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Bayesian Model Averaging in Modeling of State Specific Failure Rates in HIV/AIDS Progression

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Abstract In modeling HIV/AIDS progression, we carried out a comprehensive investigation into the risk factors for state-specific-failure rates to identify the influential co-variates using Bayesian Model averaging method (BMA). BMA provides a posterior probability via Markov Chain Monte Carlo (MCMC) for each variable that belongs to the model. It accounts for model uncertainty by averaging all plausible models using their posterior probabilities as the weights for model-averaged predictions and estimates of the required parameters. Patients' age, and gender, among other co-variates, have been found to influence the state-specific-failure rates highly. However, the impact of each of the factors on the state specific-failure was not quantified. This paper seeks to evaluate and quantify the contribution of the patient's age and gender, CD4 cell count during any two consecutive visits, and state movement on the state-specific-failure rates for patients transiting either to the same, better or worse state. We used R Studio statistical Programming software to implement the method by applying BMS and BMA packages. State movement had a comparatively large coefficient with a posterior inclusion probability (PIP) of 0.8788 (87.88%). Hence, the most critical variable followed by observation-two-CD4-cell-count with a PIP of 0.1416 (14.16%), age and gender were the last with a PIP of 0.0556 (5.56%) and 0.0510 (5.10%) respectively for patients transiting to the same state. For patients transiting to a better state, the patients' age group dominated with a PIP of 0.9969 (99.69%), followed by patients' gender with a PIP of 0.0608 (6.08%). Patients' CD4 cell count during the second observation had the least PIP of 0.0399 (3.99%). For patients transiting to a worse disease state, patients CD4 cell count during the second observation proved to be the most important, with a PIP of 0.6179(61.79%) followed by state movement with a PIP of 0.2599 (25.99%), patients gender tailed with a PIP of 0.0467 (4.67%).

Keywords Bayesian Model Averaging (BMA), Semi Markov Process, CD4+ levels, Posterior Inclusion Probability (PIP).

1 Introduction

Previous researchers applied Markov and Semi-Markov models widely to model failure rates for HIV/AIDS patients on therapy. The choice of distribution was state-specific and highly influenced by patients' gender, age, and CD4cell count in two consecutive states. Their findings showed that the risk of the disease increased with age. Elderly patients had a higher burden of competing risks and a higher rate of treatment-related complications that always conspire to dilute any form of intervention [17, 38, 17, 22]. Treatment impacted positively on the health of the patient. However, the effect was dependent on the initiation time, age, gender of the patient, and adherence to therapy in terms of medication and dietary requirements [66, 11, 27, 17, 49, 51, 67].

The transition depended on gender, with male patients more likely to transit to a worse state than female patients. They found that the capacity to produce CD4 cells after chemotherapy was inversely related to the patient's age [52]. Patients' gender was also a prognostic factor in their findings. Women had lower viral load and a higher CD4 cell count than men at diagnosis and better survival than men, although not significantly different [56, 23, 59, 31].

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 [52, 28, 10].
Gender was one of the significant predictors of the intensity of transition between states, with male patients being more likely to transit to worse disease states than their female counterparts [13, 29, 28, 23, 60, 43].
Semi-Markov models were applied more as compared to Markov models. Most researchers used Weibull distributions to model the state waiting time in the semi-Markov models allowing a non-constant failure rate [17, 36, 6, 14, 13].
The choice of the distribution was of paramount importance, and the covariates that influenced the transition depended on it [36].
The best single model could be selected using model selection criteria and used to fit the data and obtain a state-specific-failure rate and consequently predict the survival of the patients. However, selecting a single model could ignore model uncertainty, and the inferences made would be narrow, misleading, and conditional on the selected model [47].
Various researchers used Bayesian Model Averaging (BMA) to investigate the contribution of several risk factors to various diseases; childhood asthma [21], coronary heart diseases (CHD) [39], malaria prevalence [4], and trachea cancer [16]. Bayesian Model Averaging (BMA) provided posterior probability via Markov chain Monte Carlo (MCMC) that each covariate belongs to the mode. It accounts for model uncertainty by averaging all plausible covariates using their posterior probability as the weights. They used Posterior Inclusion Probabilities (PIP) to identify the most significant risk factors.
This paper investigated the influence of each covariate on the state-specific-failure rates for HIV/AIDS patients transiting either to the same state, a better state, or a worse disease state using (BMA).
Its quite evident from the results in this paper that the influence of the covariates on the state-specific transitional rates of patients transiting to either the same state, a better state, or a worse state was significantly different.

