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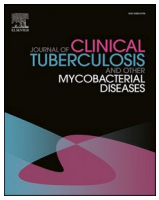

Joint modeling of longitudinal CD4 count data and time to first occurrence of composite outcome

Abdul-Karim Iddrisu [a,*], Wahab Abdul Iddrisu [b], Abu Sambor Gambedu Azomyan [a], Freedom Gumedze [c]

[a] Department of Mathematics and Statistics, University of Energy and Natural Resources, Ghana
[b] Department Statistics, Ghana Communication and Technology University, Ghana
[c] Department of Statistical Sciences, University of Cape Town, South Africa

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ABSTRACT

In this study, we jointly modeled longitudinal CD4 count data and survival outcome (time-to-first occurrence of composite outcome of death, cardiac tamponade or constriction) in other to investigate the effects of *Mycobacterium indicus pranii immunotherapy* and the CD4 count measurements on the hazard of the composite outcome among patients with HIV and tuberculous (TB) pericarditis. In this joint modeling framework, the models for longitudinal and the survival data are linked by an association structure. The association structure represents the hazard of the event for 1-unit increase in the longitudinal measurement. Models fitting and parameter estimation were carried out using R version 4.2.3. The association structure that represents the strength of the association between the hazard for an event at time point j and the area under the longitudinal trajectory up to the same time j provides the best fit. We found that 1-unit increase in CD4 count results in 2 % significant reduction in the hazard of the composite outcome. Among HIV and TB pericarditis individuals, the hazard of the composite outcome does not differ between of *M.indicus pranii* versus placebo. Application of joint models to investigate the effect of *M.indicus pranii* on the hazard of the composite outcome is limited. Hence, this study provides information on the effect of M.indicus pranii on the hazard of the composite outcome among HIV and TB pericarditis patients.

1. Introduction

In some studies design, it is required that study subjects be followed over a specified period of time in order to study the dynamics or evolution of the outcome of interest. Such study design requirement is common in Biostatistics and medical research and study design of such nature is referred to as longitudinal study design [1–4]. In longitudinal study design, which often occur in repeated measures designs, measurements are recorded repeatedly on a response variable of interest for each patient at some selected scheduled visits or time points. In addition to the longitudinal measurements, it is common in most medical research settings to also record data on time to first occurrence of an event such as time to death, recovery from a disease, progression to a disease, etc. The time to event data are often referred to as survival data.

Longitudinal and survival data can be modeled separately and methods for such separate analysis are well established in the literature, where the mixed-effects models [5] are used for modeling the longitudinal part of the data and the Cox proportional hazards (PH) models [6] are used for the time-to-event data (survival data). However, evolution or dynamics of the repeated measurements of the response variable, on the same subject, is most likely to be influenced by the event occurrence, making them endogenous [7,8]. This gives an indication that the measurement value at a given time point provides information about the future occurrence or non-occurrence of the event of interest [8]. Also, the response profiles of subjects are influenced by the occurrence of the event.

Consequently, separate analyses of the longitudinal data and the survival data would not be able to account for this relationship between the two outcomes and would not able to provide information about the strength of the association between the two outcomes. One solution to this problem to use estimated parameters from the mixed-effects models as covariates in the survival model. However, this approach has been shown to produce invalid statistical inferences as it suffers from increased bias in estimation of parameter estimates and loss of efficiency

* Corresponding author at: Department of Mathematics and Statistics, University of Energy and Natural Resources, Box 214, Sunyani, Ghana.
E-mail address: abdul-karim.iddrisu@uenr.edu.gh (A.-K. Iddrisu).

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[9,10]. This problem is avoided by joint modeling of longitudinal and time-to-event data [9–13] since this reduces bias in parameter estimation and increases the efficiency of parameter estimates. Joint modeling simultaneously estimate both longitudinal and survival components and they shown to provide better estimates because they estimate jointly the relative risk of the time-to-event outcome taking into account the longitudinal outcome [14–18]. A joint model is made up of two sub-models, a model for the longitudinal data and a model for the survival data, linked by an association structure [19]. The most commonly used joint modeling framework is the shared-parameter modeling framework, where it is assumed that the two sub-models are linked through or shared common random effects. These random effects accounts for the association between the two sub-models and also the correlation between the repeated measurements.

Joint modeling has received much attention in biostatistics and medical research [11,20–27]. For instance, Abdi et al. [20] investigated the association between longitudinal exposure to mycophenolic acid (MPA) and acute rejection (AR) risk in the first year after renal transplantation using the joint modeling framework. These authors adjusted for risk factors such as monitoring strategy (fixed-dose versus concentration-controlled) and age of the recipient. Other authors [22] applied the joint model and Multistate Markov for the analysis of the association between Red blood cell distribution width (RDW) as an independent predictor for adverse outcome (all-cause mortality and occurrence of anemia) in patients with heart failure (HF).

Also, separate and joint models has been developed under the Bayesian modeling framework for longitudinal measurements and time to death event data of HIV/AIDS patients, where the linear mixed effects model (LMEM) [5], assuming homogeneous and heterogeneous CD4 variances, is used for modeling the CD4 counts and a Weibull survival model is used for describing the time to death event [25]. Serrat et al. [26] described and implemented frequentist and Bayesian shared-parameter joint models on longitudinal measurements of prostate-specific antigen (PSA) and the risk of prostate cancer (PCa), where the results showed that PSA is highly associated with the risk of being diagnosed with PCa and that there is an age-varying effect of PSA on PCa risk. The authors revealed that both the frequentist and Bayesian paradigms produced similar parameter estimates as well 95 % confidence and credibility intervals. Long et al. [28] study applied a multivariate joint model on several longitudinal observational studies of Huntington's disease and then examined external validity performance where they computed individual-specific predictions for characterizing disease progression.

