



# Modeling Viral Suppression, Viral Rebound and State-Specific Duration of HIV Patients with CD4 Count Adjustment: Parametric Multistate Frailty Model Approach

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## ABSTRACT

**Introduction:** Combination antiretroviral therapy has become the standard care of human immunodeficiency virus (HIV)-infected patients and has further led to a dramatically decreased progression probability to acquired immune deficiency syndrome (AIDS) for patients under such a therapy. However, responses of the patients to this therapy have recorded heterogeneous complexity and high dynamism. In this paper, we simultaneously model long-term viral suppression, viral rebound, and state-specific duration of HIV-infected patients.

**Methods:** Full-parametric and semi-parametric Markov multistate models were applied to assess the effects of covariates namely TB co-infection, educational status, marital status, age, quality of life (QoL) scores, white and red blood cell parameters, and liver enzyme abnormality on long-term viral suppression, viral rebound and

state-specific duration for HIV-infected individuals before and after treatment. Furthermore, two models, one including and another excluding the effect of the frailty, were presented and compared in this study.

**Results:** Results from the diagnostic plots, Akaike information criterion (AIC) and likelihood ratio test showed that the Weibull multistate frailty model fitted significantly better than the exponential and semi-parametric multistate models. Viral rebound was found to be significantly associated with many sex partners, higher eosinophils count, younger age, lower educational level, higher monocyte counts, having abnormal neutrophils count, and higher liver enzyme abnormality. Furthermore, viral suppression was also found to be significantly associated with higher QoL scores, and having a stable sex partner. The analysis result also showed that patients with a stable sex partner, higher educational levels, higher QoL scores, lower eosinophils count, lower monocyte counts, and higher RBC indices were more likely to spend more time in undetectable viral load state.

**Conclusions:** To achieve and maintain the UNAIDS 90% suppression targets, additional interventions are required to optimize antiretroviral therapy outcomes, specifically targeting those with poor clinical characteristics, lower education, younger age, and those with many sex partners. From a methodological perspective, the parametric multistate approach

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with frailty is a flexible approach for modeling time-varying variables, allowing for dealing with heterogeneity between the sequence of transitions, as well as allowing for a reasonable degree of flexibility with a few additional parameters, which then aids in gaining a better insight into how factors change over time.

**Keywords:** Factor analysis; Hematological parameters; Liver enzyme abnormality; Principal component; Quality of life

### Key Summary Points

#### Why carry out this study?

Highly active antiretroviral therapy (ART) has allowed for improvements in CD4 cell counts, suppression of human immunodeficiency virus (HIV) RNA and increased life expectancy of HIV-infected patients.

However, in some patients, suppression of HIV-RNA has been shown not to fall to undetectable levels, while, for other patients, viral rebound occurred after initially becoming undetectable.

In this paper, we simultaneously model long-term viral suppression, viral rebound and length of stay in better clinical stages.

#### What was learned from the study?

Viral rebound was found to be significantly associated with many sexual partners, higher eosinophils count, younger age, lower educational level, higher monocytes counts, having abnormal neutrophils count, and higher liver enzyme abnormality.

To achieve and maintain the UNAIDS 90% suppression targets, additional interventions are required to optimize ART outcomes, specifically targeting those with poor clinical characteristics, lower education, younger age, and those with many sex partners.

Parametric multistate with frailty approach is a flexible approach for modeling time-varying variables factors, allowing for dealing with heterogeneity between the sequence of transitions, as well as allowing for a reasonable degree of flexibility with a few additional parameters, which then aids in gaining a better insight in how factors change over time.

## INTRODUCTION

Care for HIV-infected patients has changed dramatically over the last two decades, [1] largely due to advances in antiretroviral therapy (ART), which has, in turn, allowed for improvements in CD4 cell counts, suppression of HIV RNA and increased life expectancy of human immunodeficiency virus (HIV)-infected patients [2, 3]. However, in some patients, suppression of HIV-RNA concentration has been shown not to fall to undetectable levels, while, for other patients, viral rebound occurred after initially becoming undetectable [4]. Such cases are termed virologic failure and have been conjectured to possibly be associated with poor adherence [5], drug–drug interactions, treatment failure, drug-resistance, or unobserved factors [6, 7]. To allow timely detection of virologic failure, the World Health Organization (WHO) recommended the use of HIV-RNA testing as the gold standard for monitoring of HIV-infected patients' response to therapy [8]. Assessment of the factors that affect viral load dynamics (i.e., viral suppression and rebound) is important in order to identify whether a patient is in need of more intensive adherence counseling and the timely detection of treatment failure in order to minimize the chances of development of drug resistance and unnecessary switching to an expensive regimen [9].

In 2015, the UNAIDS set the 90-90-90 global targets in order to end the AIDS epidemic, whereby the third 90 represents the target to achieve a viral load suppression in at least 90%

of HIV-infected patients under ART [10]. Identifying the possible factors that may affect virologic failure is key to achieving these targets. Findings from previous studies highlight a number of factors that may affect the viral suppression status among HIV-infected patients initiating ART, including gender, clinician skill level, suboptimal adherence, age, treatment history, WHO stage, and baseline CD4 cell count [5, 11–14]. Although clinical covariates are more capable of explaining and capturing realistic behavioral patterns of the VL responses, and are more sensitive to the source of variations in the viral load (VL), no previous study has directly examined the effects of several clinical attributes [i.e., white blood cell (WBC) parameters, red blood cell (RBC) parameters, blood chemistry parameters, and quality of life (QoL) domain scores] on VL dynamics. In addition, the relative role of various factors related to HIV VL responses may also further be dependent on the local context and the ART program setting. This study thus gives an insight into assessing the effect of several clinical, risk, and socio-demographic factors on long-term HIV VL dynamics. Therefore, we emphasize a comparison of viral rebound and viral suppression across different clinical attributes, and identify factors contributing to virologic failure which are key to informing adjustments in the program-level strategies most amenable to intervention in this context and key to achieving UNAIDS global target goals.

Mathematical models have been used extensively in research into HIV VL dynamics because they play an important role in improving our understanding of major factors contributing to the VL dynamics of the disease. These models range from logistic regression [5, 15–17], Cox regression analysis [18–20], accelerated failure time models [21], generalized estimating equations [22–24], to generalized linear mixed-effects models [25]. It has also been argued that multistate Markov models are useful tools for studying the complex dynamics of chronic diseases such as HIV VL progression, and are further valuable for identifying factors associated with disease progression of HIV/AIDS [26–28]. However, several multi-state Markov

models assume that the intensities are homogeneous, conditional on the observed covariates. Unfortunately, it is hardly ever possible to include all the relevant factors, either due to it not being possible to measure all the relevant factors or because the researchers do not know all the relevant factors. Ignoring such frailty or unobserved heterogeneity may have a huge impact on the estimation of the parameters in multistate Markov models.

In this study, full-parametric and semi-parametric multistate Markov frailty models were used to model viral rebound, viral suppression, and state-specific duration in HIV-infected patients under treatment. Multistate frailty models are a powerful tool for modeling complex cycles of chronic diseases, encompassing the life history of a cohort [29], considering all possible pathways [30], and further allowing for dealing with heterogeneity between the sequence of transitions [31, 32]. These models can also accommodate competing risks, censored data, recurrent outcomes, and multiple outcomes [33]. In this study, we classified the sequential adverse events by the degree of chronicity based on VL, with classifications defined by patients going through undetectable, low, moderate, and high VL. Most importantly, we have presented full and semi-parametric multistate Markov models, with patient-level frailties on all VL rebound, VL suppression and state-specific duration in HIV-infected patients, thus making the current study different from previous studies. Additionally, among the surrogate markers of HIV progression and ART responses, both the CD4 cell and VL counts are included in the same model. As discussed by Chikobvu and Shoko [34], the effects of multi-collinearity on the VL count transitions can be corrected using the principal component approach. Therefore, in this study, we have presented a parametric multistate frailty model for predicting transition intensities between sequential events of HIV infection, which takes into account the CD4 cell count, in order to study several factors that may affect viral suppression, viral rebound and state-specific duration of HIV-infected patients.