2 Materials and Methods

2.1 Introduction

Actual secondary data of patients attending a teaching and referral hospital in Kenya for HIV/AIDS therapy was analyzed using a seven-state CD4 cell count levels with the following disease states categorized by their CD4 cell count levels (mm^3) distribution; S1 (> 899), S2 ($700 - 899$), S3 ($500 - 699$), S4 ($350 - 499$), S5($200 - 399$), S6 ($0 - 199$), and Death (Death). The data was also categorized by gender (Male $\&$ Female) and age groups ($20 - 39$) years and ($40 - 49$) years. However, we ignored the seventh state (Death), whose data was unavailable. We used BMA to evaluate the influence of the risk factors on the state-specific failure rates. Model selection criteria R^2 and BIC were used in selecting the best subset of the prognostic factors.

2.2 CD4 Cell Count and Viral load

CD4 cell count and viral load count are both biomarkers of HIV/AIDS. They measure patients' responses to antiretroviral treatment (ART) and HIV/AIDS progression. Clinicians perform blood tests and establish the number of CD4 cells in the body. CD4 cells are types of white blood cells. They are also a subset of the body's immune cells, referred to as T cells. They play an essential role in the body's immune system. CD4 cell count of a healthy immune system ranges from 500 to 1600 cells per cubic millimeter of blood (cells/mm3). A low CD4 cell count implies a weak body immune system. Viral load (VL) is also a blood test that measures the number of HIV particles (copies) in a milliliter (mL) of blood [3]. Patients on ART for more than two years and with strict adherence, and those with CD4 count ¡500 cells/mm3, or a viral load level of 40 to 75 copies/mL, will have a typically undetectable HIV viral load. They are slightly less likely to have an available viral load result [3]. Viral load can be up to millions of copies per mL of blood when the virus is first contracted, untreated or uncontrolled over some time and can be relatively low with an effective treatment plan. Regular viral load tests should be carried out in all patients infected with HIV/AIDS on entry into treatment, at the beginning of therapy and regularly, six months after ART initiation, and at least annually afterward. VL is the best measure of the effectiveness of HIV therapy on patients. CD4 cell count, on the other hand, is the best laboratory indicator of an HIV-infected patient's body immune status. Previous clinical trials and cohort studies found CD4 cell count as the strongest predictor of HIV/AIDS progression and subsequent survival rates [3].

2.3 Bayesian Model Averaging (BMA)

Selection of the best single model ignores the problem of model uncertainty, and the inferences made will be conditional on the selected model leading to narrow and misleading inferences. It can also lead to underestimating the uncertainty about the parameters, overestimating the confidence in a particular model being 'correct' and leads to a riskier decision and poorer predictive ability [37, 46, 54, 57, 63, 19].
We can overcome the problem by capturing all the information provided by all suitable models in the analysis, using Bayesian Model Averaging (BMA). BMA selects a subset of all possible models and averages over the subset for all inferences and predictions. It provides a convenient and flexible mechanism for identifying and estimating distributions that are not well modeled by any standard parametric family. [44, 8, 9, 19, 63, 48].
[19], considered a problem of predicting survival based on two approaches. The first approach used three alternative single models: a single Weibull, a mixture of Weibulls, and a cure model. The second approach used Bayesian Model Averaging (BMA). Bayesian Information Criterion (BIC) was used as the model identification criteria to select the best single model. Their results revealed the best single model amongst the three single models when the sample size was sufficiently large. However, no single model emerged as "best" with reduced sample size. They opted for the BMA approach to overcome

the problem, which provided robust predictions, allowing flexible, convenient, and detailed methods of investigating the relationships between risk factors and patients' survival. [8] evaluated the performance of Bayesian joint models based on the accelerated failure time distributions over their single separate models, namely, Weibull, lognormal, and log-logistic. Longitudinal observations on CD4 cell counts as growth measurements and time-to-death events of HIV/AIDS patients were analyzed. The Bayesian joint results proved consistent with higher precision than their separate respective models.

2.4 Model Development

We used the Bayesian analysis method to derive the posterior model probabilities later used to calculate the weighting of each model [58].
Consider X models, for $X = 1, 2, \dots X$, each with a parameter set θ_X based on data T.
Also consider Δ, the quantity of focus representing the posterior predictive distribution of Z.
Hence, the posterior distribution of Δ given data T [44] is:

$$p[\Delta \mid T] = \sum_{X=1}^{X} p(\Delta \mid X = x, T)p(X = x \mid T) \tag{1}$$

The posterior mean and variance of Δ will be calculated as;

$$E[\Delta \mid T] = \sum_{X=1}^{X} \hat{\Delta}_x p(X = x \mid T)$$

$$Var[\Delta \mid T] =$$

$$\sum_{X=1}^{X} \left(Var[\Delta \mid T, X = x] + \hat{\Delta}_x^2 \right) p(X = x \mid T) - E[\Delta \mid T]^2$$

Where $\hat{\Delta}_x = E[\Delta \mid T, X = x]$ [26, 50].