Joint models can also be applied in other disciplines. For instance, various authors have applied joint models in behavioral studies to evaluate the associations between the longitudinal measurements and the survival data [29–31]. That is, Ghisletta [30] simultaneously fitted a multivariate, multilevel longitudinal model and a Weibull survival model to investigate whether individual performance and change in speed and fluency predict survival, adjusting risk factors such as controlling for retest effects, initial age, gender, overall health, socioeconomic status, and sensory functioning. Ghisletta et al. [29] used statistical model that combines longitudinal and survival components to evaluate the influence of level and change in cognition on age at death in old and very old individuals. In their study, the longitudinal models on cognition adjusted for dementia diagnosis and retest effects, whereas the survival models on age at death adjusted for age, sex, socioeconomic status, sensory and motor performance, and broad personality characteristics.

In other to model trajectories of visuospatial reasoning measured using Kohs Block Design test under realistic missing data assumptions and evaluate their association with hazard of death, Muniz et al. [31] used a joint model for the longitudinal measurements and time to event data to estimate trajectories of visuospatial reasoning under a missing not at random assumption and conduct Sensitivity analyses to missing data assumptions [32–34]. Using prose recall scores from the Swedish OCTO-Twin Longitudinal Study of Aging, Terrera et al. [35] implemented a joint longitudinal-survival model to investigate the association between risk of mortality and individual differences in rates of change in memory with the mized effects model [5] assumed for the change in memory scores as following an accelerating decline trajectory and a Weibull survival model for the time to event. Cekic et al. [8] are of the view that lack of an accessible and clear guidance on how to implement joint models continue to hinder non-expert users from using such models appropriately or not using them. These authors have provided explanation on the basic features of the joint modeling framework for longitudinal and time-to-event data for users who are familiar with mixed-effects and survival models and there is a step by step guidance for readers to understand the basic concepts of joint modeling and explanation on how to apply this methodology to their own research data [8].

In this study, we used the joint modeling framework [10–13] to jointly model continuous longitudinal CD4 count measurements and time to first composite outcome of death, cardiac tamponade or constrictive pericarditis in patients with TB pericarditis [36–38]. The aim is to evaluate the effect of the longitudinal CD4 count measurements on the time-to-first occurrence of composite outcome of death, cardiac tamponade or constrictive pericarditis adjusting for risk factors of the survival outcome (outcome). For the dropout component of the joint model, we assume that the data are missing at random (MAR) [34,39]. One may also investigate the impact of the missing data on statistical inferences about the outcome by formulating sensitivity analysis to non-random dropout mechanism [2,3,40]. Sensitivity analysis to missing data is not the aim of this study since it has been demonstrated using various sensitivity analyses methods [2,3,40] that the CD4 count measurements are missing at random. The key hypotheses that derive this study are (1) there is a strong association between CD4 count measurements and the hazard of the outcome (2) treatment increases CD4 count level and CD4 count level also improves survival and (3) there is no interaction between M.indicus pranii injection and ART treatments.

2. Methods

In this section, we presented a brief overview of the joint model for longitudinal and survival data [12,13,41,42]. We then discussed the IMPI trial and presented description of the longitudinal and survival outcomes. We also discussed parameter estimation, models comparison and selection.

2.1. Joint modeling framework for longitudinal and survival data

Let T_i represents the observed event time for the i th subject $(i = 1,\cdots, N)$. We define T_i as the minimum of the true event time T_i^* and the censoring time C_i, expressed as $T_i = \min(T_i^*, C_i)$. Additionally, denote the event indicator as $\delta_i = I(T_i^* \leq C_i)$, where $I(\cdot)$ is the indicator function that equals 1 if the condition $T_i^* \leq C_i$ holds, and 0 otherwise. Consequently, the observed data for the time-to-event outcome comprise the pairs $\{(T_i, \delta_i), i = 1, \cdots, N\}$. Given the longitudinal responses, let $y_i(j)$, where $j = 1, 2, \cdots, n$, represent the longitudinal measurements.

The primary goal is to link the true and unobserved value $(m_i(j))$ of the longitudinal outcome at time j with the event outcome T_i^*. It is crucial to emphasize that $m_i(j)$ differs from $y_i(j)$, with $m_i(j)$ representing the longitudinally observed outcome at time j subject to measurement error. In this case, the model for the longitudinal measurements can be written as [13,41–45]

$$y_i(j) \quad = m_i(j) + \varepsilon_i(j) == x_i^{\top}(j)\beta + z_i^{\top}(j)b_i + \varepsilon_i(j),\ \varepsilon_i(j) \sim \mathcal{N}(0, \sigma^2) \qquad (1)$$

where, β represents the vector of unknown fixed-effects parameters, b_i is a vector of random effects, $x_i(j)$ and $z_i(j)$ are row vectors of the design matrices for the fixed and random effects, respectively. Additionally, $\varepsilon_i(j)$ is the measurement error term, assumed to be independent of b_i, with a variance of σ^2. The joint for the survival and longitudinal out-

comes can be expressed as:

$$h_i(j|M_i(j),\omega_i) = h_0(j)\exp\{\gamma^\top \omega_i + \alpha_1 \mu_i(j)\} \quad (2)$$

where $M_i(j) = \{m_i(u), 0 \le u < j\}$ represents the history of the true unobserved longitudinal process up to time point j, and ω_i is a vector of baseline covariates with a corresponding vector of regression coefficients γ for the baseline covariates in the survival model, $\mu_i(j) = x_i(j)\beta + z_i(j)b_i + \epsilon_i(j)$ is the model (1) for the longitudinal model and α_1 linked the two model two models and represents the hazard ratio of the event for every one-unit increase in the current value $\mu_i(j)$ [7,8,44]