## METHODS

### Data Description

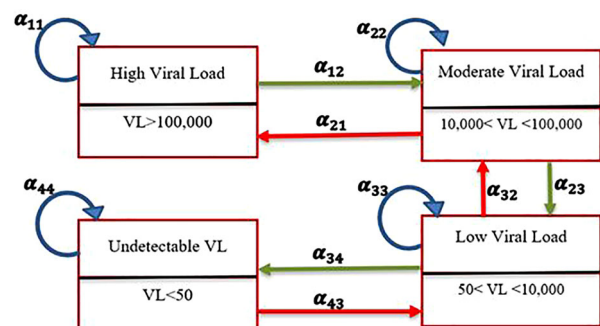
The data are from an ongoing prospective cohort study conducted among HIV-infected women from the Centre for the AIDS Programme of Research in South Africa (CAPRISA). The original study, which started in 2004, enrolled a cohort of HIV-uninfected women whose age was greater than 18 years with the aim of describing immunologic, clinical, and virologic characteristics of HIV-1 disease [35]. In this study, the participants's enrollment was conducted from August 2004 to December 2017. The participant who seroconverted during the HIV-uninfected stage of CAPRISA\_002 and other CAPRISA prevention and seroincidence trials (including the CAPRISA\_004 trials), were enrolled into the Acute HIV Infection phase, and then followed-up during chronic infection, ART initiation, and for up to 6 years on ART. Participants were recruited at two sites in KwaZulu-Natal-South Africa, a rural site in Vulindlela and an urban site in the city of Durban. Women without well-documented estimated date of HIV infection, and those who did not have at least two follow-up clinical attribute measurements, were excluded from the analysis. Finally, 219 participants were included in the study. Further information about the above-mentioned ongoing prospective HIV cohort study (CAPRISA\_002), including women's eligibility criteria and the enrollment procedure, were reported in [35–37]. All procedures performed in this study were approved by the Research Ethics Committee of the University of KwaZulu-Natal and CAPRISA. Written informed consent was obtained from all participants, and ethical approval for the original study was granted by the University of KwaZulu-Natal (E013/04), the University of Cape Town (025/2004), and the University of the Witwatersrand (M040202).

### Variables and Measurements

CAPRISA initially enrolled HIV-negative (phase I) women into different study cohorts. The

women who seroconverted were enrolled again into acute infection (i.e., phase II: weekly visits up to 3 months post-infection), early infection (i.e., phase III: monthly visits from 3 to 12 months), established infection (i.e., phase IV: quarterly visits for more than 12 months), and on ART (phase V). Samples for immunological, virological, and clinical attributes (such as VL, WBC parameters, RBC parameters, blood chemistry parameters, CD4 cell count, etc.) were measured at each visit [38]. These longitudinal immunologic, virologic, and clinical measurements were recorded for several follow-up visits. A total of 8760 follow-up visits were recorded for 219 HIV-infected women.

The primary outcomes in this current paper were viral rebound, viral suppression and state-specific duration of stay of AIDS patients. We defined disease progression of HIV/AIDS into four disease states: high VL (state 1), moderate VL (state 2), low VL (state 3), and undetectable VL (state 4) (Fig. 1). It is assumed that patients can have transitions from undetectable to detectable states and vice versa. Viral suppression transitions correspond to being from high VL to moderate VL (trans 1), or from moderate VL to low VL (trans 2), or from low VL to undetectable VL (trans 3). Likewise, viral rebound transition corresponds to a transition from undetectable VL to low VL (trans 4), or from low VL to moderate VL (trans 5), or from moderate VL to high VL (trans 6). Furthermore, state-specific duration corresponds to time spent in the high VL state, moderate VL state, low VL state, and undetectable VL state.



**Fig. 1** Progressive four-state model based on viral load counts: viral suppression (green arrows), viral rebound (red arrows) and waiting time (blue arrows)

The effect of numerous possible factors on viral suppression, viral rebound, and state-specific duration of stay of HIV patients was evaluated, including (1) demographics: date of the clinical visit, age, gender, marital status, and educational status; (2) risk variables: sex under the influence of alcohol, contraceptive use and substance use; (3) past opportunistic illness: tuberculosis and hypertension; (4) clinical attributes: blood chemistry [chloride, sodium, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein and lactate dehydrogenase (LDH)], WBC parameters (lymphocyte count, neutrophils, leucocyte count, monocytes and eosinophils), RBC parameters [hemoglobin (Hb), red cell distribution width (RDW), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and hematocrit], lipid parameters [cholesterol, triglycerides and low-density lipoproteins (LDL)] and physical examination parameters [blood pressure (BP), pulse rate (PR), weight and height]; and (5) QoL domain scores. The WHO QoL questionnaire [39] was used to measure the QoL of the participants. Therefore, the QoL scales contain the following domain scores. The first is physical health scores, which measure the impact of the disease on the activities of daily living, dependence on therapeutic substances, fatigue, lack of energy, presence of pain, and initiative and perceived working capacity. The second is the psychological wellbeing score domain, which assesses the patient's thoughts about body appearance, positive and negative feelings, personal beliefs and self-esteem, suicide, higher cognitive functions, anxiety, spirituality, and depression. The third domain is social relationships, which assesses personal relationships, social contacts, social support, and sexual activity. The fourth domain is devoted to the level of independence and assesses areas such as mobility, activities of daily living, dependence on treatments and work capacity. Further information about the above-mentioned factors has been reported in [40, 41] (Fig. 2).

## Statistical Method

Since our data have a large number of clinical variables, we used exploratory factor analysis to group and minimize the number of variables. Factor analysis was carried out by creating the principal components of the original variables and then creating the eigenvectors. By using the Kaiser criterion, eigenvectors with eigenvalues greater than 1 were kept [42]. A maximum likelihood extraction method with varimax rotation was used. Factor loadings describe the relationship of each clinical variable with each factor. The factor loading is considered strong if greater than 0.6, moderate if 0.4–0.6, and weak if less than 0.4 [43]. Each observation was assigned a score for each rotated factor based on the loading of the subject's original variable levels. Accordingly, we managed to group the 20 clinical variables in the study, to create 6 latent variables, defined as RBC component, red blood cell indices, liver abnormality component, electrolyte component, lipid component, and protein component (Table 1).

## Multistate Markov Frailty Modeling

To assess the effect of possible factors on the viral rebound, viral suppression and length of stay in each VL category of HIV/AIDS patients, we adopted a multistate frailty model to describe how patients move between a series of four VL count categories, from high VL to undetectable VL, in continuous time (Fig. 1).

Let  $S(t)$  represent the state occupied by a randomly chosen patient at time  $t$ . The transition probability of the patient being in state  $j$  at time  $t$ , given that the individual was in state  $m$  at time  $z$ , is defined by  $P_{mj}(z, t) = P(S(t) = j | S(z) = m)$ ; where  $\sum_{j \in S} P_{mj} = 1$ . The corresponding transition intensity is defined as

$$q_{mj}(t) = \lim_{\delta t \rightarrow 0} P(S(t + \delta t) = j | S(z) = m) / \delta t \\ \times \text{for } m \neq j, z < t.$$

Consequently, the  $4 \times 4$  transition intensity matrix  $Q(t)$  is defined as



