Mathematics and Statistics 10(3): 588-602, 2022
DOI: 10.13189/ms.2022.100315 http://www.hrpub.org

Weibull Distribution as the Choice Model for State-Specific Failure Rates in HIV/AIDS Progression

Nahashon Mwirigi[1,*], **Dr. Stanley Sewe**[1], **Dr. Mary Wainaina**[1], **Prof. Richard Simwa**[2]

[1]Department of Mathematics and Actuarial Sciences, Catholic University of Eastern Africa (CUEA), Kenya

[2]Department of Mathematics, University of Nairobi (UoN), University Way, Kenya

Received February 6, 2022; Revised March 16, 2022; Accepted April 15, 2022

Cite This Paper in the following Citation Styles

***(a)**: [1] Nahashon Mwirigi, Stanley Sewe, Mary Wainaina, Richard Simwa, "Weibull Distribution as the Choice Model for State-Specific Failure Rates in HIV/AIDS Progression," Mathematics and Statistics, Vol.10, No.3, pp. 588-602, 2022. DOI: 10.13189/ms.2022.100315*

***(b)**: Nahashon Mwirigi, Stanley Sewe, Mary Wainaina, Richard Simwa, (2022). Weibull Distribution as the Choice Model for State-Specific Failure Rates in HIV/AIDS Progression. Mathematics and Statistics, 10(3), 588-602, DOI: 10.13189/ms.2022.100315*

Abstract This study considered the problem of selecting the best single model for modeling state-specific failure rates in HIV/AIDS progression for patients on antiretroviral therapy with age and gender as risk factors using exponential, two-parameter, and three-parameter Weibull distributions. CD4 count changes in any two consecutive visits, the mean waiting time (μ), and transitional rates (λ) for remaining in the same state or transiting to a better or a worse state were analyzed. Various model selection criteria, namely, Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), and Log-Likelihood (LL), were used in each specific disease state. The Maximum Likelihood Estimation (MLE) method was applied to obtain the parameters of the distributions used. Plots of State-specific transition rates (λ) depicted constant, increasing, decreasing, and unimodal trends. Three-parameter Weibull distribution was the best for male patients and patients aged (40-69) years transiting in the states 1-2, 3-4, and 4-5, and 1-2, 3-4, and 5-6, respectively, and for male, female patients, and patients aged (40-69), remaining in the same state. Two-parameter Weibull distribution was the best for female patients and patients aged (20-39) years transiting in the states 1-2, 2-3, 4-5, and 1-2, 2-3, 3-4, respectively. Exponential distribution proved inferior to the other two distributions used.

Keywords Markov Chain, Markov Process, Semi Markov Process, Stochastic Process.

1 Introduction

HIV/AIDS has evolved through several successive CD4 cell count stages over time, with varying waiting times in each stage, the final stage being death [18].

Exponential and non-exponential models have been applied widely in modeling the state holding time. Exponential models assume constant hazards, while non-exponential models assume increasing, decreasing, unimodal, and bathtub hazards [2, 1, 3].

Users of constant hazards assumed that the patient progresses irreversibly through all the consecutive CD4 cell count disease states irrespective of the age or gender of the patient [2, 4, 5, 6]. They failed to consider the current development in therapy, competing risks of death between disease-specific mortality rates, and age-specific mortality rates, which may have a direct or indirect effect on the failure rate of the model and, consequently, the distribution of the waiting time [26, 27].

Treatment impacted positively on the health of the patient. However, the effect depended on the initiation time, age, gender of the patient, and adherence to therapy in terms of medication and dietary requirements [2, 4, 5, 6, 3, 28, 23].

The transition rate depended on gender. Male patients were more likely to transit to a worse stage than females. The risk of the disease increased with age. Elderly patients have a higher burden of competing risks and a higher rate of treatment-related complications that will always conspire to dilute any form of intervention [6, 22, 6, 18].

The capacity to produce CD4 cells after chemotherapy is inversely related to the patients' age [29]. Patients' gender was the other prognostic factor, with women having lower

viral load and higher CD4 cell count than men at diagnosis and better survival than men though not significantly different [30, 21, 20, 19].

Women were at an increased risk of death than men but had a lower risk of disease progression and higher infection rate in the youngest age groups. In contrast, men had a higher infection rate in older groups and experienced nearly twice the mortality of women. Both sexes showed similar immune suppression rates and higher treatment rates in older groups [29, 31, 32].

The non-exponential distributions, namely, the two-parameter and three-parameter Weibull distributions, allowed reverse transitions and transitions from the other non-absorbing states to the absorbing state [7, 8, 9, 39].

Researchers applied Weibull distributions in modeling the state waiting time in the semi-Markov models allowing non-constant failure rates [6, 33, 7, 34, 39].

Observing that the choice of the distribution was of paramount importance as the co-variate that influences the transition depends on it [33].

Modeling waiting time using Weibull distributions in semi-Markov models provided dynamic probabilities with a higher rate of decline and more minor deviations. Weibull distributions were more flexible and preferable to exponential distributions. Patients receiving therapy were more likely to transit to a better state than those not receiving it [35, 36, 37, 6, 19, 38].

Treatment failure was common in older patients [40, 6, 41, 29, 42, 43].

Patients' adherence to therapy and fluid intake impacted positively on the disease rate of progression [44].

Four states semi–Markov models were also used to model HIV/AIDS progression based on CD4 cell count levels [6, 33, 7, 34].

Gender was one of the significant predictors of the intensity of transition between states, with male patients being more likely to transit to a worse disease state than their female counterparts [39, 45, 31, 21, 25, 46].

Each of the distributions was used across all the disease states disregarding the uniqueness of the disease states in terms of CD4 cell count levels, the intervening effect of dependent and independent risk factors, and their relative effects on failure rates of specific disease states. Nevertheless, the models provided an excellent fit to the data but led to substantially different estimated failure rates and consequently different standard errors, different survival rates, and predictions. Therefore, the researcher faces a difficult decision on how to proceed [12, 13, 14, 15].

The best single model can be selected using model selection criteria to fit the data, obtain state-specific failure rates, and predict the patients' survival. However, selecting a single model ignores model uncertainty, and the inferences made will be narrow, misleading, and conditional on the selected model [24].

In addition, using a single model across all the disease states irrespective of the risk factors, the uniqueness of various disease stages in terms of the CD4 count, the impact of time-dependent risk factors, and their relative risk on the hazard rate will be ignored. This study strives to address the problem of selecting the best single model for describing failure rates of specific states in HIV/AIDS progression for patients on antiretroviral therapy.