We can also consider a joint model which assumes that the hazard of experiencing the event at time j is associated both with the current rate of change $\mu_i^{'}(j)$ (i.e., slope) at time j and can be written as

$$h_i(j|M_i(j),\omega_i) = h_0(j)\exp\{\gamma^\top \omega_i + \alpha_2 \mu_i^{'}(j)\} \quad (3)$$

Alternatively, one can also assume that the hazard of experiencing the event at time j is associated both with the true value $\mu_i(j)$ of the longitudinal process at time j and its current rate of change $\mu_i^{'}(j)$ (i.e., slope) at time j. In this case, the model (2) can be written as

$$h_i(j|M_i(j),\omega_i) = h_0(j)\exp\{\gamma^\top \omega_i + \alpha_1 \mu_i(j) + \alpha_2 \mu_i^{'}(j)\}, \quad (4)$$

where α_2 represents the association parameter for the current rate of change for the longitudinal process.

However, the assumption that the risk for an event at any time j is associated with the current value $\mu_i(j)$ and current slope $\mu_i^{'}(j)$ of the longitudinal process at the same time point may not always be realistic, as these models do not consider the longitudinal history of the CD4 count. Reparametrized the joint model to account for the realistic structure of the longitudinal process may yield more accurate estimates of the event hazard [46]. In this case, the model (2) can be expressed [41,47]

$$h_i(j|\mathcal{M}_i(j)) = h_0(j)\exp\left\{\gamma^\top \boldsymbol{w}_i(j) \alpha_3 \frac{\int_0^j \mu_i(u)du}{j}\right\} \quad (5)$$

The model (5) indicates that for any given time j, the association parameter α_3 measures the strength of the association between the hazard for an event at time point j and the area under the longitudinal trajectory up to the same time j.

On the other hand, the joint model may be specified such that the hazard of the event at time j is associated with the current value $\mu_i(j)$, its current rate of change $\mu_i^{'}(j)$ (slope) at time j and the area under the longitudinal trajectory up to the same time j. In this case, the model (2) can be written as

$$h_i(j|\mathcal{M}_i(j)) = h_0(j)\exp\left\{\gamma^\top \boldsymbol{w}_i(j) + \alpha_1 \mu_i(j) + \alpha_2 \mu_i^{'}(j) + \alpha_3 \frac{\int_0^j \mu_i(u)du}{j}\right\} \quad (6)$$

To ease communication in our write-up, we refer to joint models (2), (3), (4), (5), and (6) as **JM**1, **JM**2, **JM**3, **JM**4, and **JM**5 respectively.

2.1.1. Parameter estimation and models comparison

There are several available joint-modeling packages (**JMbayes**, **joineR**, **lcmm**, **frailtypack**, **rstanarm** and **bamlss**) in the open-source R environment for statistical computing (RCore Team, 2017) for estimating parameters from the joint model [8]. However, the **JMbayes2** package [10,11,42] is the most comprehensive, extensible, and flexible for such joint modeling. Joint modeling can also be carried out in other standard statistical software such as SAS/STAT, Stata, WinBUGS, and JAGS [16]. In this paper, we used the **JMbayes2** package with **JM** function [7,8,11,12] to estimate parameters in the joint model.

We compared the joint models using the compare_jm() function from **JMbayes2** package to select the best fitting joint model (**JM**). The compare_jm() function compares fitted joint models using the deviance information criterion (DIC) [48] and Watanabe-Akaike information criterion (WAIC) [49], which is the generalized version of the Akaike information criterion (AIC). The model with the lowest DIC and WAIC is selected as the best fitting model.

2.2. Description of the IMPI trial data

In this section, we present discussion on the IMPI trial and then described the longitudinal and the survival data. This is because the longitudinal and survival outcomes would be used in the joint model.

In this paper, we used data from the IMPI trial [38,50]. The IMPI trial was a multicentre international randomized doubled-blind placebo-controlled 2 × 2 factorial study [38,50]. The IMPI trial investigated the effects of two TB treatments, prednisolone and Mycobacterium indicus pranii (M. indicus pranii) immunotherapy, in patients with TB pericarditis (TBP) patients in Africa. TBP is a TB that occurs in the heart and is an important complication of tuberculosis, which diagnosis can be difficult to establish and is often delayed or missed, resulting in late complications such as composite outcome (death, cardiac tamponade or pericardial constriction) and increased mortality [51]. Patient who met the inclusion criteria, defined in the IMPI trial study, were randomized into four treatment arms. Randomized patients received combination of either M^+P^+or M^+P^- or M^-P^+or M^-P^-, where M^+ and M^- denote the M. indicus pranii and its corresponding placebo arm and P^+ and P^- denote prednisolone and its corresponding placebo arm. In the IMPI trial, a sample size of 1400 patients with definite probable tuberculosis pericardial effusion, from 9 African countries in 19 centres were enrolled in the four-year trial. Patients who meet the inclusion criteria were randomized to receive oral pill prednisolone for 6 weeks and M. indicus pranii or placebo for 3 months. In general, after randomization at baseline week 0, patients were followed up at weeks 2, 4, and moths 3 and 6 during the intervention period and 6-monthly thereafter for up to 4 years [50]. Randomized patients discontinue M. indicus pranii treatment after 3 months due to side effect [50,52] and hence analysis of data associated with M.indicus pranii is restricted to weeks 0, 2, 4 and 3 months data.