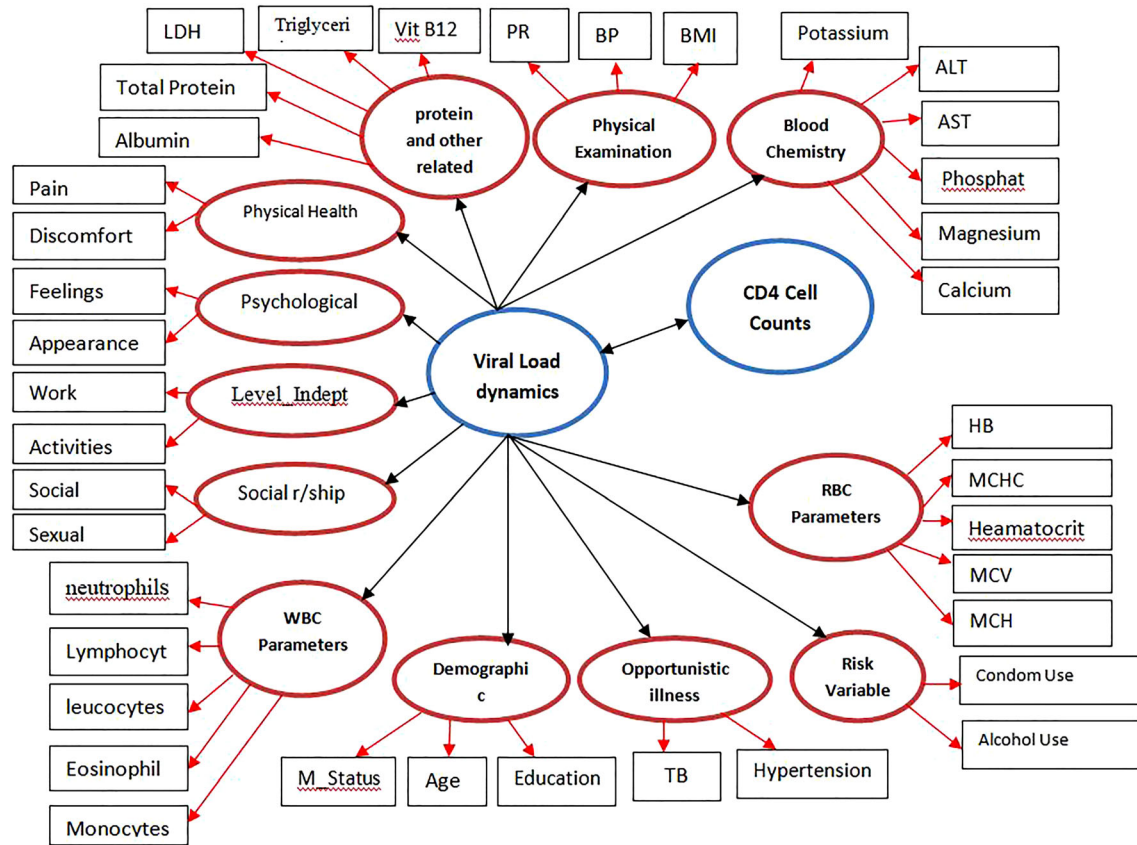


Fig. 2 The hypothesized model

$$Q(t) = \begin{bmatrix} -q_{12}(t) & q_{12}(t) & 0 & 0 \\ q_{21}(t) & -(q_{21}(t) + q_{23}(t)) & q_{23}(t) & 0 \\ 0 & q_{32}(t) & -(q_{32}(t) + q_{34}(t)) & q_{34}(t) \\ 0 & 0 & q_{43}(t) & -q_{43}(t) \end{bmatrix}$$

Note that the rows sum to zero since  $\sum_{j \in S} P_{mj} = 1$ . The off-diagonal entries are the viral suppression and the viral rebound transition intensities, respectively). The diagonal entries are defined by  $q_{mm}(t) = -\sum_{m \neq j} q_{mj}(t)$ . The average length of stay in a single state before making any transitions to either higher or lower VL states is estimated by a negative inverse of the  $m^{th}$  diagonal entry of  $Q(t)$ , that is  $\frac{-1}{q_{mm}}$ .

To examine the effect of covariates namely the educational status, age, marital status, QoL [physical health (PH) score, psychological

wellbeing (PW) score, level of independence (LI) score, social relationship (SR) score], TB co-infection, RBC indices, hemoglobin and hematocrits (HH), eosinophils, neutrophils, monocytes, electrolyte components and liver enzyme abnormality on such transitions, we employ both fully-parametric and semi-parametric multistate frailty models. In all models,

$$q_{mj}(t; \mathbf{x}, \mathbf{u}) = q_{mj}^0(t) v_{mj}^i \exp(\alpha'_{mj} \mathbf{x}_{mj}),$$

where  $q_{mj}(t; \mathbf{x}, v)$  represent the transition intensity from state  $m$  to state  $j$ , after adjusting a set of covariates  $\mathbf{x}_{mj}$ . The random effect or frailty of a patient is  $v_{mj}^i$ ,  $\alpha_{mj}$  is the effect of the covariates on the transitions hazard ( $q_{mj}$ ), where  $q_{mj}^0(t)$  represents the baseline intensity from state  $m$  to state  $j$ . We assumed  $v_{mj}^i$  to be independent and identically distributed with a

**Table 1** Clinical parameters and corresponding factor loadings from the rotated factors

Clinical parameters	Principal components	Variables	Factor loadings	Commutative variations
Red blood cell parameters	1. Hb and hematocrit component	RBC counts	0.946	81%
		Hb	0.886	
		Hematocrit	0.919	
	2. RBC indices component	MCV	0.953	
		MCH	0.825	
		MCHC	0.521	
Blood chemistry	3. Liver enzyme abnormality component	ALT	0.829	72%
		AST	0.967	
	4. Electrolyte component	Chloride	0.455	
		Sodium	0.994	
		Calcium	0.213	
		RDW	− 0.592	
Protein and lipids	5. Lipid component	Cholesterol	0.971	65%
		LDL	0.917	
		Triglycerides	0.360	
	6. Protein component	LDH	− 0.769	
		Total protein	0.670	

For explanation of the abbreviations, see text

Gamma probability distribution  $v_{mj}^i \sim \Gamma\left(\frac{1}{\gamma_{mj}}, \frac{1}{\gamma_{mj}}\right)$ ,  $\text{mean}(v_{mj}^i) = 1$  and  $\text{var}(v_{mj}^i) = \gamma_{mj}$ . The variance  $\gamma_{mj}$  represents the heterogeneity of the overall underlying baseline risk for the transition  $m \rightarrow j$ . For this model, if  $m < j$ , it is termed as the viral suppression transitions, while a transition where  $m > j$  is termed as viral rebound and for  $m = j$ , it is termed as the probability of staying in the same diseasing state. Thus the labeling is 1 for high VL, 2 for moderate VL, 3 for low VL, and 4 for undetectable VL states (See Fig. 1). Thus, viral suppression transition, viral rebound transition, and the state-specific duration of stay for a patient  $I$  in the current study are defined as:

$$q_{mj} = q_{mj}^0(t)v_{mj}^i \exp\left(\alpha_{mj}^{\text{Educ}} \text{Educ}_i + \alpha_{mj}^{\text{Age}} \text{Age}_i + \alpha_{mj}^{\text{MStatus}} \text{MStatus}_i + \alpha_{mj}^{\text{PHScore}} \text{PHScore}_i + \alpha_{mj}^{\text{PWScore}} \text{PWScore}_i + \alpha_{mj}^{\text{LIScore}} \text{LIScore}_i + \alpha_{mj}^{\text{TB}} \text{TB}_i + \alpha_{mj}^{\text{RBC}} \text{RBCIndices}_i + \alpha_{mj}^{\text{HHH}} \text{HHH}_i + \alpha_{mj}^{\text{Eosinophils}} \text{Eosinophils}_i + \alpha_{mj}^{\text{Monocytes}} \text{Monocytes}_i + \alpha_{mj}^{\text{Neutrophils}} \text{Neutrophils}_i + \alpha_{mj}^{\text{Liver}^{\text{EA}}} \text{Liver}_{\text{abnormality}_i} + \alpha_{mj}^{\text{CD4}^{\text{OR}}} \text{CD4}_i\right).$$

In the fully parametric cases, the baseline intensity is given by a full parametric function of time  $q_{mj}^0(t) = g(t, \theta)$ , so that the intensity model is a standard parametric distribution. In the current study, we used the Weibull distribution with parameters  $(\theta, \alpha)$  and transition intensity,  $q_{mj}(t; \mathbf{x}, \mathbf{u}) = \theta_{mj} t^{\theta_{mj}-1} v_{mj}^i$

$\exp(\alpha'_{mj} \mathbf{x}_{mj})$ . An important special case, which we also considered, was  $\theta_{mj} = 1$ , for all  $m$  and  $j$ , where the transition rate is constant, conditional on the value of any time-dependent variables. Since these variables are assumed to be constant between event times, the transition rate is a step function of time, and the waiting time in each state has an exponential model. Thus, the full likelihood function for all observed multistate data is given by

$$\begin{aligned} L_M(\boldsymbol{\alpha}, \theta) &= \int_{R^+} L(\boldsymbol{\alpha}, \theta; \mathbf{x}, v) f_V(v; \gamma) dv \\ &= \int_{R^+} \prod_h \prod_I \left[ \left\{ v_{hi} q_h^0(t_i) \exp(\alpha'_{hi} \mathbf{x}_{hi}) \right\}^{\delta_{hi}} \right. \\ &\quad \left. \exp\left\{ v_{hi} Q_h^0(t_i) \exp(\alpha'_{hi} \mathbf{x}_{hi}) \right\} \right] f_V(v; \gamma) dv, \end{aligned}$$

where  $h$  is the transition for patient  $i$ ,  $\delta_{hi}$  is the event indicator,  $\theta$  is a vector of parameters relating to the cumulative baseline intensity  $Q_h^0(t_i)$  and  $L_M(\boldsymbol{\alpha}, \theta)$  is the marginal likelihood for the multistate frailty model. For the computations of the above likelihood function, a maximum penalized likelihood estimation with gamma frailty (as discussed by Rondeau and Gonzalez [44]), can be applied to estimate the integrals and thereby avoids the need for intensive computations.