Equation (1) is composed of the following components;
$p(\Delta \mid X = x, T)$; Predictive distribution, which calls for integrating out the model parameter θ_x, $p(X = x \mid T)$; posterior model probabilities that requires the calculation of the integrated likelihood.

The predictive distribution is:

$$p(\Delta \mid X = x, T) = \int p(\Delta \mid \theta_x, X = x, T)p(\theta_x, X = x)\delta\theta_x \tag{2}$$

Using the maximum likelihood estimate (MLE) approximation:

$$p(\Delta \mid X = x, T) \approx p(\Delta \mid X = x, \theta_x, T) \tag{3}$$

[58, 50].

The posterior probability of model $X = x$ is given by;

$$p(X = x \mid T) \propto p(T \mid X = x)p(X = x) \tag{4}$$

Where $p(T \mid X = x) = \int p(T \mid \theta_x, X = x)p(\theta_x \mid X = x)\delta\theta_x$ (5)

The integrated likelihood of the model; $(X = x)$ and $p(\theta_x \mid X = x)$ is the prior density of θ_x, under model $(X = x)$.
The integral in equation (5) can be approximated using Laplace method, Typically the Bayesian Information Criterion (BIC). [45] approximates $p(T \mid X = x)$ accurately [41, 44, 30, 25]. This method yields;

$$\log p(T \mid X = x) = \log p(T \mid \hat{\theta}_x, X = x) - t_x \log n \tag{6}$$

$$BIC = -2 \log p(T \mid \hat{\theta}_x, X = x) + t_x \log n \tag{7}$$

The number of records is represented by n and the number of parameters in the model $X = x$, represented by t_x. $p(T \mid \hat{\theta}_x, X = x)$ is the maximized log-likelihood of models, which estimates the goodness of fit of the data.
The likelihood of the model for a given data using $\hat{\theta}_x$ can be defined by;

$$p(T \mid \hat{\theta_x}, X = x) \propto e^{(0.5 \times BIC)} \tag{8}$$

$p(X = x \mid T)$, will be the posterior probability of a specific single model being true, defined as;

$$p(X = x \mid T) = \frac{p(T \mid X = x)p(X = x)}{\sum_{x=1}^{X} p(T \mid X = x)p(X = x)} \tag{9}$$

Where $p(T/X = x) = \int p(T \mid \hat{\theta}_x, X = x)p(\theta_x, X = x)\delta\theta_x$ (10)

Here, $p(T/X = x)$ is the marginal likelihood of the data T given model $X = x$ and $p(\theta_x, X = x)$ is the prior density of θ_x given model $X = x$. $p(X = x)$ is the prior probability that model x is the true model [44].
All probabilities are conditioned explicitly on X, the set of all models considered.
The BMA weight for the x^th model from Equation ((6)) and Equation ((7)) is given by:

$$p(X = x/T) = \frac{(\exp \frac{-1}{2} BIC_x)p(X = x)}{\sum_{X=1}^{X} (\exp \frac{-1}{2} BIC_x)p(X = x)} \tag{11}$$

[30, 25].

The weight of BMA builds on the evidence of model X dominating over other models in a set of X models. The larger the BMA, the better the model. Therefore, the approximation to the posterior probability of the model X being correct can be given by $p(X = x \mid T)$ [68]. The smaller the BIC value, the better the model .

$$\text{Let } \bar{f}_{\mu\alpha} = \left(\sum_{i=1}^{N} \sum_{x=1}^{X} W_x \right) \frac{\bar{f}_{xj}}{N} \tag{12}$$

The number of simulated observations denoted by N and $W_x = p(X = x/T)$ represents the previously defined BMA weight. Where prior probabilities may be missing, $p(X = x)$ will be considered the same for all candidate models $(\frac{1}{X})$, and

therefore no model will be given a prior preference [30, 20, 19]. The prior probability for model X_i when Prior information on the importance of a variable is available,

$$\text{can be specified as } p(X_i) = \prod_{i=1}^{p} \pi_j^{X_{ij}} \left(1 - \pi_j^{X_{ij}}\right) \tag{13}$$