The study used actual secondary data collected from a referral hospital in Kenya. The data were categorized by age and gender, considering a seven CD4 cell count stages; S1 (> 899), S2 (700-899), S3 (500-699), S4 (350-499), S5(200-399), S6 (0-199), and Death (Death). However, for the seventh state (Death), there was with no data, hence ignored. Patients were categorized into the six disease states using CD4 cell count levels recorded during the hospital visits. It was pretty evident from the CD4 cell count levels that some patients remained in the same state while others transited to a worse or a better disease state within two or more consecutive visits. Patients also transited from any non-absorbing states directly to the absorbing states, though very few. These findings were consistent with the advocates of non-exponential models who reported that a patient on medication could remain in the same state, transit to a higher or a lower disease state within any two or more observation times, or transit from any of the non-absorbing states to the absorbing state. Therefore the hazard rate can be constant, decreasing, increasing, unimodal, or bathtub [7, 8, 9, 39].

Therefore, the paper strives to identify which distribution is applicable for modeling the failure rates at every disease state for male and female patients and patients in the age groups (20-39) years and (40-69) years. Modeling failure rates in all the six disease states for all patients was done using the exponential, two-parameter Weibull, and three-parameter Weibull distribution hazard rates. All patients considered were categorized as either remaining in the same state, transiting to a worse state, or transiting to a better state.

Estimating the parameters of the three single distributions was achieved through the Maximum Likelihood Estimation (MLE) method. Evaluation of the performance of the three single distributions in modeling the state-specific failure rates done using model selection criteria, namely, Akaike Identification Criteria (AIC), Bayesian Identification Criteria (BIC), and Log-Likelihood (LL).

The ideal distribution for modeling failure rates in a specific state considering the intervening effect of some risk factors, namely, therapy, age, gender, and relative risk, was identified. It was pretty evident that no single distribution can be used across all disease states in modeling state-specific failure rates for patients on antiretroviral therapy, considering the intervening effects of gender and age. The results showed that the hazard rates could be constant, decreasing, increasing, unimodal, or bathtub. The discovery improved the previous work of the advocates of the exponential distribution and the advocates of non-exponential distributions. The advocates of the exponential distribution assumed constant failure rates only. In contrast, the advocates of non-exponential distributions allowed constant, decreasing, and increasing hazards, alluding that Weibull distributions were more flexible and preferable than exponential distributions. Moreover, it is also a great stride in modeling failure rates in HIV/AIDS progression for patients on antiretroviral therapy. This paper proposes

applying a specific distribution in each state, depending on the risk factors and their relative effects on the hazard rates. This approach is different from the previous approach of applying the same distribution across all disease states irrespective of the intervening effects of risk factors, their relative risk, and the uniqueness of CD4 cell count states.

2 Materials and Methods

2.1 Statistical Model

We analyzed the performance of exponential distribution, two-parameter Weibull distribution, and three-parameter Weibull distributions. We considered a seven-state CD4 count with the following disease states categorized by their CD4 cell count (mm^3) distribution: S1 (>899), S2 (700-899), S3 (500-699), S4 (350-499), S5(200-399), S6 (0-199), and S7 (Death). However, we ignored the seventh state (Death), whose data was unavailable. The Maximum Likelihood Parameter Estimation (MLE) method was applied to obtain the exponential and two-parameter Weibull distribution parameters. For the three-parameter Weibull distribution, the maximum likelihood equations were not in closed form. Therefore, the Newton-Raphson iterative method for maximizing the Log-Likelihood (LL) function failed to converge. We, therefore, used Modified Maximum Likelihood Estimation (MMLE) method [47].
We analyzed the performance of exponential, two-parameter, and three-parameter Weibull distributions using various model selection criteria: Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), and the Log-Likelihood (LL). The analysis provided the best single model for modeling state-specific failure rates for each age group and gender.

2.2 Modeling of State Holding Time Using Exponential Distribution

The probability density function of an exponential distribution is given by;

$$f(x,\lambda) = \lambda e^{-\lambda x} \qquad x > 0, \theta > 0 \tag{1}$$

The Log-Likelihood function is;

$$L(\underline{X},\lambda) = \lambda e^{-\lambda \sum_{i=0}^{n} X_i} \tag{2}$$

Differentiating (2) with respect to (λ) and equating the derivative to zero (0):

$$\hat{\lambda} = \frac{n}{\sum_{i=0}^{n} X_i} = \frac{1}{\bar{X}_n} \tag{3}$$

It can be easily proved that $\hat{\lambda}$ is the maximum likelihood (MLE) of λ by showing that:

$$\frac{\delta^2 l(\lambda)}{\delta^2(\lambda)}\Bigg]\lambda = \hat{\lambda} = -\bar{x}_n{}^2 < \theta \tag{4}$$

Where n is a natural number,$x_i \epsilon (0,\infty)$

[48]
Therefore,$h(x) = \lambda$, a constant
Therefore from (3), the hazard function for a random sample with an exponential distribution will be given by;

$$h(x) = \lambda = \hat{\lambda} = (\bar{X})^{-1} \tag{5}$$

The hazard function of exponential distribution can only accommodate a constant failure rate.

2.3 Modeling of State Holding Time Using Two-Parameter Weibull Distribution

Weibull distribution has two parameters, namely the shape parameter λ and the scale parameter θ. The probability density function of the Weibull distribution is given by;

$$\begin{cases} \frac{\lambda X^{\lambda-1}}{\theta^{\lambda}} \exp\left[-\left(\frac{x}{\theta}\right)^{\lambda}\right] & , x > 0, \theta > 0, \lambda > 0, \\ & 0 \text{ elsewhere} \end{cases} \tag{6}$$

$$\text{The survival function is } S(t) = exp[-\frac{x}{\theta}^{\lambda}] \tag{7}$$

The hazard function is $h(t) = \frac{f(x)}{s(t)}$

$$= \frac{\frac{\lambda x^{\lambda-1}}{\theta^{\lambda}} exp\left[-\left(\frac{x}{\theta}\right)^{\lambda}\right]}{exp\left[-\left(\frac{x}{\theta}\right)^{\lambda}\right]} = \frac{\lambda x^{\lambda-1}}{\theta^{\lambda}} = \left(\frac{\lambda}{\theta^{\lambda}}\right) x^{\lambda-1} \tag{8}$$

The hazard function depends on x
For $\lambda > 1$, the rate will increase, and for $\lambda < 1$ hazard rate decreases with increasing x.
For $\lambda = 1$, the hazard rate will be constant—a case of the exponential distribution.
The hazard function, $h(t) = (\frac{1}{\theta})$, which is a constant, is similar to the hazard function of the exponential distribution. Therefore, the exponential distribution is a case of the Weibull distribution where $\lambda = 1$.
Therefore, Weibull distribution can take care of the varying hazard rates at varying stages of the disease progression, accommodating the effect of the covariates, which indirectly or directly affect the failure rates.
However, the hazard function of the Weibull distribution is limited to constant, increasing, and decreasing hazard rates. It cannot accommodate uni-modal or bathtub hazards.