In the semi-parametric case, the baseline intensity,  $q_{mj}^0(t)$ , is left completely unspecified and estimated non-parametrically. The log-linear effect of the covariates  $\alpha_{mj}$ , are estimated by maximizing the partial loglikelihood function. Thus, the partial loglikelihood for all the observed multistate data is given by

$$\begin{aligned} \ell(\boldsymbol{\alpha}; \mathbf{x}, v) &= \sum_h \left\{ d_h \log v_h + \sum_I \delta_{hi} \alpha'_{hi} \mathbf{x}_{hi} \right. \\ &\quad \left. - \log \sum_{h, i \in R(t)} v_{hi} \exp(\alpha'_{hi} \mathbf{x}_{hi}) \right\} + \log f_V(v; \gamma) \end{aligned}$$

where  $h$  is the transition for patient  $I$ ,  $d_h = \sum \delta_{hi}$  is the number of events, and  $R(t)$  is the risk set at time  $t$  for making a transition  $h$ . In this study, we used a more efficient Quasi-Newton iterative approach proposed by Kalbfleisch and Lawless [45], for the computations of the above partial loglikelihood function.

In addition to adding the frailty term, a principal component variable is created to improve the efficiency of the above models. In order to create a principal component variable, as explained by Chikobvu and Shoko [34], we carried out the following regression analysis to estimate  $\beta_0$  and  $\beta_1$  in the model:  $y_i^{\text{CD4}} = \beta_0 + \beta_1 x_i^{\text{VL}} + \varepsilon_i$ . We then defined an orthogonal CD4 cell count variable =  $\varepsilon_i = y_i^{\text{CD4}} - (\beta_0 + \beta_1 x_i^{\text{VL}})$ . The orthogonal CD4 cell count in the model explains the component of disease progression of HIV that cannot be explained by the VL alone. In order to deal with multicollinearity of the CD4 cell count and VL count, the orthogonal CD4 cell count component was used. The residual from the fitted principal component model was included with the original HIV/AIDS data model to form the new CD4 cell count component.

### Prediction from Multistate Model

To predict the probability of occupying a particular state at a given time, we calculated,  $p_{mj}(z, t)$ , the probability of being in state  $j$  at a time  $t$ , given being in state  $m$  at time  $z$ . Under all models, we used a simulation approach, which can be considered to be a more efficient and general approach (proposed by Crowther and Lambert [46]). This can be achieved by simulating a large number of patient states history from multistate frailty models, given the cumulative hazard for each transition, or covariate-specific hazard. The flexsurv and mstate commands have utilities to do this for the parametric and semiparametric multistate Markov model, respectively. All the analyses were carried out using statistical packages R-3.6 (mstate and felxurv) and SAS 9.4.



## RESULTS

### Characteristics of the ART Cohort at Enrolment

All participants were black women ( $n = 219$ ), with a mean age of 26.67 years (standard deviation of 6.9 years). The majority of participants were married or with a stable partner 174 (79.5%), not co-infected with TB 201 (91.8%), not with anemia 208 (95.0%) and overweight 137 (62.8%), based on their body mass index (BMI) measurements. Over two-thirds, 153 (69.9%), reported having completed grades 11/12 of schooling. Considering the baseline virologic state, 40.2% and 32.4% of patients had an initial VL of  $10,000 < VL < 1000,000$  copies/ml and  $50 < VL < 10,000$  copies/ml, respectively. The median baseline CD4 count of the participants included in the analysis was 519.0 cells/mm<sup>3</sup> (IQR 419–655.5 cells/mm<sup>3</sup>) (Table 2).

### Estimated Transition Probability and Length of Stay

The plot in Fig. 3 displays the non-parametric estimated probability of transitions of viral suppression, viral rebound, and the state-specific length of stay of AIDS patients. From Fig. 3a, b, it is interesting to observe that, when a patient's VL is above 10,000, rates of change of viral rebound (transitions 5 and 6), are smaller than the rates of change of viral suppression (transitions 1 and 2). However, the probability of achieving an undetectable VL for patients (transition 3) is smaller than the probability of a viral rebound from the undetectable VL (transition 4) (Fig. 3c). Furthermore, patients with lower VL (particularly those in the undetectable VL state) had a higher probability of staying in the same state throughout the duration of follow-up periods, compared to those with a higher VL (Fig. 3d).

### Assessment of the Fitted Models

We applied three Markov multistate models, the Exponential, Weibull, and the Semi-Parametric Multistate models. The estimates of these full

and semi-parametric multistate models were compared with non-parametric estimates to assess the goodness of fit of the model (as discussed by Ieva et al. [47] and Titman and Sharples [48]) (Fig. 4). From this plot, we noted that the Weibull model accounted better for the decrease in the survival function of the length of stay and transitions since the time of the last visit. The model selection criteria in Table 3 further confirm this finding.

Besides selecting the best fit model for our data, the effect of patient-level frailties and orthogonal CD4 cell count components on VL dynamics were also analyzed. This was achieved by fitting a Weibull multistate model without patient-level frailties and orthogonal CD4 cell count components on VL dynamics. Secondly, we fitted a Weibull model for the effects of the factors, where only a frailty term was included in the model. Finally, we fitted a Weibull multistate model with patient-level frailties and orthogonal CD4 cell counts. A comparison of these three models was based on the AIC and likelihood ratio tests (LRT). The AIC and LRT from Table 4 showed that the Weibull multistate model with patient-level frailties and with CD4 cell count orthogonal adjustment gives the best fit to the data (i.e., gives improvements in estimation) (Table 4).

### Predictors of Viral Suppression

Analysis results for modeling viral suppression, viral rebound, and length of stay using Weibull multistate frailty are presented in Figs. 5, 6 and 7, respectively. Focusing on the effect of predictors on viral suppression, an increase in eosinophils count decreases the probability of experiencing viral suppression from high to moderate VL (aHR = 0.33, 95% CI 0.14–0.78). Compared to patients without TB co-infection, we note that patients with TB co-infection were associated with a decreased probability of achieving viral suppression to undetectable VL (aHR = 0.44, 95% CI 0.23–0.83) and to low VL (aHR = 0.60, 95% CI 0.38–0.95). Considering QoL domain scores of the patients, as the score of psychological wellbeing (aHR = 1.02, 95% CI 1.01–1.15) increases, the transitions to viral

**Table 2** Baseline characteristics of the ART cohort in the CAPRISA 002 study

Variables	Count/mean (percentage/SD)
BMI categories [ <i>n</i> (%)]	
Underweight	5 (2.3)
Healthy weight	76 (34.9)
Overweight/obese	137 (62.8)
Age categories [ <i>n</i> (%)]	
18–20 years	29 (13.2)
21–39 years	178 (81.3)
40–59 years	12 (5.5)
Marital status [ <i>n</i> (%)]	
Single/no partner	34 (15.5)
Married/stable partner	174 (79.5)
Many partners	11 (5.0)
Educational status [ <i>n</i> (%)]	
≤ Grade 8	16 (7.31)
Grade 9–10	50 (22.8)
≥ Grade 11	153 (69.9)
Baseline virologic state [ <i>n</i> (%)]	
High VL: VL > 100,000 copies/ml	55 (25.1)
Moderate VL: 10,000 < VL < 1000,000 copies/ml	88 (40.2)
Low VL: 50 < VL < 10,000 copies/ml	71 (32.4)
Undetectable VL: VL < 50 copies/ml	5 (2.3)
TB co-infection [ <i>n</i> (%)]	
Yes	18 (9.2)
No	201 (91.8)
Anemia [ <i>n</i> (%)]	
Yes	11 (5.0)
No	208 (95.0)