The prior probability that $\beta_x \neq \pi_{j\epsilon[0,1]}$. ∂_{ij} shows whether the variable j is included in the model X_i.
For $\pi_j = 0.5$ for all j results in a uniform prior across the model space, $\pi_j < 0.5$ for all j puts a penalty on large models, for $\pi_j = 1$ results in the inclusion of variable j in all models.
Averaging will be done only over the best models, where the best will depend on the value of posterior model probabilities. Therefore, only models belonging to the set below will be averaged

$$A = \left\{ X = x : \frac{\max p(X_i \mid T)}{p(X = x/T)} \leq C \right\} \tag{14}$$

Averaging over the best models proved to be better in predictive ability than any single model X_i conditional on X , the Occam's window criterion. [63, 47].
The value of C used will depend on the context of the problem. In most cases, the value of C is set to 20 to emulate the popular 0.05 cutoff for P-value [2].
Averaging will be done only over models whose posterior probability is at least $(\frac{1}{20})$ of the best model. The best model is selected using the BIC value; the more significant the BIC value, the better the model. The best model corresponds to the model with the highest posterior probability.

2.5 Identifying Models in *A*

A fast and effective method of screening the models without fitting them is required, targeting only those whose posterior probability is close to the best model, averaging the reduced set of models. The method exists for nonlinear regression models, a modification of the leaps-and-bounds algorithm [69], providing an approximate likelihood ratio test (LRT) statistics giving a good approximation of the BIC.
The following is the method:
Let θ and θ_k be the parameter vector of the full model and the vector for a given sub-model k, respectively.
We can rewrite θ_k as (θ_1, θ_2) so that the model M_k, corresponds to the sub-model $(\theta_2 = 0)$,
Then, let $V = \tau^{-1} = \begin{Bmatrix} V_{11} & V_{12} \\ V_{21} & V_{22} \end{Bmatrix}$,
denoting the inverse observed information matrix.
Let $L(\tilde{\theta})$ be the maximized likelihood under the full model and $L(\hat{\theta})$) be the maximized likelihood under $(\theta_2 = 0)$, then $\wedge = -2\log L(\tilde{\theta}) - \log L(\hat{\theta}))$
The usual likelihood ratio statistics for the test of the sub-model versus the full model whereas $\wedge' = \hat{\theta}_2' V_{22}^{-1} \hat{\theta}_2$, an approximation to $\wedge$ based on the Wald statistics.
Finally, the method will eliminate a large portion of the model space by sweep operations from the leaps and bounds algorithm on the matrix; $\begin{Bmatrix} \tau & \tau\hat{\theta} \\ \theta'\tau & \hat{\theta}'\tau\hat{\theta} \end{Bmatrix}$, [47]
This function will achieve the following;
(i) An estimate of the best q models.
(ii) The LRT approximation of $\wedge'$ for each model.
(iii) The MLE for the parameters of the sub-model, an approximation to $\hat{\theta}$
(iv) V_{11}^{-1} the asymptotic covariance matrix.
As long as q is sufficiently large, this procedure returns the models in A plus many models that are not in A. We reduce the remaining subset of models to only those most likely to be in A using the approximate LRT, keeping only the models with posterior probability at least $\frac{1}{C'}$ of the posterior model probability PMP of the best model.

3 Data

3.1 Data Analysis

Secondary data for over three thousand patients who visited a referral hospital in Kenya from 2003 to 2014 were collected using a customized data collection tool and categorized by age and gender. Categories of gender were male and female, while the age categories were (20-39) years and (40-69) years. We calculated transition rates (λ) for any two consecutive visits.

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

From Tables 1, 2, 3, and 4, female patients dominated the list of patients visiting the hospital for antiretroviral therapy from 2003 to 2014, registering 2165 (64%) patients, with male patients registering a total of 1,216 (36%). Patients aged (40-69) registered a total of 2,007 (59%), while patients aged (20-39) registered a total of 1,374 (41%).
The results showed clearly that the female gender and older group of patients have higher treatment rates. Findings consistent with [52, 28, 10].

Patients in both age groups and genders transited to either a better state, a worse disease state, or remained in the same state within two consecutive visits. The patients' were more likely to remain in the same state than to transit to either a better state or a worse state, especially patients in states one and 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 still in the same state during the second visit. 14 out of 46 (30.4%) male patients in state one and 163 out of 305 (53.44%) male patients in state six remained in the same state. 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. 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