2.4 Modeling of State Holding Time Using Three-Parameter Weibull Distribution

A random sample has a three-parameter with parameters $\alpha, \beta, \& \mu$. The density functions is given by:

$$f(x;\alpha,\beta,\mu) = \begin{cases} \frac{\alpha}{\beta}\left(\frac{x-\mu}{\beta}\right)^{\alpha-1} exp\left[-\left(\frac{x-\mu}{\beta}\right)^{\alpha}\right] & , x \geq \alpha \\ & , 0 \text{ Elsewhere} \end{cases} \tag{9}$$

X $\sim We(\alpha,\beta,\mu)$, α, β, and μ (the shape, scale, and location parameters).

Holding α, and β constant and changing μ will result in a parallel movement of the density curve over the abscissa. Changing β while α and μ are constants, changes the density at x in the direction of the ordinate, shape parameter α is responsible for the appearance of a Weibull density. For location $(\mu = 0)$;

$$f(x;\alpha,\beta,0) = \begin{cases} \frac{\alpha}{\beta}\left(\frac{x}{\beta}\right)^{\alpha-1} exp\left[-\left(\frac{x}{\beta}\right)^{\alpha}\right] & , x \geq \alpha \\ & , 0 \text{ Elsewhere} \end{cases} \tag{10}$$

a special case of two-parameter Weibull distribution that allows constant, increasing, and decreasing hazard rates.

3 Data

Secondary data for over three thousand patients who visited a referral hospital in Kenya from 2003 to 2014 was collected using a customized data collection tool and categorized by age and gender. Categories of gender were male and female, while age categories were (20-39) years and (40-69) years. Patients with only one visit were left-censored, and we considered all other patients with at least two visits. We concealed patients' identities by assigning each patient a unique code. We calculated CD4 cell count change for any two consecutive visits and the waiting time between two consecutive states (higher or a lower disease state). We also calculated a patient's time in the same disease state in two consecutive visits.

4 Data Analysis

4.1 Summary of Observed Transitions for Male and Female Patients and Patients aged (20-39) Years and (40-69) Years

Female patients dominated the list of patients visiting the hospital for antiretroviral therapy from 2003 to 2014, registering 2165 visits, followed by patients aged (40-69) years, registering 2007 visits, while patients aged (20-39) registered 1374 visits. Male patients registered were the least, registering only 1216 visits within the period showing clearly that the female gender and older group of patients have higher treatment rates, findings consistent with [29, 31, 32]. In Table 1, patients in both age groups and both gender transited to a better, worse disease state or remained in the same state within any two consecutive visits and were more likely to remain in the same state than to transit to a better or a worse state—especially patients in state one and state six. For example, for female patients, 71 out of 134 (52.99%) and 166 out of 357 (46.47%) of patients in state one and state six, respectively, were found to be still in the same state during the second visit (Table 2). For male patients, 14 out of 46 (30.4%) and 163 out of 305 (53.44%) of patients in states one and six, respectively, remained in the same state (Table 1). For patients aged (20-39) years, 39 out of 76 (51.32%) and 123 out of 238 (51.68%) of patients in states one and six, respectively, remained in the same state (Table 3). For patients aged (40-69) years, 46 out of 104 (44.23%) and 206 out of 424 (48.58%) of patients in states one and states six, respectively, remained in the same state (Table 4). However, patients transiting to a worse or a better diseases state were likely to transit to only a single state higher or lower (preceding state or succeeding state), for example, S2-S3 and S2-S1, S3-S4 and S3-S2, S5-S6, and S5-S4. Transition from state 1 , 2 & 3 to state 6 was confirmed to be very rare, with 0, 3, & 7 patients transiting from states 1,2, & 3 to state 6 respectively. The transition from states 4, 5, & 6 to state 1 was rare, with only 9, 3, & 3 patients transiting to state 1, respectively. (Table 1). For Female patients (Table 2) transition from state 1, 2, & 3 to state 5 & 6 was rare with 2, 2, & 6 patients transiting from state 1, 2, & 3 to state 6 respectively. On the other hand, the transition from states 4, 5, & 6 to states 1 & 2 was rare, with only 15, 13, & 6 patients transiting from states 4, 5, & 6 respectively to state 1, and only 5 patients transiting from state 6 to state 2. For patients aged (20-39) years, only 2 out of 76 (2,36%) and 0 out of 76 (0%) transited from state 1 to states 5 and 6, respectively. On the other hand, only 6 out of 238 (2.5%) and 2 out of 238 (0.84%) transited from state 6 to states 1 and 2, respectively. Similarly, for patients aged (40-69) years only 7 out of 104 (6.73%) and 2 out of 104 (1.92%) transited from state 1 to states 5 and 6, respectively. Of the 424 patients in state 6, only 3 (0.707%) and 10 (2.36%) transited to states 5 and 6, respectively. Therefore, the results showed that antiretroviral therapy treatment positively impacted the patients' health for both age groups and gender. However, the impact varied with the age and gender of the patient, findings consistent with previous researchers [2, 4, 5, 6, 3, 28, 23].

4.2 Transition Rates (λ) and Waiting times (μ) for Male and Female Patients

The monthly transition rate (λ) to a worse state depends on the specific state and patients' gender; for example, male patients' transition rates in states 2-3 and 3-4 were 0.0975 and 0.0809, respectively, and female patients in the same states were 0.0884 and 0.0806, respectively (Table 5), indicating that male patients were more likely to transit to a worse state than female patients. Findings consistent with previous researchers [39, 45, 31, 21, 25, 46].

Female patients were more likely to transit from 4 to 5 and 5 to 6 (a worse state) than male patients, transiting at a rate of 0.0949 and 0.0875, respectively, against a rate of 0.0842 and 0.0735 for male patients in the same states. The result depicts that female patients have a higher risk of death than their male counterparts and a lower risk of disease progression, agreeing with other researchers [29, 31, 32].

For cumulative waiting time (years), male patients had a higher waiting time in all the states than their female counterparts in all the disease states.