**Table 2** continued

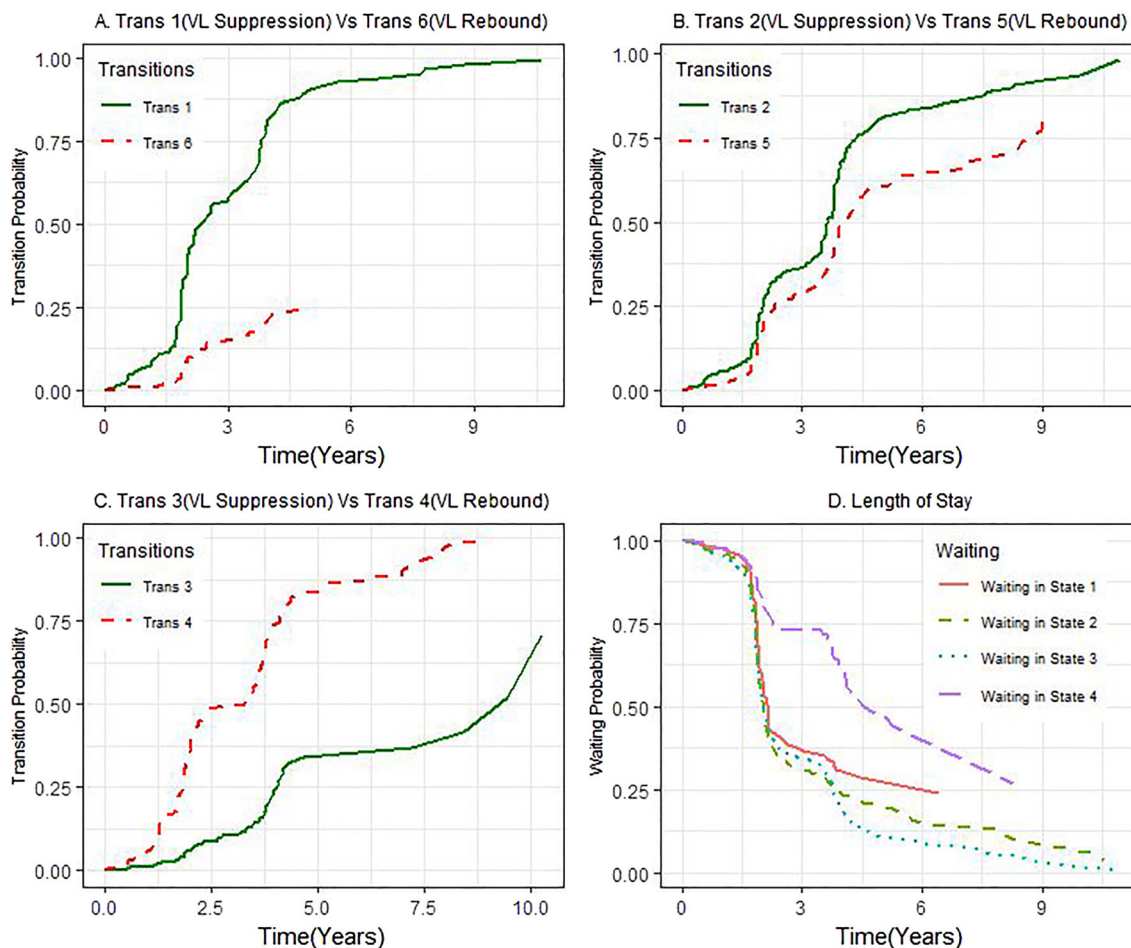
Variables	Count/mean (percentage/SD)
Contraceptive use [ <i>n</i> (%)]	
Yes	179 (81.7)
No	40 (18.3)
Sex acts under influence of alcohol [ <i>n</i> (%)]	
Yes	22 (10.0)
No	197 (90.0)
Baseline CD4 cell count, Median (IQR)	519.0 (419.0–655.5)

suppression (particularly from high VL to moderate VL) increase. Similarly, having a high level of independence score was associated with a higher probability of achieving viral suppression.

Age was shown to have a strong association with suppression of VL (particularly from high VL → moderate VL). These results suggest that the likelihood of achieving viral suppression to moderate VL is lower for patients in the younger age group (age < 20 years) (aHR = 0.19, 95% CI 0.08–0.46) and middle age group (21–39 years), evidenced by (aHR = 0.41, 95% CI 0.26–0.66), compared to those in an older age group (age > 40 years). In addition, the time for transition from high VL to moderate VL (aHR = 1.65, 95% CI 1.03–2.64) and from moderate VL to low VL (aHR = 1.67, 95% CI 1.22–2.29), was accelerated for patients with stable sex partners (married), compared to those with no sex partner. Moreover, the result further showed that patients with many sex partners (aHR = 0.24, 95% CI 0.08–0.70), had significantly decreased viral suppression to undetectable levels, as compared to those with no sex partner (Fig. 5).

### Predictors of Viral Rebound

The effect of several predictors on viral rebound of HIV/AIDS is given in Fig. 6. Based on the parameter estimates, we noted that the neutrophils had significantly decreased transition