For the comparison of prednisolone with placebo, 706 patients were assigned to receive prednisolone and 694 to receive placebo. For the comparison of M. indicus pranii with placebo, 625 were assigned to receive M. indicus pranii and 625 to receive placebo. The trial was powered for a rate of non-adherence of 10 % in the active-treatment groups. This rate was almost achieved (with non-adherence rate of 11 %) in the prednisolone group and non-adherence rate was higher in the M. indicus pranii group (21 %), owing mainly to injection-site side effects [50]. Also, there was approximately 133(18.8 %) and 115 (16.6 %) all causes of deaths for prednisolone and placebo respectively [50,52].

The IMPI trial aim was to assess the effectiveness and safety of oral pill prednisolone and M.w injection in reducing the time to first occurrence of the primary composite outcome of death, pericardial constriction, or cardiac tamponade requiring pericardial drainage in patients with TB pericardial effusion [50,52]. These authors have revealed that there is no interaction between the two TB treatments and hence M. indicus pranii and its corresponding placebo arm as well as prednisolone and its corresponding placebo arm were analyzed separately [50,52].

For the longitudinal outcome, we used CD4 count measurements. This study restricted the analysis to patients who have at least two CD4 count values observed. We considered analysis of M. indicus pranii versus placebo arms. The analysis of CD4 count data is restricted to the mandated periods for CD4 count measurements; baseline week 0, week 2 (0.5 months), months 1 and 3. In this study, we implemented the joint model to the monotone missing CD4 count data and time to composite outcome of death, cardiac tamponade or pericardial constriction as a survival outcome. For monotone missing data, if the ith patient is missing at schedule visit time j, then this same patient will be missing at the next scheduled visit time j + 1. This means that, if the ith patient's

value is missing at a particular scheduled visit time point, then such patient's values would be missing in the remaining schedule visit times. However, analysis can be repeated for the non-monotone and both analyses have shown to produce identical statistical inferences [2].

2.2.1. Description of the monotone CD4 count data

Out of the 584 HIV + patients, the monotone data consist of 126 HIV + patients with 55 were in the placebo arm and 71 in the M.indicus pranii arm. Some patients dropped out at month 0.5 or month 1 and some completed the study (clearly shown in the bottom panel of Fig. 1). The top-left panel of Fig. 1 showed the observed $\sqrt{CD4}$ count profiles plots for all subjects. The right panel of Fig. 1 displays the mean $\sqrt{CD4}$ count profiles plots by treatment arm and shows that CD4 count level increase across the measurement visits and M.indicus pranii arms and a linear trend in the CD4 count measurement in both the placebo and M. indicus pranii arms.

The top-right panel of Fig. 1 showed possible interaction between treatment and time, so we included treatment and time interaction term in the fitted linear mixed model. Table 1 gives the number and proportion of patients remaining at each visit by treatment arms. There is a lower completion rate 37 (67 %) in the placebo arm, compared with 50 (70 %) in the M.indicus pranii treatment arm.

Table 1
Percentage of patients remaining in the study at each visit.

	M.w	Placebo
Month	N(%)	N(%)
0	55(100)	71(100)
0.5	55(100)	71(100)
1	47(85)	63(89)
3	37(67)	50(70)

We have provided summaries of the main outcome $\sqrt{CD4}$ count) stratified per dropout patterns and treatment groups, as a function of time in Table 2. There are three dropout patterns and the Table 2 shows the mean $\sqrt{CD4}$ count for each of the patterns at each visit by treatment arm. The dropout patterns 3, 2 and 1 represent completers (those patients who completed the study) and those who dropped out at months 3 and 1 respectively. The distributions of the patterns of missingness between the two treatment groups do not differ (chi-squared test statistic = 3.5, p = 0.825).

Fig. 2 shows the profile plots of the mean $\sqrt{CD4}$ count of the three deviation patterns for patients in the placebo and M.indicus pranii