Table 1. Number of Observed Transitions in the Data (Males)

		To State						
From State	CD4 Cell Count (mm^3)	S1	S2	S3	S4	S5	S6	Total
S1	> 899	14	10	12	6	4	0	46
S2	700-899	14	17	27	14	6	3	81
S3	500-699	10	28	81	40	25	7	191
S4	350-499	9	12	60	126	70	9	286
S5	200-349	3	10	37	98	124	35	307
S6	< 200	3	7	12	36	84	163	305
Total								1216

Table 2. Number of Observed Transitions in the Data (Females)

		To State						
From State	CD4 Cell Count (mm^3)	S1	S2	S3	S4	S5	S6	Total
S1	> 899	71	29	20	7	5	2	134
S2	700-899	36	89	76	19	11	2	233
S3	500-699	32	83	192	98	30	6	441
S4	350-499	15	38	148	205	97	16	519
S5	200-349	13	20	62	151	181	54	481
S6	< 200	6	5	25	44	111	166	357
Total								2165

Table 3. Number of Observed Transitions in the Data (Age 20-39)

		To State						
From State	CD4 Cell Count (mm^3)	S1	S2	S3	S4	S5	S6	Total
S1	> 899	39	16	15	4	2	0	76
S2	700-899	24	42	43	14	5	1	129
S3	500-699	18	45	124	72	24	8	291
S4	350-499	9	21	86	133	71	11	331
S5	200-349	8	16	50	87	118	30	309
S6	< 200	6	2	12	26	69	123	238
Total								1374

Table 4. Number of Observed Transitions in the Data (Age 40-69)

		To State						
From State	CD4 Cell Count (mm^3)	S1	S2	S3	S4	S5	S6	Total
S1	> 899	46	23	17	9	7	2	104
S2	700-899	26	64	60	19	12	4	185
S3	500-699	24	66	149	66	31	5	341
S4	350-499	15	29	122	198	96	14	474
S5	200-349	8	14	49	162	187	59	479
S6	< 200	3	10	25	54	126	206	424
Total								2007

4.3 Transition Rates (λ) and Waiting times (μ) for Patients Aged (20-39) Years and (40-69) Years

(Table 8) Patients aged (40-69) years had a long waiting time in transitions 1-2, 3-4, and 5-6 compared to patients aged (20-39) years, showing that they had less chance of transiting to a better state than those aged (20-39) years. We attributed the results to the higher burden of competing risks and a higher rate

Table 5. Estimated Parameters (λ) and Mean Waiting Time (μ) in Each State of Infection with Male & Female Gender as Co-factors (Transition to Worse state)

		T-Rate / M [1]		Mean W-T (M) [2]		Mean W-T (Y) [3]		Cumm. W-T (Y) [4]	
State	CD4 Count [5]	M	F	M	F	M	F	M	F
1 to 2	700≥x≤899	0.0585	0.0884	17.10	11.31	1.425	0.943	1.43	0.94
2 to 3	500≥x≤699	0.0975	0.0838	10.26	11.93	0.855	0.995	2.280	1.937
3 to 4	350≥x≤499	0.0809	0.0806	12.36	12.41	1.030	1.034	3.310	2.971
4 to 5	200≥x≤349	0.0842	0.0949	11.88	10.54	0.990	0.878	4.300	3.849
5 to 6	0≥x≤199	0.0735	0.0875	13.60	11.43	1.133	0.952	5.433	4.801

Table 6. Estimated Parameters (λ) and Mean Waiting Time (μ) in Each State of Infection with Male & Female Gender as Co-factors (Remaining in the Same State)

		T-Rate / M [1]		Mean W-T (M) [2]		Mean W-T (Y) [3]		Cumm. W-T (Y) [4]	
State	CD4 Count [5]	M	F	M	F	M	F	M	F
1 to 1	x>899	0.0683	0.0966	14.64	10.35	1.22	0.86	1.22	0.86
2 to 2	700≥x≤899	0.0895	0.0791	11.18	12.64	0.93	1.05	2.15	1.92
3 to 3	500≥x≤699	0.0861	0.0858	11.61	11.65	0.97	0.97	3.12	2.89
4 to 4	350≥x≤499	0.0839	0.0921	11.91	10.86	0.99	0.91	4.11	3.79
5 to 5	200≥x≤349	0.0819	0.0991	12.21	10.09	1.02	0.84	5.13	4.63

Table 7. Estimated Parameters (λ) and Mean Waiting Time (μ) in Each State of Infection with Male & Female Gender as Co-factors (Transition to a Better State)

		T-Rate / M [1]		Mean W-T (M) [2]		Mean W-T (Y) [3]		Cumm. W-T (Y) [4]	
State	CD4 Count [5]	M	F	M	F	M	F	M	F
2 to 1	700≥x>899	0.083	0.099	12.07	10.14	1.01	0.84	1.01	0.84
3 to 2	500≥x>699	0.085	0.085	11.82	11.78	0.99	0.98	1.99	1.83
4 to 3	350≥x>499	0.060	0.077	16.72	12.91	1.39	1.08	3.38	2.90
5 to 4	200≥x>349	0.077	0.077	12.93	12.93	1.08	1.08	4.46	3.98
6 to 5	0≥x>199	0.092	0.081	10.85	12.35	0.90	1.03	5.37	5.01

Table 8. Estimated Parameters (λ) and Mean Waiting Time (μ) in Each State of Infection with Age as a Co-factor (Transition to a Worse State)

		T-Rate / M [1]		Mean W-T (M) [2]		Mean W-T (Yrs) [3]		Cumm. W-T (Yrs) [4]	
State	CD4 Count [5]	(20-39)	(40-69)	(20-39)	(40-69)	(20-39)	(40-69)	(20-39)	(40-69)
1 to 2	700≥x≤899	0.0796	0.0772	12.56	12.96	1.05	1.08	1.05	1.08
2 to 3	500≥x≤699	0.0841	0.0892	11.88	11.22	0.99	0.93	2.04	2.01
3 to 4	350≥x≤499	0.1006	0.0662	9.94	15.11	0.83	1.26	2.87	3.27
4 to 5	200≥x≤349	0.0886	0.0914	11.28	10.95	0.94	0.91	3.81	4.19
5 to 6	0≥x≤199	0.0826	0.0808	12.10	12.37	1.01	1.03	4.81	5.22

Table 9. Estimated Parameters (λ) and Mean Waiting Time (μ) in Each State of Infection with Age as a Co-factor (Remaining in the Same State)

		T-Rate / M [1]		Mean W-T (M) [2]		Mean W-T (Yrs) [3]		Cumm. W-T (Yrs) [4]	
State	CD4 Count [5]	(20-39)	(40-69)	(20-39)	(40-69)	(20-39)	(40-69)	(20-39)	(40-69)
1 to 1	x>899	0.0869	0.0937	11.51	10.67	0.96	0.89	0.96	0.89
2 to 2	700≥x≤899	0.0817	0.0799	12.24	12.52	1.02	1.04	1.98	1.93
3 to 3	500≥x≤699	0.0915	0.0816	10.93	12.2	0.91	1.02	2.89	2.95
4 to 4	350≥x≤499	0.0907	0.0876	11.03	11.419	0.92	0.95	3.81	3.90
5 to 5	200≥x≤349	0.0980	0.0875	10.20	11.422	0.85	0.95	4.66	4.86