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

		To State												
From	CD4	S1		S2		S3		S4		S5		S6		
State	Count	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	Total
S1	> 899	14	30.43%	10	21.74%	12	26.09%	6	13.04%	4	8.70%	0	0.00%	46
S2	700-899	14	17.28%	17	20.99%	27	33.33%	14	17.28%	6	7.41%	3	3.70%	81
S3	500-699	10	5.24%	28	14.66%	81	42.41%	40	20.94%	25	13.09%	7	3.66%	191
S4	350-499	9	3.15%	12	4.20%	60	20.98%	126	44.06%	70	24.48%	9	3.15%	286
S5	200-349	3	0.98%	10	3.26%	37	12.05%	98	31.92%	124	40.39%	35	11.40%	307
S6	< 200	3	0.98%	7	2.30%	12	3.93%	36	11.80%	84	27.54%	163	53.44%	305
Total														1216

CD4 Count - CD4 Cell Count (mm^3)

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

		To State												
From	CD4	S1		S2		S3		S4		S5		S6		
State	Count	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	Total
S1	> 899	71	52.99%	29	21.64%	20	14.93%	7	5.22%	5	3.73%	2	1.49%	134
S2	700-899	36	15.45%	89	38.20%	76	32.62%	19	8.15%	11	4.72%	2	0.86%	233
S3	500-699	32	7.26%	83	18.82%	192	43.54%	98	22.22%	30	6.80%	6	1.36%	441
S4	350-499	15	2.89%	38	7.32%	148	28.52%	205	39.50%	97	18.69%	16	3.08%	519
S5	200-349	13	2.70%	20	4.16%	62	12.89%	151	31.39%	181	37.63%	54	11.23%	481
S6	< 200	6	1.68%	5	1.40%	25	7.00%	44	12.32%	111	31.09%	166	46.50%	357
Total														2165

CD4 Count - CD4 Cell Count (mm^3)

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

		To State												
From	CD4	S1		S2		S3		S4		S5		S6		
State	Count	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	Total
S1	> 899	39	51.32%	16	21.05%	15	19.74%	4	5.26%	2	2.63%	0	0.00%	76
S2	700-899	24	18.60%	42	32.56%	43	33.33%	14	10.85%	5	3.88%	1	0.78%	129
S3	500-699	18	6.19%	45	15.46%	124	42.61%	72	24.74%	25	8.25%	8	2.75%	291
S4	350-499	9	2.72%	21	6.34%	86	25.98%	133	40.18%	71	21.45%	11	3.32%	331
S5	200-349	8	2.59%	16	5.18%	50	16.18%	87	28.16%	118	38.19%	30	9.71%	309
S6	< 200	6	2.52%	2	0.84%	12	5.04%	26	10.92%	69	28.99%	123	51.68%	238
Total														1374

CD4 Count - CD4 Cell Count (mm^3)

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

		To State												
From	CD4	S1		S2		S3		S4		S5		S6		
State	Count	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	Total
S1	> 899	46	44.23%	23	22.12%	17	16.35%	9	8.65%	7	6.73%	2	1.92%	104
S2	700-899	26	14.05%	64	34.59%	60	32.43%	19	10.27%	12	6.49%	4	2.16%	185
S3	500-699	24	7.04%	66	19.35%	149	43.70%	66	19.35%	31	9.09%	5	1.47%	341
S4	350-499	15	3.16%	29	6.12%	122	25.74%	198	41.77%	96	20.25%	14	2.95%	474
S5	200-349	8	1.67%	14	2.92%	49	10.23%	162	33.82%	187	39.04%	59	12.32%	479
S6	< 200	3	0.71%	10	2.36%	25	5.90%	54	12.74%	126	29.72%	206	48.58%	424
Total														2007

CD4 Count - CD4 Cell Count (mm^3)

confirmed to be very rare, with zero out of 46 (0.00%), 3 out of 81(3.700%), & 7 out of 191 (3.66%) of patients transiting from states 1,2, & 3 to state 6 respectively. The transition from states 4, 5, & 6 to state 1 was rare. Only 9 out of 286 (3.15%), 3 out of 307(0.98%), & 3 out of 305 (0.98%) of patients, respectively, transited to state 1. (Table 1). For Female patients (Table 2) transition from state 1, 2, & 3 to state 5 & 6 was rare with 2 out of 134 (1.49%), 2 out of 233 (0.86%), & 6 out of 441(1.36%) of 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. Only 15 out of 519 (2.89%), 13 out of 481 (2.70%), and 6 out of 357 (1.68%) of patients transiting from states 4, 5, and 6 respectively to state 1, only 1.40% of patients in state 6 transited state 2. For patients aged (20-39) years, only 2 out of 76 (2.36%), and 0 out of 76 (0%) patients in states 1 transited to states 5 and 6, respectively. On the other hand, only 6 out of 238 (2.5%), and 2 out of 238 (0.84%) patients in state 6 transited to states 1 and 2, respectively. Similarly, 7 out of 104 (6.73%) patients in the age group (40-69) years and 2 out of 104 (1.92%) patients in state 1 transited to states 5 and 6, respectively. From 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 clearly that antiretroviral therapy treatment positively impacted the patient's health for both age groups and gender. However, the impact varied with the age and gender of the patient, findings consistent with

previous researchers [66, 11, 27, 17, 49, 51, 67].

