely; the principal, upper and lower diagonal transition probabilities. The principal diagonal presents the probabilities of the unchangeable states of health. The upper diagonal indicates the transition probabilities from better state of health to worst states, therefore implying reduction of immunity of infected persons. The lower diagonal matrix explains the probabilities of rejuvenating HIV/AIDS infected persons from the weaker states of immunity to stronger states.

Survival analysis

i **Cohort definition:** The observation of patients based on ART stages over time to assess the relationship between the exposures and the development of the health outcome.

ii **Time-to-event data:** Time-to-event data is used to analyze the duration patients spend in each ART stage and the factors influencing progression.

Survival models

Here, the survival models (e.g., Kaplan-Meier estimator and Cox proportional hazards model) are applied to estimate survival probabilities and identify predictors of progression and survival.

Kaplan-meier estimator: This is also known as the **product limit estimator**, it is used in non-parametric statistics to estimate the survival function from lifetime data. In medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment. It is important to note that the Kaplan–Meier curve can take into account some types of censored data particularly right-censoring, which occurs if a patient withdraws from a study, is lost to follow-up, or is alive without event occurrence at last follow-up. On the plot, small vertical tick-marks state individual patients whose survival times have been right-censored. When no truncation or censoring occurs, the Kaplan–Meier curve is the complement of the empirical distribution function. The estimator of the survival function is given by:

Where t_i is the time when at least one event happened, $d_i = d(t_i)$ is the number of events (e.g. deaths) that happened at time t_i and $n_i = n(t_i)$ is the individuals known to have survived (have not yet had an event or been censored) up to time t_i .

Cox proportional hazards model

Cox proportional hazards (PH) model is one of the mathematical models designed for analysis of time until an event or time between events. It shows the hazard at time t of an individual given the covariates. The hazard at time t is a product of baseline hazard function $h_0(t)$, which is only a function of time, and exponential to the linear sum of $\beta_i x_i$ which is a function of time independent covariates.The Cox Proportional Hazard model is given by;

$$h(t|x,\ ) = h_o(x)\exp\left[\sum_{i=1}^{n} {}_i x_i\right] = h_o(x)\exp\left[\hat{a}'xi\right]$$

Where $h(t|x,\ )$ is the hazard function at time t for a subject with co-variant values $x_1, x_2, \ldots, x_n$ and the estimated coefficients of the co-variant of $\beta_1, \beta_2, \ldots, \beta_n$. $h_0(t)$ is the baseline hazard function, which is the hazard function for an individual for whom all the variables included in the model are zero, $\boldsymbol{X} = (x_1, x_2, \ldots, x_n)$ is the value of the vectors of the explanatory/predictor variables for a particular individual, $\hat{\boldsymbol{a}} = (\beta_1, \beta_2, \ldots, \beta_n)$ is a vector of the estimated coefficients of explanatory/predictor variables and *exp* is the exponential function. Cox PH model is therefore preferred over parametric event history analysis models when there is no clear theoretical reason for positing a particular baseline hazard ratio.

Empirical study

Analysis using markov decision process

Progression of HIV/AIDs patients on ART drugs using probability transition matrix

The Data is grouped into five stages and the frequencies recorded according to the number of years after the intake of the ART treatment as follows:

Group 1: 1 – 4 years

Group 2: 5 – 8 years

Group 3: 9 – 12 years

Group 4: 13 – 16 years

Group 5: 17 – 20 years

Group 1

Data on the number of patients in each of the states between 1 – 4 years of the intake of the antiretroviral drugs and their distributions are summarized in Table 1a and Table 1b, while Table 1c is the multi-state probability transition matrix given respectively as follows:

Group 2

Data on the number of patients in each states of the Markov chain between 5 – 8 years of ART regimen and their distributions are summarized in Table 2a and Table 2b, while Table 2c is the multi-state probability transition matrix given respectively as follows:

Group 3

The number of patients in each states of the Markov chain between 9 – 12 years of ART regimen and their distributions are summarized

in Table 3a and Table 3b, while Table 3c is the multi-state probability transition matrix given respectively as follows:

Group 4

The number of patients and their distributions in each states of the Markov chain between 13 – 16 years of ART intake are summarized in Table 4a and Table 4b, while Table 4c is the multi-state probability transition matrix given respectively as follows:

Group 5

The number of patients and their distributions in each states of the Markov chain between 17 – 20 years of ART intake are summarized in Table 5a and Table 5b, while Table 5c is the multi-state probability transition matrix given respectively as follows:

The state transition of HIV/AIDS Patient's ART intake

In this section, emphasis will be on computation of the conditional probabilities of being in next state S_j after t months given that the

starting state is S_i , $i \in \{S_1, S_2, S_3, S_4\}$, $j \in \{S_1, S_2, S_3, S_4, D\}$ .The results are presented in Tables 6&7 respectively. Table 8 is a display of the conditional probabilities that a patient under the ART program will be in state S_j after *t* months given that his/her current state is S_i , $i \in \{S_1, S_2, S_3, S_4\}$, $j \in \{S_1, S_2, S_3, S_4, D\}$. The results are presented as follows:

Progression of HIV/AIDs Patients on ART drugs using the n^{th} probability transition matrix

This section summarizes in Tables 9,10&11, the computation of the n^{th} transition probability of a patient being in state S_j, $j \in \{S_1, S_2, S_3, S_4, D\}$

after 12 months of the initial transition (T_1) and 240 months (T_{20})

respectively given that the starting state is S_i , $i \in \{S_1, S_2, S_3, S_4\}$ for each group. The results are as follows;

Survival models analysis

Kaplan meier estimates (K-M)

The Kaplan Meier Survival Probability is given in Table 12 to display the survival rate with time while the log-rank test is given in Table 13 to compare if there is no difference in the survival probability of an event at any time point in each of the groups.

Log rank

The log-rank test is non-parametric hypothesis test to compare two or more survival or time-to-event functions which tests the null hypothesis that there is no difference in the probability of an event at any time point in each of the groups.

$$\chi^2(log\ rank) = \sum_{i=1}^{5} \frac{(O_i - E_i)^2}{E_i}$$

Where

O_i is the observed number of deaths in each group

E_i is the expected number of deaths in each group

H_0: The Survival Probability for all groups are the same

H_1: The Survival Probability for all groups are not the same

$$\chi^2(log\ rank) = \sum_{i=1}^{5} \frac{(O_i - E_i)^2}{E_i} = 0.1791$$

$$\chi^2_{crit} = \chi^2_{0.05,4} = 9.48$$

Since chi-square critical value is greater than the log rank, therefore, the null hypothesis is accepted. Hence, the survival probability of all groups is the same.

Cox PH models

The cox regression model is given as;

$$h(t, y_i) = h_0(t)\exp[\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4]$$

Where the independent variables are defined in Table 14 and the hazard rate estimates are given in Tables 15&16 as follows

The Hazard function is given as;

$$H_o = \sum_{i:t_j \le t} \frac{d_j}{r_j}$$

Therefore $H_o = \sum_{i:t_j \le t} \frac{d_j}{r_j} = 8386$

$$h_o(t) = \exp(H_o) = \exp(0.8386) = 2.3131$$

Here, the model's parameter estimates for each group are presented in Tables 17,18,19,20&21 with the baseline hazard function $h_o(t)$ for the respective groups while the overall model for all the groups is presented in Table 22 with $h_o(t) = 2.313$ as follows:

$$h(t, y_1) = 1.2224\{\exp(-64.867x_1 - 0.614x_2 + 0.564x_3 + 18.884x_4)\}$$

From the parameter estimates in Table 17, the significant parameters were, β_1 and β_3. Therefore, the variable (Gender and Initial CD4 count) contributes significantly in the survival of HIV/AIDS status of patients. This is might be because the year of intake of ART drugs is at initial stage of [1-4] years.

From the parameter estimates in Table 18, the significant parameters were β_1 , β_3 and β_4 . Therefore, the variable (Gender, Initial CD4 count and Years of ART Intake) contributes significantly in the survival of HIV/AIDS status of patients.

From the parameter estimates in Table 19, the significant parameters were β_1 , β_2 and β_3 . Therefore, the variable (Gender, Weight and Initial CD4 count) contributes significantly in the survival of HIV/AIDS status of patients.