T-Rate / M - Transition rate per Month, Mean W-T (M) - Mean Waiting Time in Months, Mean W-T (Y) - Mean Waiting Time in Years, Cumm. W-T (Y) - Cumulative Waiting Time in Years, CD4 Count - CD4 Cell Count (mm^3)

Table 10. Estimated Parameters (λ) and Mean Waiting Time (μ) in Each State of Infection with Age as a Co-factor (Transition to a Better State)

		T-Rate / M [1]		Mean W-T (M) [2]		Mean W-T (Yrs) [3]		Cumm. W-T (Yrs) [4]	
State	CD4 Count [5]	(20-39)	(40-69)	(20-39)	(40-69)	(20-39)	(40-69)	(20-39)	(40-69)
2 to 1	700≥x>899	0.1455	0.0705	6.88	14.19	0.57	1.18	0.57	1.18
3 to 2	500≥x>699	0.0886	0.0824	11.29	12.14	0.94	1.01	1.51	2.19
4 to 3	350≥x>499	0.0841	0.0645	11.90	15.50	0.99	1.29	2.50	3.49
5 to 4	200≥x>349	0.0943	0.0705	10.61	14.18	0.88	1.18	3.39	4.67
6 to 5	0≥x>199	0.0932	0.0817	10.72	12.24	0.89	1.02	4.28	5.69

T-Rate / M - Transition rate per Month, Mean W-T (M) - Mean Waiting Time in Months, Mean W-T (Y) - Mean Waiting Time in Years, Cumm. W-T (Y) - Cumulative Waiting Time in Years, CD4 Count - CD4 Cell Count (mm^3)

of treatment-related complications among elderly patients that conspire to dilute the effect of therapy findings consistent with other researchers [6, 22, 6, 18, 32].
(Table 9) Patients aged (20-39) years are more likely to remain in the same state in all the states except state 1, where the rate was 0.869 against 0.937 for patients aged (40-69). For the cumulative waiting time, patients aged (40-69) had a long waiting time in states 4 and 5 only, while patients aged (20-39) years dominated in the rest of the states (Table 9).
(Table 10) Transition rates for patients aged (20-39) years were higher than for patients aged (40-69) years in all disease states and significantly so in the transition 2-1, which had a transition rate of 0.1455 against 0.0705, implying that younger patients are more likely to transit to a better diseases state than elderly patients. The cumulative waiting time for patients aged (40-69) years was higher in all the disease states, implying that elderly patients are less likely to transit to a better or worse state. Findings were consistent with those in Table 9, which shows that patients aged (40-69) years had a longer waiting time than patients aged (20-39) years.

4.4 Comparison of Transition Rates (λ) per Month with Age & Gender as Co-Factors

Figure 1 depicts increasing, constant, decreasing trends for male and female patients and patients aged (20-39) years and (40-69) years. Females depict a decreasing transition rate while all the other patients show an increase in the transition rate. Females' transition rate decreased gradually between states 1 to 2 and 2 to 3, rising steadily and slowly in 3 to 4 and decreasing gradually in states 4 to 5. For male patients, states 2 to 3 had the highest transition rate, followed by 3 to 4 and 4 to 5. States 1 to 2 had the lowest. Patients aged (20-39) years' transition rate gradually increased between 1 to 2, rising steadily between 2 & 3 and then dropping slowly between 4 & 5. Patients aged (40-69) increased gradually between 1 & 2, dropped down between 2 & 3, increased again between 3 & 4, reaching a maximum at 4, and dropped gradually between 4 & 5.
Figure 2 shows female patients and patients aged 40-69 had a similar trend, decreasing between 1 to 2 and then rising steadily between 2 to 3, 3 to 4, and 4 to 5. Male patients had an increasing trend in states 1 to 2, stationary between 2 to 3, and then decreasing gradually between 3 to 4 and 4 to 5. Patients aged (20-39) years had a constant transition rate (λ) for states 1 to 2, increasing in 2 to 3, constant in 3 to 4, and an increase between 4 to 5.

Figure 3 Male patients and patients aged (40-69) years depict a similar trend in states 1 to 2, 2 to 3, 3 to 4, and 4 to 5. However, males show a sharp increase between 4 to 5. Patients aged (20-39) show a sharp decrease in 1 to 2, stationary in 2 to 3, increasing in 3 to 4, and stationary in 4 to 5. Female patients show a gradual decrease between 1 to 2 and 2 to 3, with 3 to 3 and 4 to 4 being almost constant.

In Figure 4, patients aged (20-39) years, patients aged (40-69) years, males and females, depict a transverse wave with patients aged (20-39) years being higher in most of the states and the rest almost the same with contrasting peaks.

5 Results

AIC, BIC, and LL in Table 11 depict varying results, agreeing in some states and contrasting in other states. In states 1 to 2, for males and patients aged (40-69) years, all the three criteria supported the three-parameter Weibull distribution as the best model, while for the females, all the three criteria supported the two-parameter Weibull distribution as the best model. LL supported the three-parameter Weibull distribution for patients aged (20-39) and states 2 to 3 for both male and female gender and age groups. AIC and BIC supported the two-parameter Weibull distribution in both male and female gender and age groups. For states 3 to 4, all criteria supported the three-parameter Weibull distribution in males, females, and patients aged 40-69. However, for (20-39) years, LL and AIC supported the three-parameter Weibull distribution while BIC supported the two-parameter Weibull distribution. For states 4 to 5, in males and patients aged (20-39) years, all the criteria supported the three-parameter Weibull distribution. LL supported the three-parameter Weibull distribution in females, while AIC and BIC supported the two-parameter Weibull distribution. In patients aged (40-69) years, LL, AIC, and BIC supported the three-parameter Weibull distribution. For states 5 to 6, female patients and patients aged (20-39) years and (40-69) years, all the three criteria supported the three-parameter Weibull distribution. LL supported the three-parameter Weibull distribution in males, while AIC and BIC supported the two-parameter Weibull distribution. No criteria supported exponential distribution in all states