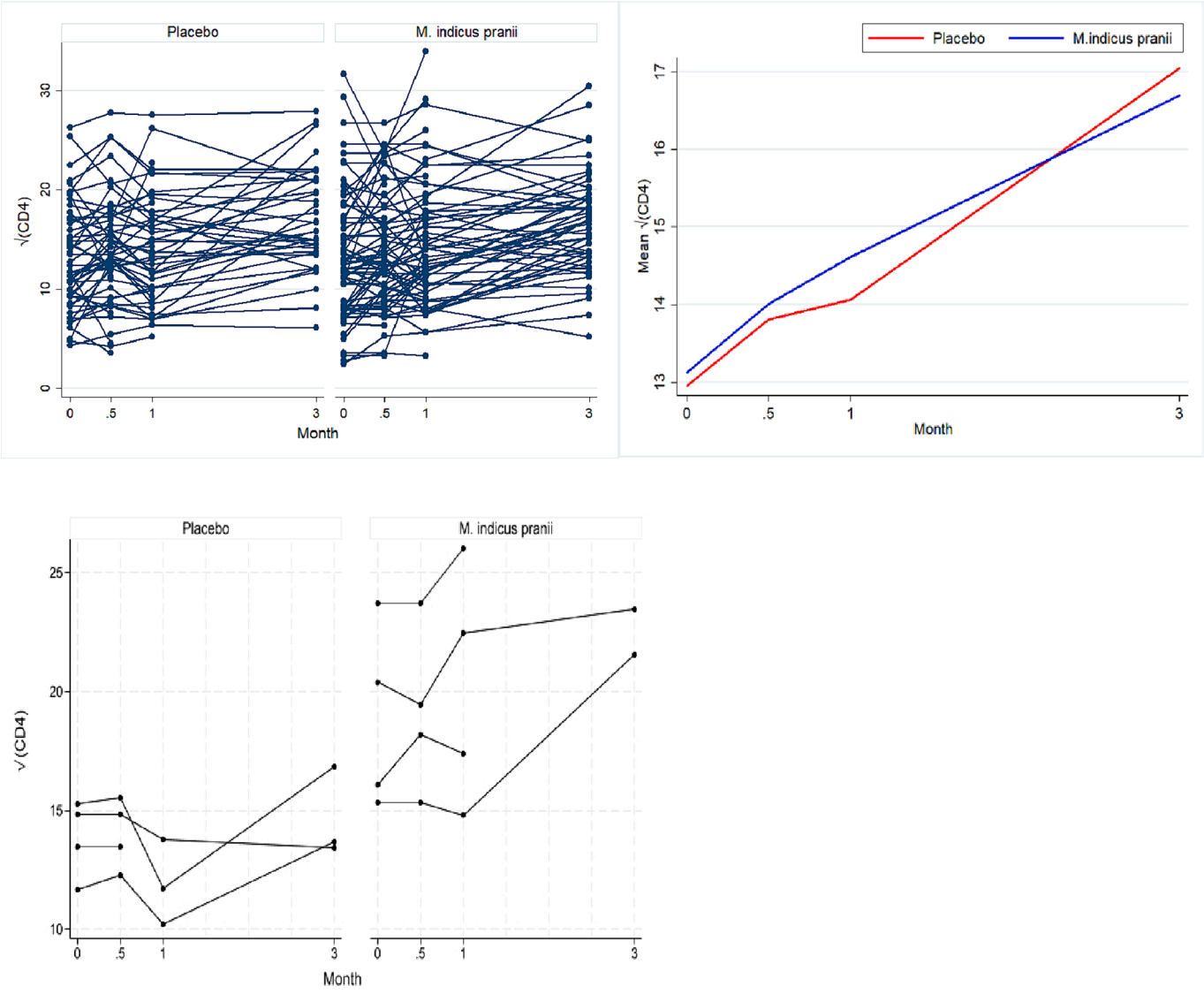

Fig. 1. Individual profiles plots of the monotone $\sqrt{CD4}$ count data (top-left panel), the mean $\sqrt{CD4}$ count (top-right panel), and profiles plots of some selected subjects' $\sqrt{CD4}$ count (bottom-left panel), by treatment arms.

Table 2
Mean $\sqrt{\text{CD4}}$ count measurements at each visit by dropout pattern and treatment arm.

Dropout[a] pattern	Dropout time (months)				N(%)
	0	0.5	1	3	
Placebo arm					
3	14.014	15.284	14.625	17.045	37(67)
2	9.835	11.664	12.006	–	10(85)
1	11.971	9.662	–	–	8(1)
All patients mean (std)	12.957(5.237)	13.808(5.217)	14.068(5.355)	17.045(5.101)	55(100)
M.w arm					
3	13.238	14.171	14.292	16.696	50(70)
2	12.038	14.252	15.852	–	13(89)
1	9.04	12.546	–	–	8(16)
All patients mean (std)	13.126(6.276)	14.003(5.785)	14.614(6.324)	16.696(5.072)	71(100)

[a] std is standard deviation, Dropout patterns: 3 = subjects who had all measurements up to 3 months (completers), 2 = subjects who had measurements up to 1 month, 1 = subjects who had measurements up to 0.5 month.

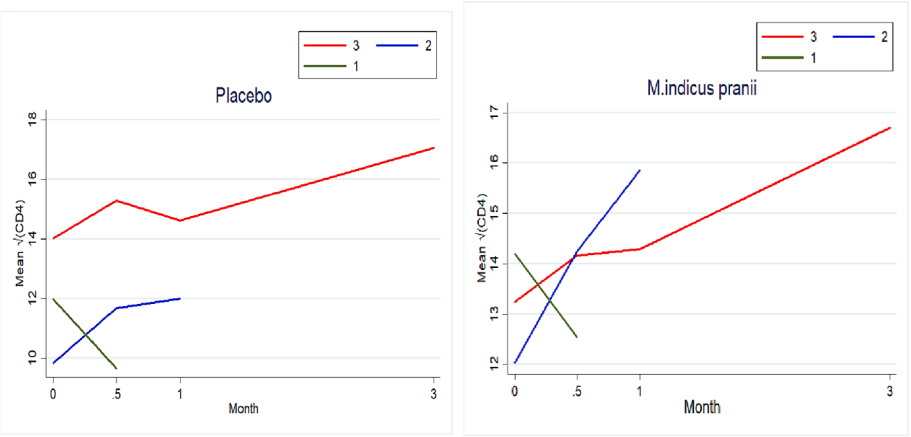

Fig. 2. Profile plots of the mean of the $\sqrt{CD4}$ count for each deviation pattern under the placebo arm (left panel) and the M.indicus pranii arm (right panel). Red pattern: group of patients who completed the study (completers); blue pattern: group of patients who dropped out after month 3; green pattern: group of patients who dropped out after month 1.

groups. This figure gives an indication that the $\sqrt{\text{CD4}}$ count increases over time. Fig. 2 agrees with the mean profiles plot and Fig. 1 that there is slight increase in the $\sqrt{\text{CD4}}$ count among patients in the placebo arm compare with those in M.indicus arm.