3.3 Summary of Observations on the Patients Transition Rates by Gender and Age Group

From Tables 5, 6, and 7, females are less likely to progress to a worse state than males in transitions, S2-S3 and S3-S4. However, they have higher transition rates in states S4-S5 and S5-S6, implying they are more likely to transit to the worst states than males. Findings consistent with previous researchers who have found females to have a low disease progression rate and a higher risk of death [56, 23, 59, 31]. Females are more likely to transit to a better state than males in S2-S1. However, both gender depicts the same transitional rates in S3-S2, S4-S3, and S5-S4. However, females have a low transition rate in S6-S5. Results are consistent with Table 7, which shows that they have a higher chance of transiting to a worse state when in S5. Females are likely to remain in states S1, S4, and S5, while male patients are more likely to remain in states S2-S2 and S3-S3. It is clear that a female patient is likely to remain in a better state (S1) and also likely to remain in a worse state (S5). Findings were consistent with other previous research where females had a high level of adherence to therapy in terms of medication and dietary requirement, lower viral load and higher CD4 cell count than males at diagnosis, and better survivors, though not significantly different [56, 23, 59, 31]. Tables 5 and 6show that the transition rate for patients aged 40-69 is higher in S1-S1 (0.0937) than in patients aged 20-39 (0.0869). However, they have a lower chance of remaining in the same state in all the other states. They are less likely to move to a better state than the young patients in all the disease states. The results can be attributed to their strong adherence to therapy, although they have a higher burden of competing risks that conspire to dilute the impact of therapy. From Table 7, the transition rate from S5-S6 for patients aged 20-39 was 0.0826 and 0.0808 for patients aged 40-69. For S1-S2, the transition rate for patients aged 20-39 was 0.0796 and 0.0772 for 40-69. We could attribute the results to poor adherence to medication by young patients. Young patients are more likely to move to a better or worse state. They are at a higher risk of death than older patients, which we could attribute to poor adherence to therapy and poor treatment intake. Findings consistent with [56, 23, 59, 31, 17, 38, 22, 11, 52, 28, 10].

4 Results

From Table 8, 9, and 10: Female data was coded using dummy variables; 1 for females and 2 for males. We used the medians of the age groups 20-39, 40-59, 50-59, and 60-69 in the variable AgeGrp, the minimum age being 24.5 for age group 20-39 and the maximum being 64.5 for age group 60-69. CD4 cell counts for patients during the first visit (CD4-1) and CD4 cell counts for patients during the second visit (CD4-2) were also used. We also coded state movement using dummy variables, with S1-S1 being 11, S2-S2 being 22 onwards, S6-S6 being 66, the minimum being 11, and the maximum being 66. The mean transition rate is highest in the same state with 0.2085, followed by a worse state with 0.1832, and lastly, a better state with 0.1741, the impact of the covariates in play notwithstanding.

From Table 11: State Movement covariate had the highest PIP for patients remaining in the same state (87.8%), followed by observation 2 CD4 (14.2%). Age group covariate was the least (0.5%). From Table 12: Age-group had the highest PIP for patients transiting to a better state (99.7%), followed by Gender (60.8%). Observation CD4-2 had the lowest PIP (0.4%). From Table 13: For patients transiting to a worse state, CD4-2 had the highest PIP (61.8%), followed by state movement (26.0%), and gender was the least (0.4%).

From Table 14: Model 1 had an intercept, best CD4-1, and a BIC of -2.72E+01, r^2 of 0.024, and post-prob of 0.633. Model 2 included an intercept, CD4-1, and Gender with a BIC of -2.57E+01, r^2 of 0.028, and post-prob of 0.288. Model 3 and model 4 included; intercept, CD4-1, and Age Group, with a BIC of -2.18E+01 and -2.16E+01, r^2 of 0.025 and 0.025, and a post-prob of 0.042 and 0.037, respectively.

From Table 15: The model including the intercept and Age Group was the best with a BIC of -2.14E+01, r^2 of 0.034, and post-prob of 0.949. Model 2 included the intercept, Age Group, and Gender with a BIC of -1.55E+01, r^2 of 0.035, and post-prob of 0.051.