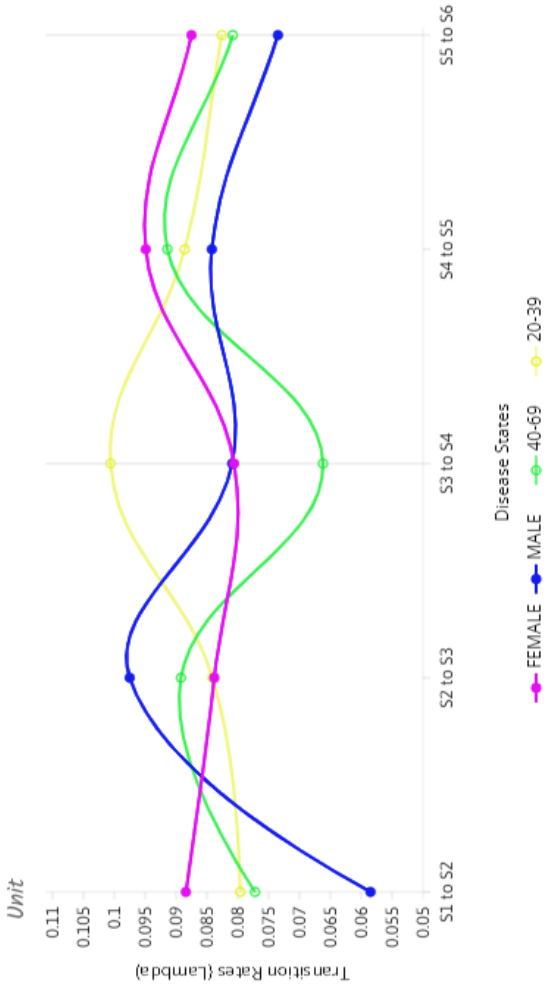

Figure 1. Comparison of Transition Rate Per Month for Patients Moving to a Worse State (with Gender & Age as Co-factors)

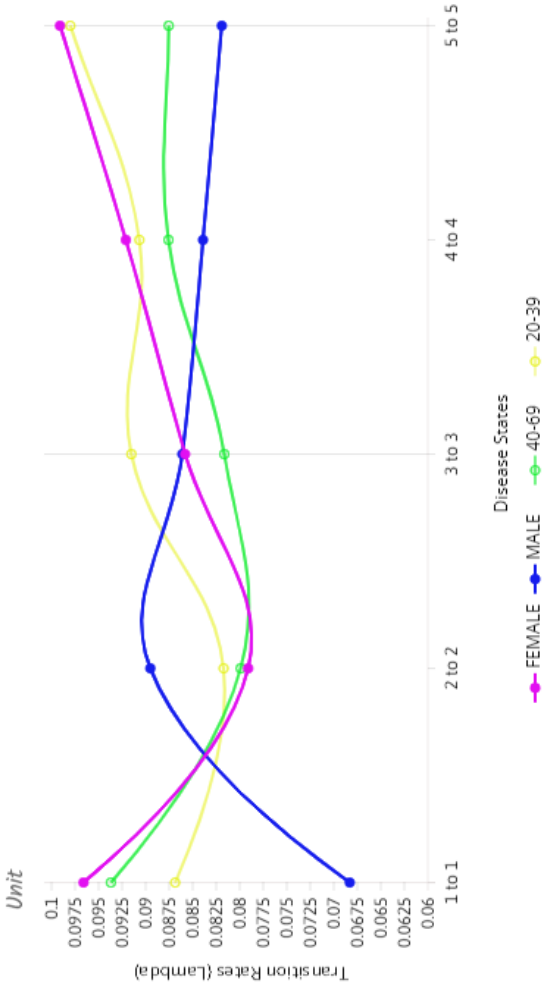

Figure 2. Comparison of Transition Rate Per Month for Patients Remaining in the Same State (with Gender & Age as Co-factors)

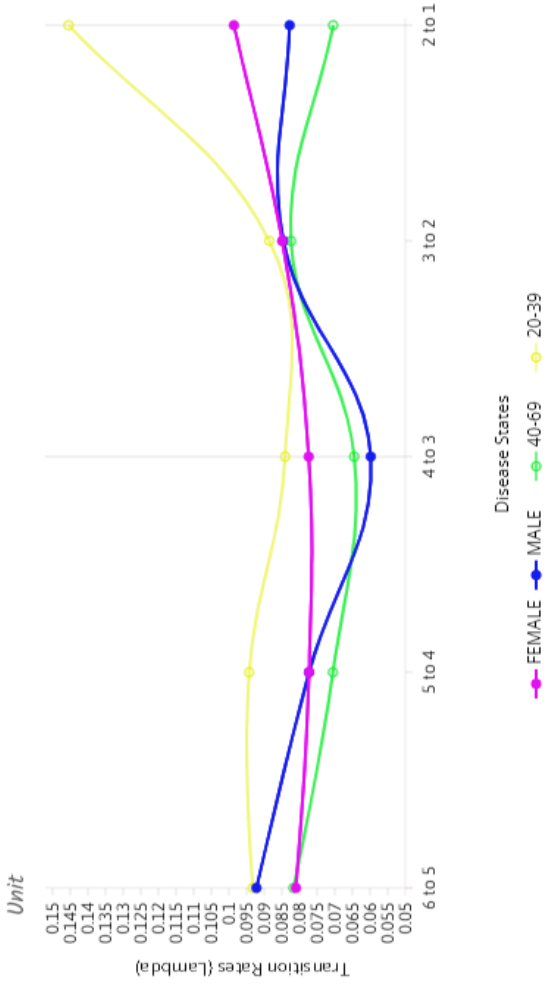

Figure 3. Comparison of Transition Rate Per Month for Patients Transiting to a Better State (with Gender & Age as Co-factors)

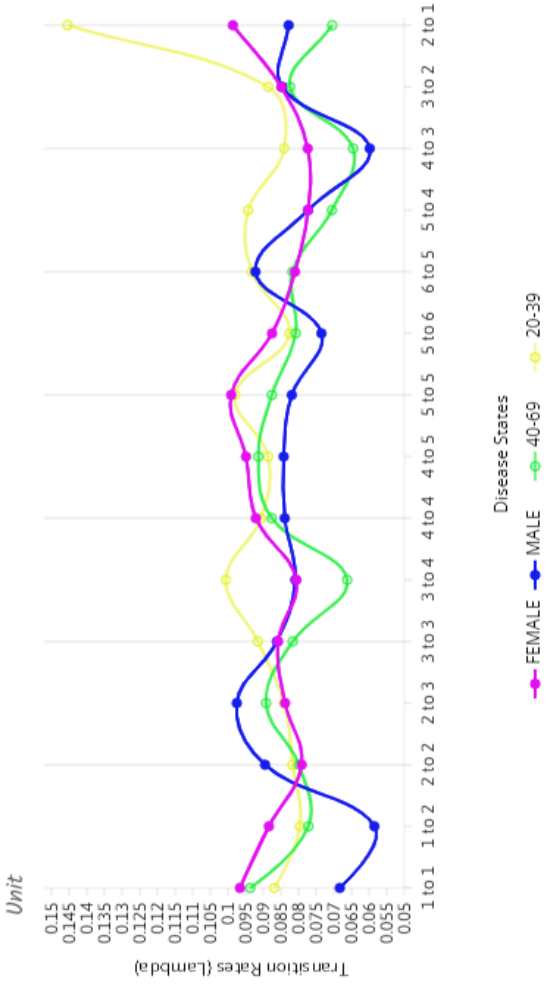

Figure 4. Comparison All Transition Rates Per Month (with Gender & Age as Co-factors)

In Table 12, the three-parameter Weibull distribution dominated, and the two-parameter Weibull distribution supported by AIC and BIC for patients aged (20-39) years in state 1, by BIC for female patients in state 3, by AIC and BIC for patients aged (20-39) years in state 3, and by BIC for patients aged (40-69) years in state 3. No criteria supported exponential distribution in all states.