2.2.2. *Description of the survival data*

The survival outcome in this study is time-to-first occurrence of composite outcome of death, constrictive pericarditis or cardiac tamponade. We have also noted previously that the main objectives of survival analysis are to derive and describe the distribution of survival times as well as investigate how survivals time is affected by covariates or risk factors. Both the life-table and Kaplan-Meier methods [53–55] can be used to estimate survival probabilities. However, the Kaplan-Meier method has advantage over the life-table [55]. We estimate the survival probabilities of the composite outcome in both treatment group (M.indicus pranii versus placebo) using the Kaplan-Meier method and then assess significance difference in the incidence of experiencing the event in both groups using the log-rank test presented in Fig. 3.

The Kaplan-Meier curves crossed, an indication that there is no significant difference in the risk of composite outcome between M.indicus versus placebo groups. The log-rank Chi-square = 0.69, p-value = 0.4071) also confirm this conclusion of no significance difference in the risk of the composite outcome between the two treatment groups.

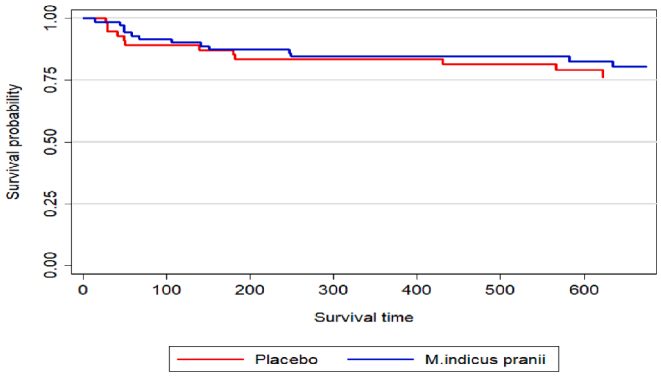

Fig. 3. Survival time probabilities of time to composite outcome of death, cardiac tamponade or pericardial constriction.

3. Results

This section, we analyzed and provide interpretation of results from the best fitting joint model.

3.1. *Analysis and results from the joint model for the longitudinal and survival data*

We considered a joint model (JM1-model (2)) where it is assumed

that the hazard of experiencing the event at time j is associated with the current value $\mu_i(j)$ of the longitudinal process at time j. This joint model has the form

$$\begin{cases} \dfrac{y_i(j)}{\sqrt{CD4_{ij}}} = m_i(j) + \varepsilon_i(j) \\ \qquad = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2 \text{M.indicus}_i + \beta_3\big(\text{M.indicu}_i \times t_{ij}\big) + \beta_4 ART_{ij} \\ +\beta_5\big(\text{M.indicu}_i \times ART_{ij}\big) + \beta_6\,\text{agegrp}_{\,i} + \beta_7\,\text{TBmed}_i + \beta_8\,\text{gender}_{\,i} + \epsilon_{ij}, \\ h_i(t) = h_0(t)\exp\{\beta_1\,\text{M.indicu}_i + \beta_2\,\text{ART}_{\,i} + \beta_3(\,\text{M.indicu}_i \times \text{ART}_{\,i}) + \beta_4\,\text{agegrp}_{\,i}\} \\ \times\exp\{\beta_5\,\text{TBmed}_{\,i} + \beta_7\,\text{gender}_{\,i} + \alpha_1\mu_i(j)\}. \end{cases} \tag{7}$$

Results from this joint model for the longitudinal sub-model (LsubM) and survival sub-model (SsubM) are shown in Table 3. The association parameter α_1 suggests that CD4 count is significantly associated with the hazard of the composite outcome. That is, an increase in the level of CD4 count results in approximately 11 % (95 % CI: [0.854, 0.904]) significant reduction in the hazard of the composite outcome. There is also considerable variability captured by the random effects in the longitudinal sub-model.

The results showed that the hazard of the composite outcome decreased by 75 % among those in the M.indicus pranii arm relative to those in the placebo arm. The hazard of the composite outcome decreased by 85 % among those who were ever on ART during at study compared with those who were never. There was no significant M.indicu pranii and ART interaction effect with 6.5-fold increase in the hazard of the composite outcome. There is an increased hazard of the composite outcome among patients who are 46 years and above relative to those who are below 46 years. The joint model results also revealed that there is no baseline TB medication effect. However, there is 1.8-fold increased in the hazard of the composite outcome. Insignificant reduced hazard of the composite was observed among gender groups.

Since the association parameter is significant and may results in changes in estimates and conclusions, we considered the different parametrization in models (3), (4), (5), and (6) and compared these models. The joint model (2), **JM1**, is already specified in model (7). The joint models (3), (4), (5) and (6), referred to as **JM2**, **JM3**, **JM4**, and **JM5** are respectively specified in equations (A.1), (A.2), (A.3) and (A.4) in Appendix A.

Table 3
Parameter estimates from separate models for longitudinal and survival outcomes and joint model for the sub-models.

LsubM			
Variable	Est.	s.e	95% CI
Intercept	14.80	1.288	(12.326, 17.369)
Month	−2.50	0.920	(−4.353, −0.987)
M.indicus pranii	−1.84	1.391	(−4.743, 0.751)
M.indicus pranii × Month	4.37	1.192	(2.435, 6.760)
ART	4.18	1.445	(1.521, 7.246)
M.indicus pranii × ART	−2.25	1.710	(−5.838, 0.924)
Age	−1.07	1.875	(−4.714, 2.661)
TBmed	1.02	1.683	(−2.354, 4.254)
Gender	−1.21	1.033	(−3.229, 0.815)
G	δ		
$G_{11}(\delta)$	32.676		
$G_{22}(\delta)$	8.049		
SsubM			
Variable	HR	s.e	95% CI
M.indicus pranii	0.254	0.947	(0.030, 1.241)
ART	0.152	0.824	(0.028, 0.754)
M.indicus pranii × ART	6.540	1.126	(0.798, 70.105)
Age	1.368	0.666	(0.366, 5.094)
TBmed	1.767	0.831	(0.375, 9.346)
Gender	0.590	0.496	(0.224, 1.606)
α_1	0.992	0.0011	(0.989, 0.993)

These models were fitted and compared using the deviance information criterion (DIC) and Watanabe Akaike information criterion (WAIC) presented in Table 4. It can be observer that, among the candidate models fitted, the model with the lowest DIC and WAIC is the **JM4**, making **JM4** the best fitting joint model for the longitudinal CD4 count measurements and the time to first occurrence of the composite outcome.