From Table 16, The model including the intercept was the best with a BIC of 0.00E+00, r^2 of 0.000, and post-prob of 0.321. Model 2 included the intercept and CD4-1 with a BIC of 8.49E-01, r^2 of 0.012, and post-prob of 0.210. Model 3 included the intercept and CD4-2 with a BIC of 1.13E+00, r^2 of 0.011, and post-prob of 0.182. Model 4 included the intercept and state movement with a BIC of 2.54E+00, r^2 of 0.008, and post-prob of 0.090. Model 5 included the intercept, CD4-1, and the Age Group with a BIC of 3.25E+00, r^2 of 0.020, and post-prob of 0.063.

4.1 Graphical Presentation of the Posterior Model Size Distribution

The posterior model size distribution means for the same state, better state, and worse state are not significantly different: figure 1, same state = 1.1972; figure 2, better state = 1.1998; and figure 3, worse state = 1.1871. Model priors imply a symmetrical distribution around $\frac{K}{2}$ = 2.5. We assumed a uniform model prior. However, with data, the posterior probability puts more weight on parsimonious models (single models with high explanatory predictive power).

4.2 Graphical Presentation of the Posterior Model Probabilities

The posterior model probabilities for Markov Chain Monte Carlo (MCMC) simulation and "exact" depict a correlation of 1 for all the three; same state, a better state, and worse state; figure 4, same state = 1.0000; figure 5, better state = 1.0000; and figure 6, worse state = 0.9999.

Table 5. Summary of Transition Rates for Patients Remaining in the Same State

		Age Group		Gender	
StateMvt	CD4 Count	20-39	40-49	Male	Female
1 to 1	x>899	0.0869	0.0937	0.0683	0.0966
2 to 2	700≥x≤899	0.0817	0.0799	0.0895	0.0791
3 to 3	500≥x≤699	0.0915	0.0816	0.0861	0.0858
4 to 4	350≥x≤499	0.0907	0.0876	0.0839	0.0921
5 to 5	200≥x≤349	0.0908	0.0875	0.0819	0.0991

Table 6. Summary of Transition Rates for Patients Transiting to a Better State

		Age Group		Gender	
StateMvt	CD4 Count	20-39	40-49	Male	Female
2 to 1	700≥x>899	0.1455	0.0705	0.083	0.099
3 to 2	500≥x>699	0.0886	0.0824	0.085	0.085
4 to 3	350≥x>499	0.0841	0.0645	0.060	0.077
5 to 4	200≥x>349	0.0943	0.0705	0.077	0.077
6 to 5	0≥x>199	0.0932	0.0817	0.092	0.081

Table 7. Summary of Transition Rates for Patients' Transiting to a Worse State

		Age Group		Gender	
StateMvt	CD4 Count	20-39	40-49	Male	Female
1 to 2	700≥x≤899	0.0796	0.0772	0.0585	0.0884
2 to 3	500≥x≤699	0.0841	0.0892	0.0975	0.0838
3 to 4	350≥x≤499	0.1006	0.0662	0.0809	0.0806
4 to 5	200≥x≤349	0.0886	0.0914	0.0842	0.0949
5 to 6	0≥x≤199	0.0826	0.0808	0.0735	0.0875

Table 8. Summary Statistics for Patients Remaining in the Same State Data

Item	Rate (y)	Gender	AgeGrp	CD4-1	CD4-2	StateMovt
Min.	0.0072	1.0000	24.50	1.0	1.0	11.00
1st Qu.	0.0714	1.0000	34.50	210.8	218.8	33.00
Median	0.1111	1.0000	44.50	379.0	384.0	44.00
Mean	0.2085	1.3650	42.66	419.1	424.7	45.74
3rd Qu.	0.2000	2.0000	44.50	568.0	567.5	55.00
Max.	1.0000	2.0000	64.50	2857.0	2078.0	66.00

Table 9. Summary Statistics for Patients Moving to a Better State Data

Item	Rate (y)	Gender	AgeGrp	CD4-1	CD4-2	StateMovt
Min.	0.0076	1.0000	24.50	10.0	200.0	21.00
1st Qu.	0.0625	1.0000	34.50	205.0	353.0	43.00
Median	0.0909	1.0000	44.50	331.0	457.0	54.00
Mean	0.1741	1.3490	43.15	360.7	512.4	48.79
3rd Qu.	0.1667	2.0000	44.50	480.0	643.0	54.00
Max.	1.0000	2.0000	64.50	898.0	2857.0	65.00

4.3 Graphical Presentation of the Marginal Densities for Variable Gender

The PIP for co-variate "Gender" has got a higher impact on transition rates for patients transiting to the same state than those transiting to a better or worse state: figure 7, same state = 7.54%; figure 8, better state = 6.08%; and figure 9, worse state = 4.67%.