In Table 12, 3-parameter dominated, with 2-parameter supported by AIC & BIC for patients aged (20-39) years in state 1, by BIC for female patients in state 3, by AIC & BIC for patients aged (20-39) years in state 3, and by BIC for patients aged (40-69) years in state 3. No criteria supported exponential distribution in all states.

From Table 13, BIC supported exponential distribution for male patients in states 2 to 1 and 5 to 4. The two-parameter dominated in states 3 to 2 for males and states 4 to 3 for patients aged (40-69) years. AIC and BIC supported the two-parameter in states 2 to 1 for females, states 3 to 2 for females and patients aged (40-69) years, in states 5 to 4 for patients aged (20-39) years, and states 6 to 5 for males and patients aged (20-39) years. However, the three-parameter dominated in most of the other states.

6 Conclusion

6.1 Summary of the Methodology Used

The researchers used the Maximum Likelihood Estimation (MLE) method to obtain the exponential, two-parameter, and three-parameter Weibull distributions parameters. Estimating the parameters of three-parameter Weibull distributions using the Maximum Likelihood Estimation (MLE) proved difficult because its maximum likelihood equations were not in closed form. Therefore, the Newton-Raphson method for maximizing the log-likelihood function failed to converge. We applied the Modified Maximum Likelihood Estimation method (MMLE) recommended by [47] to mitigate the challenge. The maximum likelihood equations for two-parameter Weibull distribution and exponential distributions were in closed form. We obtained the parameters using maximum likelihood estimators. Model selection criteria: AIC, BIC, and LL results were contrasting in some specific disease states, with two selection criteria supporting the same distribution and the third supporting a different distribution on the choice of the best single model. In Table 11, LL supported three-parameter Weibull, and AIC and BIC supported two-parameter Weibull distribution for patients aged (20-39) years transiting in states 1-2. For male and female patients transiting in states 2-3, LL supported three-parameter Weibull distribution while AIC and BIC supported two-parameter Weibull distributions. In Table 13 BIC supported exponential distribution for male patients in states 2-1 and 5-4 with LL and AIC supporting three-parameter Weibull distributions. In all such instances this study considered the distribution supported by two criteria as the best single distribution in the specific state.

6.2 Modelling of the Parameters using Exponential Distribution, Two-Parameter, and Three-Parameter Weibull Distributions

This article's analyses reveal that failure rates in HIV/AIDS progression are state-specific and highly dependent on the risk factors in play. The hazard rates can be constant, decreasing, increasing, or unimodal. It is pretty evident that although the three-parameter Weibull distribution depicts some level of dominance, we can not ignore the two-parameter Weibull distribution and the exponential distribution, especially the two-parameter Weibull distribution. Therefore, no single distribution suffices to model all the state-specific waiting times for a patient on therapy with gender and age as risk factors. We identified the best single model for modeling failure rates in each state. Results from this article provide a clear guide on which model to apply in each state with gender and age as risk factors (Tables 14, 15 & 16).

6.3 Summary of the Best Single-Models for Modeling State Specific Rates with Gender and Age Group as Risk Factors

Two-Parameter Weibull distribution is the best single distribution for modeling failure rates for female patients and patients in the age group (20-39) years transiting in the states 1-2, 2-3, 4-5, and 1-2, 2-3, 3-4 respectively. Three-Parameter Weibull distribution is the best single model for modeling failure rates for male patients and patients aged (40-69) years transiting in the states 1-2, 3-4, 4-5, and 1-2, 3-4, and 5-6 respectively.
Three-Parameter Weibull is the best single model for modeling the state-specific failure rates for patients remaining in the same state for male patients, female patients, and patients aged (40-69) years.
Three-Parameter Weibull distribution dominates over two-parameter in all the disease states. However, the limitations of a best single model in modeling hazard rates include and are not limited to ignoring model uncertainties; therefore, the need to develop more robust ways to help mitigate the shortcomings of single models.

Declarations

1. **List of Abbreviations**
   - **HIV** : Human Immunodeficiency Virus
   - **AIDS** : Acquired Immunodeficiency Syndrome
   - **ART** : Anti-Retroviral Treatment.
   - **CD4** : Cluster of Differentiation 4
   - **BMA** : Bayesian Model Averaging.
   - **HAART**: Highly Active Antiretroviral Therapy
   - **AIC** : Akaike Information Criteria
   - **BIC** : Bayesian Information Criteria
   - **LL** : Log-Likelihood
2. **Ethical Approval**

Table 11. Model Selection Criteria (Using LL, AIC, & BIC) (Transition to a Worse State)

State	CD4 Count [1]	Criteria	Male	Female	Age 20-39	Age 40-69
1 to 2	700≥x≤899	LL	3-Par.	2-Par.	3-Par.	3-Par.
		AIC	3-Par.	2-Par.	2-Par.	3-Par.
		BIC	3-Par.	2-Par.	2-Par.	3-Par.
2 to 3	500≥x≤699	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	2-Par.	2-Par.	2-Par.	2-Par.
		BIC	2-Par.	2-Par.	2-Par.	2-Par.
3 to 4	350≥x≤499	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	3-Par.	3-Par.	3-Par.	3-Par.
		BIC	3-Par.	3-Par.	2-Par.	3-Par.
4 to 5	200≥x≤349	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	3-Par.	2-Par.	3-Par.	2-Par.
		BIC	3-Par.	2-Par.	3-Par.	2-Par.
5 to 6	0≥x≤199	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	2-Par.	3-Par.	3-Par.	3-Par.
		BIC	2-Par.	3-Par.	3-Par.	3-Par.