4. Discussion

In this paper, we investigated the impact of longitudinal CD4 count measurements on the hazard of time-to-first occurrence of composite outcome of death, cardiac tamponade or constriction [56]. We also investigated the effects of M.indicus pranii, ART, M.indicus pranii-ART, age, gender and baseline TB medication on the hazard of the composite outcome. This was achieved using a joint model for the longitudinal and survival outcomes. In this joint model, the linear mixed-effects model [5] was assumed for the longitudinal outcome and the Cox-proportional hazard model [6] for the survival outcome. These models were then modeled jointly, where the models were linked by an association structure which accounts for the association between the models [10–13,41,45].

Table 4
Joint models comparison using DIC and WAIC.

JM	Association Structure	DIC	WAIC
JM1	$\alpha_1\mu_i(j)$	1.710178e + 08	6.556393e + 18
JM2	$\alpha_2\mu_i^{'}(j)$	6.257170e + 26	7.825283e + 55
JM3	$\alpha_1\mu_i(j) + \alpha_2\mu_i^{'}(j)$	3.277127e + 18	2.952213e + 39
JM4	$\alpha_3\dfrac{\int_0^j \mu_i(u)du}{j}$	4.769682e + 07	2.453573e + 17
JM5	$\alpha_1\mu_i(j) + \alpha_2\mu_i^{'}(j) + \alpha_3\dfrac{\int_0^j \mu_i(u)du}{j}$	3.241171e + 13	5.412782e + 28

Parameter estimates (Est.), hazard ratios (HR), standard errors (s.e) and 95 % confidence intervals (95 % CI), from the best fitting model **JM4**, specified in model (A.3), are presented in Table 5. The association parameter α_3 indicates significant association between the hazard of the composite and longitudinal outcomes and results in approximately 1-exp(0.98) = 2 % (HR = 0.98, 95 % CI: [0.977, 0.986] significant reduction in the hazard of the composite outcome. The hazard of composite outcome reduced by 1-exp(0.98) = 74 % (HR = 0.0.26, 95 % CI: [0.033, 1.229] among patients in the M.indicus pranii arm relative to those in the placebo arm. However, this reduction is not statistically significant. There is 1-exp(0.15) = 85 % significant reduction in the hazard (HR = 0.15, 95 % CI: [0.024, 0.657] of the composite outcome among patients who received ART at each visit relative to those who did not. For M.indicus pranii-ART interaction, we observed 6.23-fold increase in the hazard (HR = 6.23, 95 % CI: [0.879, 77.751] of the composite outcome. However, the interaction effect is not statistically significant. The hazard (HR = 1.34, 95 % CI: [0.323, 4.968] of the composite outcome increased by approximately 34 % among patients who are 46 years and above compared with those who are below 46 years. There is a reduced hazard of the composite outcome among those who are males compared with those who females. However, this effect was not statistically significant. A considerably higher variability in the longitudinal measurements has been captured by the joint model.

Parameters in the joint model were estimated using the **JM** function from **JMbayes2** package in Rsoftware [8,11–13,41] For the joint model, different joint models, differed by the association structures, we fitted, compared and best model selected. The best fitting joint model **JM4**, model (A.3) assumes that for any given time j, the association structure represents the strength of the association between the hazard for an event at time point j and the area under the longitudinal trajectory up to the same time j. This finding agrees with the finding by et al. [57]. It is important to note there is no one particular parameterization or association structure of the joint model that provides best fit to data than the other. This is because, performance of such joint models, measured by the different paramterization of the the association structure, depends on the study or trial design. For instance, the **JM1** does not differentiate among subjects who, at a particular time, share an identical longitudinal score but exhibit varying rates of change in this score [7,8,11,12,41]. That is, one subject may have an increasing trajectory while another displays a decreasing trajectory in the longitudinal score. This means that the JM1would provide a worse fit of the data in a study where most subjects have identical longitudinal scores and vice versa.

The results of the best fitting model JM4 are presented in Table 5. The results indicate a significant connection between the hazard of the composite outcome and longitudinal outcome. This correlation led to a considerable decrease in the hazard of the composite outcome, meaning that every 1-unit increase in the longitudinal outcome results in a significant reduction in the hazard of the composite outcome. This finding aligns with previous research findings. For instance, Mchunu et al. [57] observed in their study on TB/AIDS patients that an increase in CD4 count is associated with a decrease in the risk of survival outcome (mortality). In a cohort study conducted by various authors [58] involving patients commencing antiretroviral therapy, it was noted that lower CD4 count values were linked to an elevated risk of mortality. Similarly, Temesgen et al. [59] identified a noteworthy association between longitudinal CD4 count measurements and survival outcomes among HIV/TB co-infected individuals.