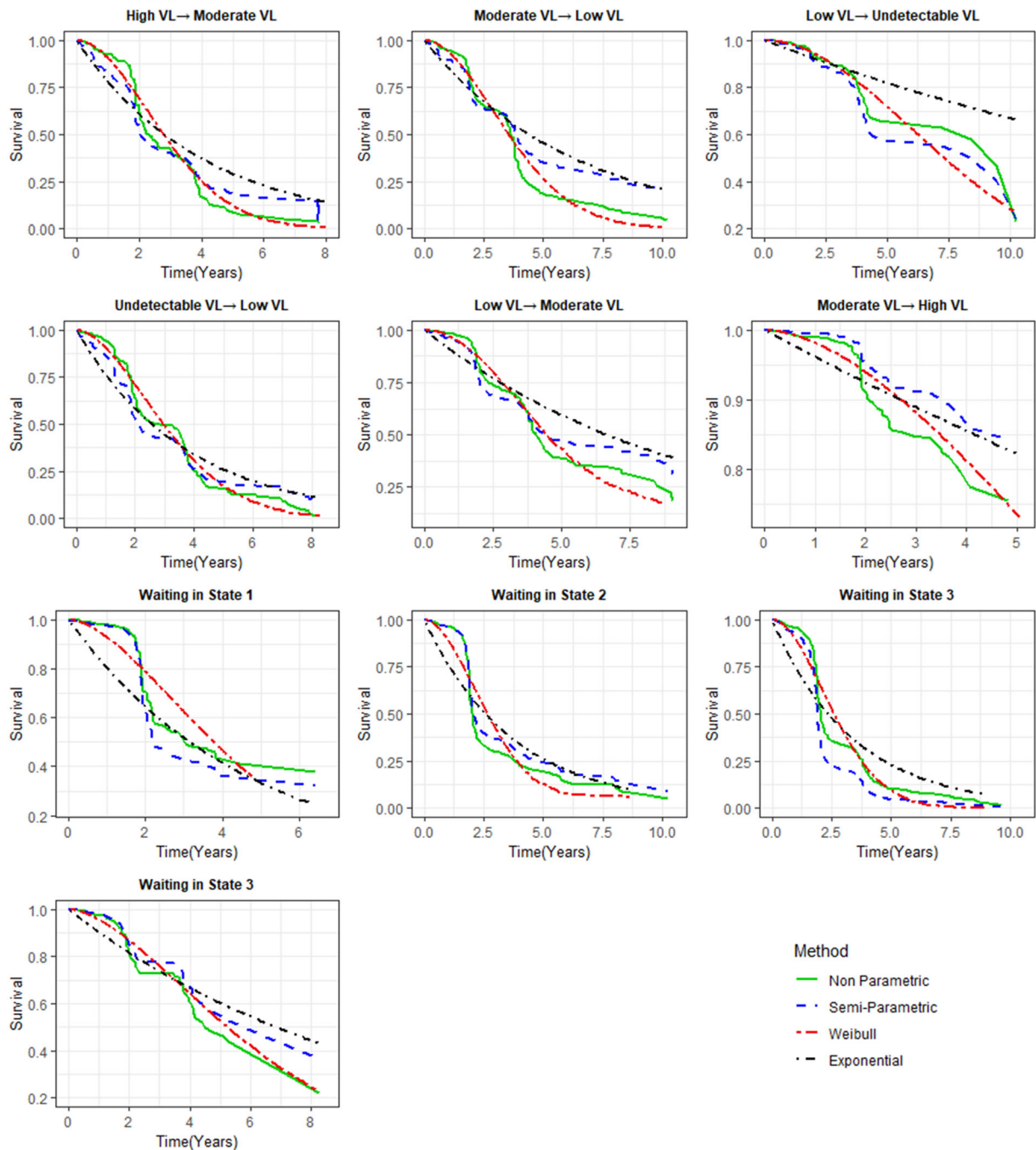


**Fig. 3** Estimated probability of transition and probability of being in each disease state, over the follow-up time

intensity to viral rebound. As the score of this covariate increases, the probability of experiencing viral rebound from low VL to moderate VL (aHR = 0.88, 95% CI 0.80–0.97), and from moderate VL to high VL (aHR = 0.70, 95% CI 0.59–0.84) decreases. In addition, having high monocyte counts accelerates viral rebound from low to moderate VL (aHR = 2.20, 95% CI 1.90–3.31) and from moderate to high VL (aHR = 1.25, 95% CI 1.01–1.67). Similarly, having a higher eosinophil score was associated with an increased probability of experiencing viral rebound, from low to moderate VL (aHR = 1.83, 95% CI 1.41–2.38) and from moderate to high VL (aHR = 2.36, 95% CI 1.64–3.88). Furthermore, having high liver abnormality scores accelerates viral rebound

from moderate to high VL (aHR = 1.23, 95% CI 1.01–1.67).

Considering QoL domain scores of the patients, we note that, as the score of physical health increases, the transitions to viral rebound from low to moderate VL (aHR = 0.91, 95% CI 0.83–0.99) and from moderate to high VL (aHR = 0.85, 95% CI 0.75–0.97), decreases. Patients in the younger age group (age < 20 years) were more likely to experience viral rebound (aHR = 1.26, 95% CI 1.09–2.25), compared to those in older age groups (age > 40 years). In addition, patients with higher educational levels were less likely to experience viral rebound from moderate to high VL. Furthermore, having many sex partners accelerates viral rebound from moderate to high VL (aHR = 1.32, 95% CI 1.02–3.36) see Fig. 6.



**Fig. 4** Non-parametric (green) survival functions of time to initiation of ART, from the starting state, and estimated transition and waiting probabilities in that state from semi-parametric (blue) models, Weibull distribution (red) and Exponential distribution (black)

### Predictors of Length of Stay

As seen from Fig. 7, monocytes and eosinophils were shown to have a strong association with

time spent in this moderate VL state. These results suggest that patients with high monocytes (aHR = 1.78, 95% CI 1.29–2.46) and high eosinophils (aHR = 1.54, 95% CI 1.12–2.12) are

**Table 3** Model selection criteria for each semi and full-parametric model

Criterion	Weibull multistate Markov model	Exponential multistate Markov model	Semi-parametric multistate Markov model
– 2 LOG L	11,605.44	19,789.32	39,388.57
AIC	12,029.44	12,860.29	38,970.57

AIC akaike information criteria, – 2 LOG L – 2Log-likelihood

**Table 4** Assessment of the fitted model with and without frailty and CD4 orthogonal component

Criterion	Weibull distribution without orthogonal CD4 counts and frailty	Weibull distribution with gamma frailty but without orthogonal CD4 counts	Weibull distribution with gamma frailty and orthogonal CD4 counts
– 2 LOG L	11,605.44	10,586.84	7940.94
AIC	12,029.44	11,012.83	8386.94

AIC akaike information criteria, – 2 LOG L – 2Log-likelihood

more likely to stay longer in a moderate VL state (between 10,000 and 100,000). In addition, patients with high neutrophils were less likely to stay longer in a high VL state (aHR = 0.76, 95% CI 0.63–0.92) and moderate VL (aHR = 0.90, 95% CI 0.84–0.96). High RBC indices scores (aHR = 0.75, 95% CI 0.62–0.92) and high electrolyte component scores (HR = 0.78, 95% CI 0.63–0.97) were significantly associated with a decreased probability of staying in a higher VL state. Furthermore, having high liver abnormality scores were associated with an increased probability of staying in a higher VL state (aHR = 1.35, 95% CI 1.16–1.57).

Patients with higher educational levels were found to be associated with an increased probability of staying in a lower VL state.

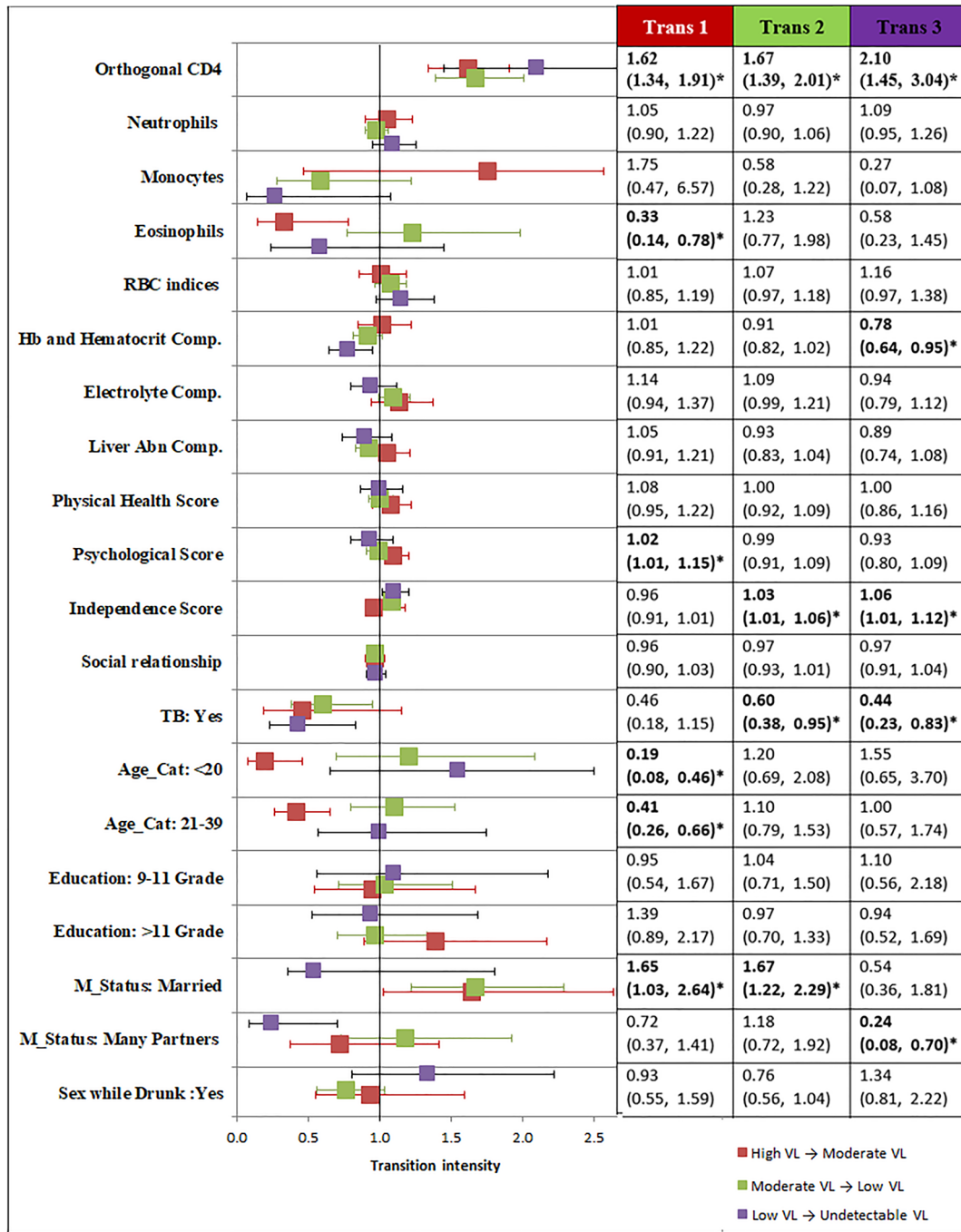
Considering QoL domain scores of the patients, high physical health scores were significantly associated with an increased probability of staying at an undetectable level (aHR = 1.09, 95% CI 1.01–1.26). Patients in the younger age group (age < 20 years) were also associated with an increased probability of staying in a higher VL state (aHR = 1.81, 95% CI 1.23–3.39), compared to those in the older age group. Furthermore, an increased probability of staying in moderate VL states (between 10,000 and 100,000) was associated with having many sex partners (aHR = 2.36, 95% CI 1.63–3.42), as compared to those with no sex partner (Fig. 7).