4.4 Graphical Presentation of the Marginal Densities for Variable Age Group

The PIP for co-variate "Age Group" has got a higher impact on transition rates for patients transiting to a better than those

Table 10. Summary Statistics for Patients Moving to a Worse State Data

Item	Rate (y)	Gender	AgeGrp	CD4-1	CD4-2	StateMovt
Min.	0.0072	1.0000	24.50	200.0	2.0	12.00
1st Qu.	0.0667	1.0000	34.50	377.8	267.2	23.00
Median	0.1111	1.0000	44.50	556.0	440.0	34.00
Mean	0.1832	1.4110	41.86	577.1	423.2	35.64
3rd Qu.	0.1667	2.0000	44.50	726.2	560.0	45.00
Max.	1.0000	2.0000	64.50	2016.0	898.0	56.00

AGeGrp - Age Group, CD4-1 - Observation 1 CD4 Cell Count, CD4-2 - Observation 2 CD4 Cell Count, & StateMovt - State Movement

Table 11. BMS Summary Results for Patients Remaining in the Same State

Item	PIP	Post Mean	Post SD	Cond.Pos.Sign	Index
StateMovt	8.79E-01	2.37E-03	1.04E-03	1.00E+00	5
CD4-2	1.42E-01	-1.68E-05	4.70E-05	0.00E+00	4
Gender	7.54E-02	-1.62E-03	6.92E-03	0.00E+00	1
CD4-1	5.56E-02	3.33E-06	2.15E-05	9.47E-01	3
AGeGrp	5.11E-02	-4.02E-05	2.29E-04	0.00E+00	2

Table 12. BMS Summary Results for Patients Moving to a Better State

Item	PIP	Post Mean	Post SD	Cond.Pos.Sign	Index
AGeGrp	9.97E-01	-3.40E-03	8.15E-04	0.00E+00	2
Gender	6.08E-02	1.12E-03	6.04E-03	1.00E+00	1
CD4-1	5.35E-02	4.01E-05	2.91E-04	1.00E+00	3
StateMovt	5.17E-02	-2.28E-06	1.72E-05	7.29E-05	5
CD4-2	4.00E-02	5.88E-07	1.38E-05	2.06E-01	4

Table 13. BMS Summary Results for Patients Moving to a Worse State

Item	PIP	Post Mean	Post SD	Cond.Pos.Sign	Index
CD4-2	6.18E-01	-1.16E-04	1.18E-04	0.00E+00	4
StateMovt	2.60E-01	4.11E-04	1.40E-03	8.49E-01	5
CD4-1	1.36E-01	-4.03E-06	4.70E-05	3.96E-01	3
AGeGrp	1.22E-01	-2.01E-04	6.69E-04	0.00E+00	2
Gender	4.67E-02	7.87E-05	5.10E-03	5.40E-01	1

AGeGrp - Age Group, CD4-1 - Observation 1 CD4 Cell Count, CD4-2 - Observation 2 CD4 Cell Count, & StateMovt - State Movement

Table 14. BMA: bicreg Summary Results for Patients Remaining in the Same State

Item	$p! = 0$	EV	SD	Model 1	Model 2	Model 3	Model 4
Intercept	100.0	-1.27E+00	1.83E-01	-1.31E+00	-1.22E+00	-8.21E-01	-1.42E+00
StateMovt	0.0	0.00E+00	0.00E+00	.	.	.	.
CD4-2	3.7	-5.76E-06	3.77E-05	.	.	.	.
CD4-1	100.0	-1.31E-01	2.37E-02	-1.29E-01	-1.38E-01	-1.30E-01	-1.55E-04
AGeGrp	4.2	-5.52E-03	3.30E-02	.	.	-1.31E-01	-9.84E-02
Gender	28.8	-4.95E-02	8.70E-02	.	-1.72E-01	.	.
nVar	.	.	.	1	2	3	2
r^2	.	.	.	0.024	0.028	0.025	0.025
BIC	.	.	.	-2.72E+01	-2.57E+01	-2.18E+01	-2.16E+01
post prob	.	.	.	0.633	0.288	0.042	0.037

transiting to the same state or worse state: figure 10, same state = 5.11%; figure 11, better state = 99.7%; and figure 12, worse state = 12.2%.

4.5 Graphical Presentation of the Marginal Densities for Variable Observation 1 CD4 Cell Count

The PIP for co-variate "Observation 1 CD4 Cell Count" had a more significant influence on transitions for patients transiting to a worse state than those transiting to a better or same state:

Figure 24. BMS Cumulative Model Probabilities for Patients Transiting to a Worse State

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