From the parameter estimates in Table 20, the significant parameters were, β_1 and β_3 . Therefore, the variable (Gender and Initial CD4 count) contributes significantly in the survival of HIV/AIDS status of patients.

From the parameter estimates in Table 21, β_1 is the only significant parameter. Therefore, the variable (Gender) contributes significantly in the survival of HIV/AIDS status of patients.

From the parameter estimates in Table 22 shows the Cox regression analysis of survival rates of patients from all the groups. The result shows the overall parameters estimates in all the groups and the significant parameters are $\beta_1, \beta_2, \beta_3$, and β_4 . Therefore, the variables (Gender, Weights, Initial CD4 count and Years of ART intake) contribute significantly in the survival of HIV/AIDS status of patients.

Discussion of result

This section considers a comprehensive discussion of the step by step results of analysis carried out using the semi Markov chain and the survival analysis approaches. As seen from Table 1c of Group1, the percentage of patients remaining in State 1 S_1 is 81% while that of transitioning from state 1 to states 2, 3, 4 and D remain approximately 8%, 4%, 3% and 3% respectively. In considering state 2 S_2, the percentage of patients remaining in state S_2 is 30% while that of transitioning from state 2 to state 1, 3, 4 and D remain approximately 44%, 18%, 4% and 4% respectively. Again, in State 3 (S_3), the percentage of patients remaining in the same state is approximately 28% while that of transitioning from state 3 to state 1, 2, 4 and D remain 41%, 24%, 2% and % respectively. Also, considering State 4 S_4 ,the percentage of patients remaining in state S_4 is 24% while that of regaining immunity from state 4 to state 1, 2 and 3 remain approximately 15%, 19% and 36% respectively. However, 7% of the patients moved from S_4 to D. As stated in the literature, State D remains the absorbing state. This result shows that, even when a patient's immunity state has been classified into the poor states, with the intake of ART, there are possibilities that within the first four years, such individuals could regain immunity to a good state. Again, higher percentages of gaining immunity from bad states to a better state have been recorded during this time frame and agrees with Ofori et al.[7]

Result from Table 2c of Group 2 reveals that, the percentage of patients whose health status or immune system still remain in the same S_1 is 75% while those whose immune system have changed from state 1 to states 2, 3, 4 and D remain 9%, 12% 2% and 2% respectively. Considering S_2, the percentage of patients remaining in the same S_2 is 18% while that of transitioning from state 2 to states 1, 3 4 and D remain approximately 63%, 12%, 3% and 3% respectively. Again, in S_3, the percentage of patients remaining in S_3 is 13% while that of moving from state 3 to states 1, 2, 4 and D remain 58%, 23%, 4% and 2% respectively. Also, S_4 in the percentage of patients not having the chance to leave their worst state of health challenge stands at 16% while that of regaining immunity from state 4 to states 1, 2 and 3 remain 27%, 29% and 26% respectively. Moreover, 3% of the lost immunity and were absorbed in state D. This result still affirms the fact that a patient whose CD4 count is less than 200 cells/microliter, after taking the ART regimen could regain his/her immunity. Again, the result suggest an increase percentage of gaining immunity from bad states 2, 3 and 4 to a good state S_1 after 5-8 years of ART intake.

The result of Group 3 in Table 3c reveals that, the percentage of patients remaining put in state S_1 is approximately 78% while that of transitioning from state 1 to state 2, 3, 4 and D remain 10%, 7%, 3% and 1% respectively. The development in S_2 reveals that 13% of the patients remained in the same state S_2 while 65% gained immunity with an improved CD4 counts to state 1, 13%, 5% and 4% of the patients loss CD4 counts from state 2 to state 3, 4 and D respectively. Again, in State S_3, the CD4 counts level of 15% of the patients remained unchanged while 50% and 24% of the patients had improved gains in CD4 counts from state 3 to states 1 and 2 respectively. However, 4% of the patients had a loss in CD4 counts from state 3 to states 4 and D respectively. Also, considering S_4, the percentage of patients remaining in S_4, is 8% while that of transiting from states 4 to state 1, 2, 3 and D remain approximately 45%, 20%, 19% and 4% respectively. Again, the result has further confirmed that greater percentage of patients moved from the worst state to better states. In addition, this result has established that one can progress from low immunity states to the high immunity states with the intake of ART drugs.