## DISCUSSION

The current study was aimed to simultaneously model viral rebound, viral suppression, and state-specific duration of stay of AIDS patients, and to determine how these depend on level of educational status, age, marital status, quality of life scores, TB co-infection, RBC indices, hemoglobin and hematocrits, eosinophils, neutrophils, monocytes, electrolyte components, and liver enzyme abnormality. These factors may not adequately be modeled using constant hazards, although the bias in estimates of the hazard ratios was not large in this population. Thus, we have presented and compared full-parametric and semi-parametric multistate models. Results from the diagnostic plots, AIC and LRT, showed that the Weibull multistate model, fitted significantly better than the exponential and semi-parametric multistate models. We also improved the selected model, the Weibull multistate model, by including patient-level frailties and an orthogonal CD4 cell count component. This further improved the efficiency and predictive accuracy of the model.

Some of the results of this study supported the previous literature findings, while some results of this study provided new insights. The results of this study showed that young adolescents were significantly associated with decreased viral suppression and were associated with an increased probability of experiencing viral rebound, compared to those patients in

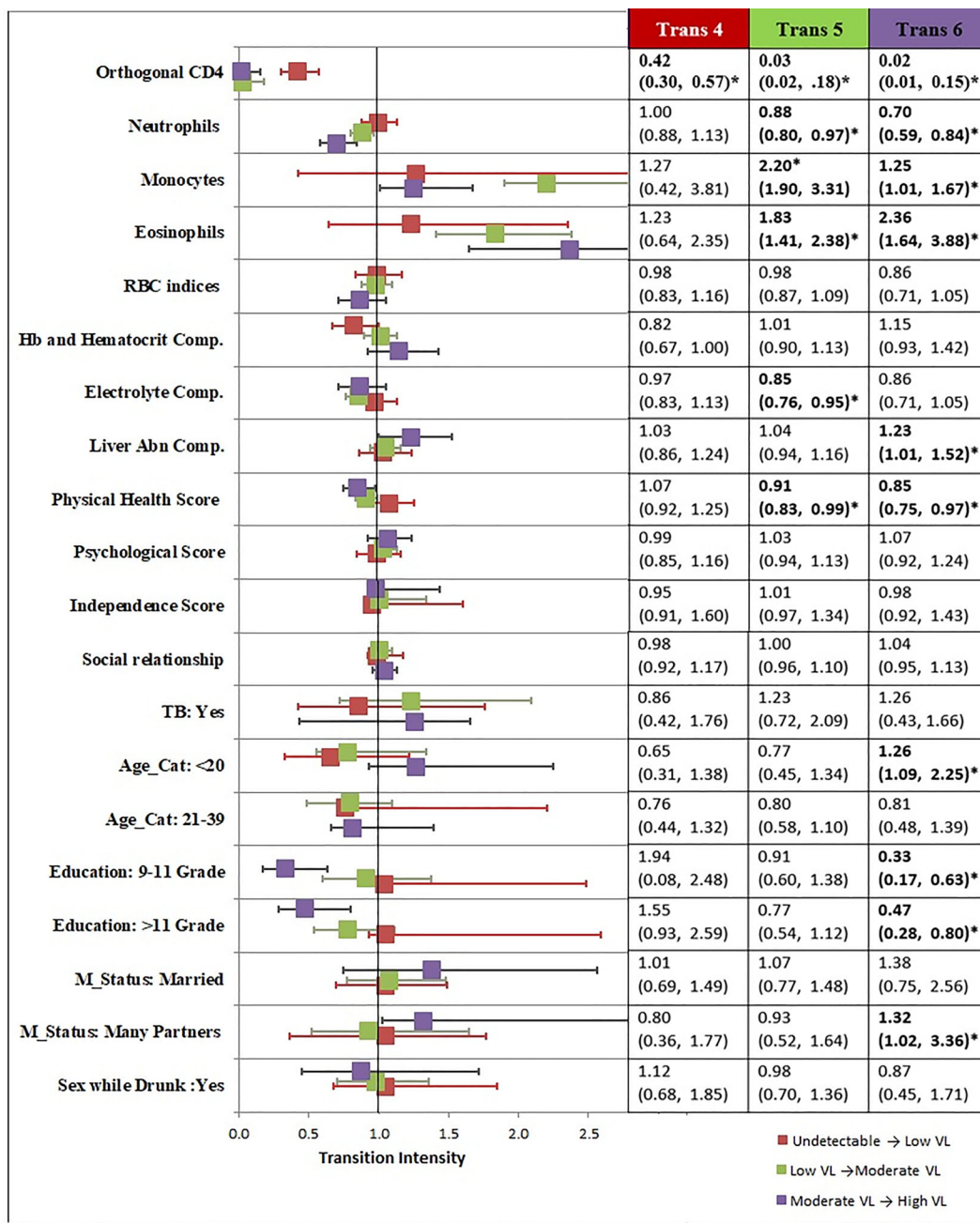




**Fig. 5** Parameter effects (with 95% CI) of socio-demographics variables, risk variables, QoL domain scores, and clinical measurements on viral suppression for the Weibull multistate frailty Markov model

older age groups (age > 40 years). This was supported by previous studies ([5, 49, 50]), in which older age groups were more likely to achieve viral suppression compared to those in

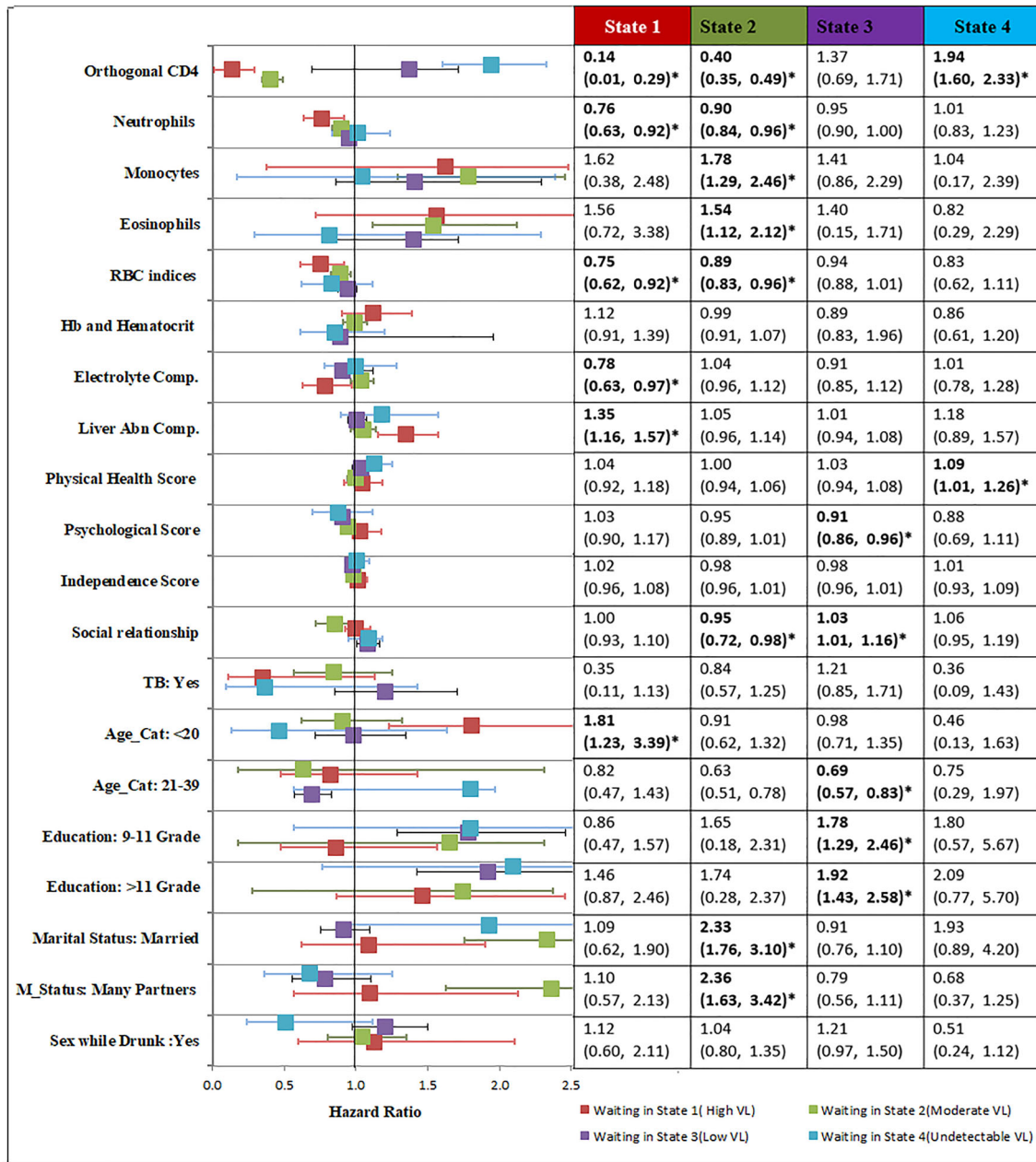
younger age groups. A plausible reason for this is that the treatment for adolescents may be affected by alcohol and recreational drug use [51], lack of disclosure, stress, HIV-associated