Table 12. Model Selection Criteria (Using LL, AIC, & BIC) (Remaining in the Same State)

State	CD4 Count [1]	Criteria	Male	Female	Age 20-39	Age 40-69
1 to 1	x>899	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	3-Par.	3-Par.	2-Par.	3-Par.
		BIC	3-Par.	3-Par.	2-Par.	3-Par.
2 to 2	700≥x≤899	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	3-Par.	3-Par.	3-Par.	3-Par.
		BIC	3-Par.	3-Par.	3-Par.	3-Par.
3 to 3	500≥x≤699	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	3-Par.	3-Par.	2-Par.	3-Par.
		BIC	3-Par.	2-Par.	2-Par.	2-Par.
4 to 4	350≥x≤499	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	3-Par.	3-Par.	3-Par.	3-Par.
		BIC	3-Par.	3-Par.	3-Par.	3-Par.
6 to 6	200≥x≤349	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	3-Par.	3-Par.	3-Par.	3-Par.
		BIC	3-Par.	3-Par.	3-Par.	3-Par.

- Approved by Mount Kenya University ERC Committee
- Approved by National Commission for Science and Technology (NACOSTI) Kenya

3. **Consent of Publication**

- The authors agree to the publication of this article.

4. **Availability of Data** & **Materials**

- HIV/AIDS Patients' CD4 cell count data used to support the findings of this study are available from the corresponding author upon request.

5. **Conflict of Interest/ Competing Interests**

- The authors declare that there are no conflicts of interest regarding the publication of this article.

6. **Funding**

- The authors received no financial support for the research authorship and publication of this article

7. **Author's Contributions**

[1] Mr. Nahashon Mwirigi (Catholic University of Eastern Africa - CUEA): Conceived and designed the analysis, Designed the Data Analysis Tools, Collected the data with the help of the Hospital Administrators and Data Officers, Performed the analysis, and Wrote the Paper.
[2] Dr. Stanley Sewe (Catholic University of Eastern Africa - CUEA): Supervised the entire process of Conception, Designing the analysis, and Writing of the Paper.
[2] Dr. Mary Wainaina (Catholic University of Eastern Africa - CUEA): Supervised the entire process of Conception, Designing the analysis, and Writing of the Paper.
[2] Prof Richard Simwa (University of Nairobi - UoN): Supervised the entire process of Conception, Designing the

Table 13. Model Selection Criteria (Using LL, AIC, & BIC) (Transition to a Better State)

State	CD4 Count [1]	Criteria	Male	Female	Age 20-39	Age 40-69
2 to 1	700≥x>899	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	3-Par.	2-Par.	3-Par.	3-Par.
		BIC	Exp.	2-Par.	3-Par.	3-Par.
3 to 2	500≥x>699	LL	2-Par.	3-Par.	3-Par.	3-Par.
		AIC	2-Par.	2-Par.	3-Par.	2-Par.
		BIC	2-Par.	2-Par.	3-Par.	2-Par.
4 to 3	350≥x>499	LL	3-Par.	3-Par.	3-Par.	2-Par.
		AIC	3-Par.	3-Par.	3-Par.	2-Par.
		BIC	3-Par.	3-Par.	3-Par.	2-Par.
5 to 4	200≥x>349	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	3-Par.	3-Par.	2-Par.	3-Par.
		BIC	Exp.	3-Par.	2-Par.	3-Par.
6 to 5	0≥x>199	LL	3-Par.	3-Par.	3-Par.	3-Par.
		AIC	2-Par.	3-Par.	2-Par.	3-Par.
		BIC	2-Par.	3-Par.	2-Par.	3-Par.

[1] CD4 Count - CD4 Cell Count (mm^3)

Table 14. Model Selection Criteria (Using LL, AIC, & BIC) (Transition to a Worse State)

State	CD4 Cell Count (mm^3)	Male	Female	Age 20-39	Age 40-69
1 to 2	700≥x≤899	3-Parameter	2-Parameter	2-Parameter	3-Parameter
2 to 3	500≥x≤699	2-Parameter	2-Parameter	2-Parameter	2-Parameter
3 to 4	350≥x≤499	3-Parameter	3-Parameter	2-Parameter	3-Parameter
4 to 5	200≥x≤349	3-Parameter	2-Parameter	3-Parameter	2-Parameter
5 to 6	0≥x≤199	2-Parameter	3-Parameter	3-Parameter	3-Parameter

Table 15. Model Selection Criteria (Using LL, AIC, & BIC) (Remaining in the Same State)

State	CD4 Cell Count (mm^3)	Male	Female	Age 20-39	Age 40-69
1 to 1	x>899	3-Parameter	3-Parameter	2-Parameter	3-Parameter
2 to 2	700≥x≤899	3-Parameter	3-Parameter	3-Parameter	3-Parameter
3 to 3	500≥x≤699	3-Parameter	3-Parameter	2-Parameter	3-Parameter
4 to 4	350≥x≤499	3-Parameter	3-Parameter	3-Parameter	3-Parameter
5 to 5	200≥x≤349	3-Parameter	3-Parameter	3-Parameter	3-Parameter
6 to 6	x<200	3-Parameter	3-Parameter	3-Parameter	3-Parameter

Table 16. Model Selection Criteria (Using LL, AIC, & BIC) (Transition to a Better State)

State	CD4 Cell Count (mm^3)	Male	Female	Age 20-39	Age 40-69
2 to 1	700≥x>899	3-Parameter	2-Parameter	3-Parameter	3-Parameter
3 to 2	500≥x>699	2-Parameter	2-Parameter	3-Parameter	2-Parameter
4 to 3	350≥x>499	3-Parameter	3-Parameter	3-Parameter	2-Parameter
5 to 4	200≥x>349	3-Parameter	3-Parameter	2-Parameter	3-Parameter
6 to 5	0≥x>199	2-Parameter	3-Parameter	2-Parameter	3-Parameter

analysis, Designing the Data Analysis Tools, Performing the analysis, and Writing the Paper.

8. Acknowledgments

The author acknowledges with appreciation the concrete suggestions and comments of his supervisors, Prof Richard Simwa, Dr. Stanley Sewe, and Dr. Mary Wainaina, which led to the overall improvement of the paper. The author is also grateful to the Catholic University

of Eastern Africa (CUEA) – Faculty of Science – Department of Mathematics & Computer Science.

9. **Author's Information**
Nahashon Mwirigi is a Ph.D. (Statistics) student at the Catholic University of Eastern Africa (CUEA). Holds a Master of Science Degree in Statistics (MSc. Statistics) from the same institution and a Bachelor's degree in Education-Science (Double Mathematics with a bias in Statistics) from Kenyatta University - Kenya. He has over twenty (20) years of experience teaching mathematics in various secondary schools in Kenya and over ten years of experience teaching mathematics and statistics in various universities in Kenya. He has an immense interest in statistical modeling, with three papers applying Markov Models to students' progression in academic institutions in Kenya.

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