Result from Table 4c of Group 4 reveals that, the percentage of patients whose immune system did not change in state S_1 is 70% while those whose CD4 counts dropped from state 1 to state 2, 3, 4 and D remain at 18%, 5%, 5% and 2% respectively. Again, the result shows that 6% of patients remained in S_2, while a greater percentage of 65% of the patients gained immunity from state 2 to state 1. However, 15%, 7% and 7% of the patients transitioned from state 2 to states 3, 4 and D respectively. In State S_3, the percentage of patients remaining put in state S_3 is 14% while that of transiting from state 3 to a higher CD4 count states 1 and 2 are 61% and 15% respectively. It was also noticed that 7% and 3% of the patients moved from S_3 to S_4 and D respectively. More so, in S_4, the percentage of patients remaining in state S_4 is 6% while those whose CD4 counts have significantly increased from state 4 to state 1, 2 and 3 remain 52%, 23% and 16% respectively. But 3% of the patients lost their CD4 counts from S_4 to D.

Result from Table 5c of Group 5 reveals that, the percentage of patients who's CD4 remained unchanged in state S_1 is 100% while the percentage of transitioning from state 1 to state 2, 3, 4 and D remained at 0% respectively. This is an indication that once a patient has maintained a higher CD4 count over a long period of time, say, 17-20 years, there is a high probability that such a patient will remain healthy and not loose CD4 count to any other state. In S_2, the percentage of patients remaining in state S_2 is 23% while that of transitioning from S_2 to S_1 is 46%. However, 15%, 8% and 8% of the patients moved to S_1, S_4 and D respectively. Again, in S_3, the percentage of patients remaining in S_3 is 17% while that of transitioning from state 3 to states 1 and 2 remained at 56%, and 17% respectively. However, 6% of the patients lost immunity to states 4 and D respectively. Also, in S_4 the percentage of patients remaining put in state S_4 is 16% while that of transitioning from state 4 to states 1, 2 and 3 remain 52%, 10% and 14% respectively. Eventually, 10% of the patients transitioned from state 4 to death.

The results from Tables 1c to 5c show the significant higher probabilities of transitioning from lower to higher CD4 counts in the lower diagonals of the matrices against the negligible lower probabilities in transitioning from higher to lower CD4 counts in the upper diagonal of the matrices. This result is in contrast with Ofori et. al.[14]

The conditional probability of a patient transitioning given the current status is computed and displayed in Tables 6 and 7. The results show the probabilities of being in state $j \in \{S_1, S_2, S_3, S_4, D\}$ after t months given that the patient entered at $t = 1$ in state $i \in \{S_1, S_2, S_3, S_4, D\}$ .The result can be interpreted as follows: For an HIV/AIDS patient in a given state of the disease undergoing ART regimen, the probability of being in same state ie. $S_2 \to S_2, S_3 \to S_3$ and $S_4 \to S_4$ decreases over time. However, the "good" state $S_1 \to S_1$, maintained a higher probability of improvement with time after the ART intake. With the good or alive states, the results show that the probability of being in a better state is non-zero and greater than the probability of being in worst states. For example, $S_2 \to S_1$, $S_3 \to S_1$, $S_4 \to S_1$, etc. It is clearly seen that there is a very high probability of moving from a bad state to the next good state than moving from a good state to a bad state. The probability of transitioning from state 1 to any bad states 2, 3, 4 and D reduces completely to zero after 240 months while that of moving from state 2 to any bad states 3, 4 and D reduces to 15%, 8% and 8% respectively after 240 months. Again, transitioning from state 3 to states 4 and D fluctuates between 2% and 6% respectively from 48 to 240 months. That is, for a patient undergoing the ART program, it is more likely probable to be in good

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state than to be in worse state as clearly demonstrated by the transition probabilities. This further agrees and aligned with the results in Ofori et al.,[14] Shoko and Chikobvu,[23] and Pandey and Galvani.[24]