**Fig. 6** Parameter effects (with 95% CI) of socio-demographics variables, risk variables, QoL domain scores, and clinical measurements on the viral rebound for Weibull multistate frailty Markov model

discrimination and stigma [5, 52], and feelings of invulnerability to the consequences of HIV disease [53]. These factors may mediate the observed association among younger aged individuals and viral rebound. We also found that patients with lower educational levels were

associated with an increased probability of experiencing viral rebound, a finding that is in accordance with the literature [54–56], where patients who have lower educational attainment were associated with viral rebound. It may reflect lower levels of health literacy or indicate



**Fig. 7** Parameter effects (with 95% CI) of socio-demographics variables, risk variables, QoL domain scores, and clinical measurements on length of stay (waiting time) for Weibull multistate frailty Markov model

a marker of overall poverty. Lower health literacy and greater poverty-related stress have been linked to medication non-adherence and poor virologic outcomes [57, 58].

Having a high QoL domain score in our study was associated with increased suppression and reduced likelihood of viral rebound. As has

been previously shown [59, 60], patients with anxiety, depression, and low QoL are less likely to exhibit adherence to ART. Poor adherence may be associated with increased probability of experiencing viral rebound [61–63], showing that at least part of the effect of low QoL scores on incomplete viral suppression is mediated

through combination ART adherence. Patients diagnosed with TB after ART initiation are associated with increases in plasma HIV viremia [64–66]. The risk of viral suppression may also be decreased by patients with TB co-infection, due to an increased risk of drug toxicity, drug–drug interactions, and the potential for lower adherence due to the high pill burden [67]. Our data add to this literature by showing that patients with TB co-infection were associated with a decreased probability of experiencing viral suppression. Therefore, patients on ART with active TB should thus be prioritized for VL monitoring and adherence support. Furthermore, having many sex partners exposes them to an accelerated risk of viral rebound, from moderate to high VL.

Among the different hematological parameters for HIV-infected patients, as expected, an abnormally high number of eosinophils in the blood significantly decreased viral suppression and increased the probability of experiencing viral rebound, a finding that is in accordance with the literature [68], where it has been found that patients with a higher eosinophils counts were more likely to have higher long-term viral rebound. We also found that patients having higher neutrophil counts were significantly associated with a decreased probability of experiencing viral rebound. This finding agrees with studies that have shown that worsening HIV disease, demonstrated by increasing VL rebound, has been associated with abnormality of neutrophils (neutropenia: absolute neutrophil counts < 500) [69, 70]. We further observed that patients with high monocyte count were associated with a higher probability of experiencing viral rebound. Our finding is concurrent with those from prior reports, which noted that the monocyte CD69 expression rate was significantly positively correlated with the HIV-1 RNA [71]. Consequently, caution is needed for risk assessment measures to monitor and screen patients' pre- and post-ART initiation in African clinical settings to curtail potential risks associated with an increased probability of experiencing viral rebound. Moreover, liver enzyme abnormalities were significantly associated with a higher probability of experiencing viral rebound. Our findings are

concurrent with those from prior reports [72, 73], which noted that a positive correlation exists between VL and aminotransferase (ALT and AST). Thus, there is a need to monitor ALT and AST levels after initiation of ART, mainly in high-risk patients, to reduce side effect concerns.

We further found that patients having higher educational levels were more likely to spend a longer time in good states (particularly lower VL state), as compared to those with lower educational levels. This could be due to better knowledge about their treatment and disease, access to health services, or functional status. Similarly, higher QoL scores (particularly physical health scores) were significantly associated with longer time spent in lower VL states. Furthermore, those of younger age (< 20 years) with high liver abnormality scores and high social relationship scores were associated with an increased probability of staying in a higher VL state.

Readers should be cautious when interpreting the findings of this study since the study findings were limited to adult females, and hence the findings may not be generalized to all HIV-infected patients. In addition, this study has also some limitations, including missing data, which are expected for a study conducted on data collected from patients' files and when dealing with a long-term follow-up period. Moreover, we did not assess some other clinical and risk factors, such as adherence level, hepatitis status, treatment change, drug–drug interactions, and drug abuse, that may affect VL dynamics. Despite these limitations, important information regarding clinical factors associated with viral rebound and viral suppression for women were identified. This information is of value in identifying women at risk for suboptimal therapeutic outcomes. Additionally, it will help to inform cART retention strategies for HIV-infected patients.

## CONCLUSIONS

We have simultaneously modeled long-term viral suppression, viral rebound, and state-specific duration of stay of AIDS patients in



seroconversion among South African women, using the Weibull multistate frailty model. This has resulted in precise estimates of covariate effects, time spent in each state, and expected survival times. Additionally, we have examined important information regarding factors that affect long-term viral dynamics. This information is of value in identifying women at risk for suboptimal therapeutic outcomes. Moreover, to achieve and maintain the UNAIDS 90% suppression targets, additional interventions are required to optimize ART outcomes, specifically targeting poor clinical characteristics, lower education, younger age individuals, and those with many sex partners.

From a methodological perspective, the parametric multistate with frailty approach is a flexible approach for modeling time-varying variable factors, allowing for dealing with heterogeneity between the sequence of transitions, allowing for a reasonable degree of flexibility with few additional parameters, and gaining a better insight into how the factors change over time. Furthermore, the parametric multistate frailty model further extends the knowledge as to the HIV disease burden transitions and can be used to learn more about the disease progression of other chronic diseases.

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**Authorship Contributions.** Zelalem G. Dessie designed the study, collected the data, analysed the data and wrote the article. Temesgen Zewotir designed the study, advised on analysis and edited the manuscript. Henry Mwambi and Delia North reviewed the study designed and critically edited the manuscript. All authors read and approved the final manuscript.

**Disclosures.** Zelalem G. Dessie, Temesgen Zewotir, Henry Mwambi and Delia North declare that they have no conflict of interest.

**Compliance with Ethics Guidelines.** All procedures performed in this study were approved by the Research Ethics Committee of the University of KwaZulu-Natal and Centre for the AIDS Programme of Research in South Africa (CAPRISA). Written informed consent was obtained from all participants, and ethical approval for the original study was granted by the University of KwaZulu-Natal (E013/04), the University of Cape Town (025/2004), and the University of the Witwatersrand (M040202).

**Data Availability.** The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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