Furthermore, the conditional probability that an HIV/AIDS patient who is currently in a given state $i \in \{S_1, S_2, S_3, S_4\}$ will be in the subsequent "worse" state, say, $j \in \{S_2, S_3, S_4.D\}$ after t months is displayed in Table 8. Here transitions within the "good" states moving to the next "worst" states are considered. The progressions are from $S_1 \to S_2$, $S_2 \to S_3$, $S_3 \to S_4$ and $S_4 \to D$. The peaks may indicate there is time when a patient will attend the probability of being at good state. On average, transitioning from a good state to the next bad state in each of $S_1 \to S_2$, $S_2 \to S_3$, $S_3 \to S_4$ and $S_4 \to D$ is given as 9%, 15%, 5% and 5% respectively. The transition probabilities from $S_1 \to S_2$ show an improvement over time with zero probability of going to worst state at t=240 months while $S_3 \to S_4$ and $S_4 \to D$ has the least average probability of transitioning to the next worst state 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 decreases with increasing time. This can be interpreted as the probability that an HIV/AIDS patient in states 3 and 4 have minimal average probability of transitioning to next worst/death states respectively with time. This is in line with the literature by Ofori et al.,[7] and Mirahmadizadeh.[19]

The n^{th} transition probability for all the groups are computed and displayed in Tables 9, 10 and 11. The result shows the probabilities of being in state $j \in \{S_1, S_2, S_3, S_4, D\}$ after 12/240-months of transitioning to multiple steps given that the patient entered at t=1 in state $i \in \{S_1, S_2, S_3, S_4\}$. It is observed that the result of analysis has conformed to the established theory in literature of a steady-state probabilities of the Markov Chain. After 240 months of sufficient transitions, the system reaches a stable distribution where the probabilities of being in each state can no longer change significantly in groups 1-4. However, in group 5, the result shows that after 240 months of n^{th} state transition, the probability of a patients remaining in state 1 $S_1 \to S_1$ is 1. Also, patients in other bad state of health regained 100% immunity to retain state 1. The result further revealed that after 12 months of ART program, the probability of being in same state i.e. $S_2 \to S_2, S_3 \to S_3$ and $S_4 \to S_4$ after a sequence of n^{th} transitions decreases with time. However, in the "good" state $S_1 \to S_1$, the patients maintained a higher probability of improvement after n transitions with increasing time. With the good or alive states, the results show that the probability of being in a better state is non-zero and almost 5 times greater than the probability of being in worst states. As shown in the Tables 9-11, the average probability of 88% is recorded in moving from $S_2 \to S_1$, $S_3 \to S_1$, $S_4 \to S_1$, after 12 months of n transitions and a steady-state is reached after 240 months in groups 1-4, while group 5 recorded a perfect transition to state 1 from all the states with probability 1. That is, for a patient undergoing the ART program, it is more likely probable to be in good state than to be in worse one as clearly demonstrated by the transition probabilities. Again, transitioning within the "good" states to the next "worst" states are considered. The progressions are from $S_1 \to S_2$, $S_2 \to S_3$, $S_3 \to S_4$ and $S_4 \to D$ .The peaks indicate that there is time when a patient will attend the probability of being at good state. Moreover, the transition probabilities from $S_1 \to S_2$, $S_2 \to S_3$ and $S_3 \to S_4$ decreases in probability in the four groups and over time with zero probability in group 5 of going to the next worst state at t=240 months while $S_1 \to D$ remain 0%, the transitioning from $S_2 \to D$, $S_3 \to D$ and $S_4 \to D$ remained at 13%, 11% and 14% respectivly. It is interesting to find out that, within the good states, the transition probability from a given state to the next worse state decreases to zero with time while every other state transitioned to state 1 only with minimal probability absorbed in death case with increasing time. This can be interpreted as the probability that an HIV/AIDS patient in state 2, 3 and 4 will be in the state 1 with an increasing probability with time. That is, a patient who is in the second, third and fourth states has a higher chance of living after 240 months of ART intake. This findings agrees with Mirahmadizadeh,[19] however, in contrast, Ofori et al.[14] observed significant increase in probability of transitioning from higher to lower CD4 counts of patients.

From Table 12, the Kaplan Meier approach is used to estimate the unadjusted survival probability beyond a certain time point. It is clearly seen that, the probability of survival started with 97% in 1-4 years and increases with time mostly at its peak in 5-8 years to about 98%. However, it drops back to 97%, 92% and 89% at 9-12 years, 13-16 years and 17-20 years respectively. The result shows a typical Kaplan Meier property of stepwise decrement from state 1 to state 4 in each of the groups and this is in agreement with the result from the semi Markov chain. Also, the log-rank test shown in Table 13 demonstrates an unadjusted comparison between the groups and reveals that the survival probabilities in each group are the same.

From the parameter estimates in Table 17, the significant parameters are Gender and Initial CD4 counts which contribute significantly in the survival of HIV/AIDS status of patients. This could be because the year of intake of ART drugs is at initial stage of [1-4] years. Again, the parameter estimates in Table 18 shows that the significant parameters Gender, Initial CD4 count and Years of ART Intake that contribute significantly in the survival of HIV/AIDS status of patients. In Table 19, the significant parameters are Gender, Weight and Initial CD4 count are significant in the survival of HIV/AIDS status of patients. Gender and Initial CD4 counts are the significant parameters in the survival of status of patients from Table 20. However, it was only Gender that was significant in the survival of patients Table 21 of group 5.

In summary, the overall parameters estimates of the Cox regression analysis of survival rates of patients from all the groups as shown in Table 22 reveals that Gender, Weights, Initial CD4 count and Years of ART intake contribute significantly in the survival of HIV/AIDS status of patients.

Conclusion

In utilizing a combination of Markov Decision Process and Survival Analysis, this study has successfully and effectively modeled the progression of HIV/AIDS patients as they go through different stages of antiretroviral intake. This approach provides a robust method for comprehending and enhancing the outcomes of antiretroviral therapy. This project has been able to generate valuable insights that will be useful to optimize treatment strategies and inform public health policies in Akwa Ibom State and in extension Nigeria. The ultimate goal is to improve patient care and health outcomes. Again, the application of survival analysis to study the trend of survival with right and left censored data has been very insightful. The Kaplan Meier survival technique shows an incremental stepwise probability of survival with increasing time of ART intake. In addition, the Cox regression analysis has simultaneously appraise the association between multiple covariates and survival outcome of patients. In the overall evaluation, the result reveals that all the parameters considered in this study are significant and contribute immensely to the survival of patients. The challenges encountered in this study is that the hospital did not keep track of most of the deaths in their records as some patients might discontinue the ART Programme

without a feedback resulting in censored data. Again, worthy of note in this study is the choice of State 4 as a bad state which is based on existing definition in literature of CD4 counts of less than 200 cells/microliter. However, the result of this study has shown that patients considered to be in State 4 (CD4 count less than 200 cells/microliter) has more than 80% chances to move to the "Good State" after 12/240 months and survive. This study has revealed and confirmed that considering the states of a semi Markov chain for studying the transition of patients from one state of health to another, patients with CD4 count less than 200 cells/microliter can actually survive with intensive care on their ART regimen and this supports that a patient with AIDS could still survive. Hence, it is save to categorize the Death state as absorbing state. The study has also establish a comparative analysis of the inferential power associated with each of the Survival modelling techniques and the Markov Decision Process. Again, the findings of this study have created a pathway on the benefits of intake of ART. In addition, this study has reveal an enhance and effective comparison approach of the failure times distribution given the proportional hazards assumptions of the survival models and Markov decision process. While the Markov chain gave a higher probability of transitioning from other states to the good state after 240 months, the survival analysis summarizes that all the covariates contributed significantly after 240 months.

There should be a feedback mechanism to monitor patients who reneges from the program as a result of improvement/no improvement and those who lost their lives during the process. Other researches could make use of viral loads to determine the survival rates. Researchers in epidemiological studies are encouraged on using the model for patient monitoring and tailored interventions/care for HIV/AIDS patients in ART.

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Conflicts of interest

The authors declare there are no conflicts of interest.

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