The results revealed no significance difference in the hazard of the composite outcome between those who received M. indicus pranii versus those who received placebo. This finding agrees with the primary results from trial [50]. Research [60] conducted through a randomized trial, employing M. indicus pranii as supplementary therapy in Category II pulmonary tuberculosis, revealed significant implications for disease control. Given that live bacteria are the primary drivers of sustained TB incidence, the potential of M. indicus pranii in eradicating bacilli suggests far-reaching effects in limiting disease spread. Our analysis revealed that patients consistently receiving ART during each visit exhibit a notable decrease in the hazard of experiencing the composite outcome compared to those who do not receive it regularly. This observation aligns with the results reported by Gebrerufael et al. [61] and Luvanda et al. [62], indicating that poor adherence to ART is associated with an increased risk of patient mortality.

Patients who are over 46 years demonstrated an increased hazard of the composite outcome compared to those who are 46 years and below. Similar finding has been revealed by various authors [62], indicating that increase in age was associated with an increased risk of death among HIV/AIDS patients. In contrast, findings from a study [57] involving HIV/TB patients indicated that age was linked to a decreased risk of mortality. Our results also revealed no significant reduction in the hazard of death among males compared to females among the study population. On the contrary, a study [62], among HIV/AIDS patients population, revealed that being male was associated with higher risk of death compared to females. Those who were on TB medication before randomization also exhibited an increased hazard of the composite outcome.

While the interaction between M.indicus pranii and ART did not exhibit statistical significance, it resulted in a 6.23-fold increase in the hazard of the composite outcome. CD4 count level is significant predictor of the composite outcome (death, cardiac tamponade, or constrictive pericarditis) and hence measures that increase CD4 count level have the potential to decrease the hazard of the composite outcome, there by improving patient condition. Improving TB pericarditis patients' condition is central to increasing patient's CD4 count level since the trial medication has no significant effect on the composite outcome. Trial medication (M.indicus pranii) and standard of care, antiretroviral therapy (ART), does not interact and hence there is no way such combination of treatment can significantly influence the benefit of the trial medication.

Although analyses for joint modeling in these study are based on JM1-JM5, one may also consider alternative parameterization of the joint model. For instance, one may parameterized the joint model by assuming that the longitudinal process and the survival process shared common random effects, where these random effects account for the association between longitudinal measurement and the hazard of the event as well as the correlation between the longitudinal measurements. Also, the joint model can be parametrized such that the hazard of an event at j is associated with the level of the longitudinal outcome at a previous time point. These parameterization can also be considered for application to the data used in this study and other studies with similar data structures.

Table 5
Parameter estimates from separate models for longitudinal and survival outcomes and joint model for the sub-models.

LsubM Variable	Est.	s.e	95% CI
Intercept	14.80	1.329	(12.269, 17.535)
Month	−2.47	1.197	(−5.409, −0.706)
M.indicus pranii	−1.84	1.458	(−4.903, 0.838)
M.indicus pranii × Month	4.30	1.602	(1.925, 8.273)
ART	4.21	1.601	(1.459, 7.932)
M.indicus pranii × ART	−2.26	1.862	(−6.515, 0.991)
Age	−1.03	1.867	(−4.688, 2.635)
TBmed	0.96	1.724	(−2.523, 4.255)
Gender	−1.21	1.025	(−3.215, 0.801)
G	δ		
$G_{11}(\delta)$	32.492		
$G_{22}(\delta)$	8.054		
SsubM			
Variable	HR	s.e	95% CI
M.indicus pranii	0.26	2.464	(0.033, 1.229)
ART	0.15	2.320	(0.024, 0.657)
M.indicus pranii × ART	6.23	3.153	(0.879, 77.751)
Age	1.34	1.994	(0.323, 4.968)
TBmed	1.86	2.306	(0.384, 10.308)
Gender	0.61	1.648	(0.234, 1.672)
α_3	0.98	1.002	(0.977, 0.986)

5. Conclusion

Among individuals with HIV and tuberculous pericarditis, the administration of M. indicus pranii did not yield any significant difference in reducing the hazard of the composite outcome of death, cardiac tamponade, or constrictive pericarditis. This is true even after adjusting for the effect of CD4 count level and other covariates such as age, gender, baseline TB medication, M.indicus pranii-ART interaction, and ever on ART during the study. Application of joint models to investigate the effect of M.indicus pranii on the hazard of the composite outcome of death, cardiac tamponade and constriction is limitted. Hence this study provides information on the effect of M.indicus pranii on the hazard of the composite outcome among HIV and TB pericarditis patients.

Ethical statement

The authors declare that the study does not require ethical clearance.

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CRediT authorship contribution statement

Abdul-Karim Iddrisu: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Wahab Abdul Iddrisu:** Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Abu Sambor Gambedu Azomyan:** Formal analysis, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Freedom Gumedze:** Conceptualization, Data curation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

The authors have no right to distribute the data.

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Appendix A. Specification of JM2, JM3, JM4 and JM5

$$\begin{cases} y_i(j) & = m_i(j) + \varepsilon_i(j) \\ \sqrt{CD4_{ij}} & = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2\ \text{M.indicus}_i + \beta_3\big(\text{M.indicus}_i \times t_{ij}\big) + \beta_4 ART_{ij} \\ +\beta_5\big(\text{M.indicus}_i \times ART_{ij}\big) + \beta_6\text{agegrp}_i + \beta_7\text{TBmed}_i + \beta_8\text{gender}_i + \epsilon_{ij}, & \\ h_i(t) = & h_0(t)\exp\{\beta_1\text{M.indicus}_i + \beta_2 A_R T_i + \beta_3\text{M.indicus}_i \times \text{ART}_i) + \beta_4\text{agegrp}_i\} \\ \times\exp\big\{\beta_5\text{TBmed}_i + \beta_7\text{gender}_i + \alpha_2\mu_i^{'}(j)\big\}. & \end{cases} \tag{A.1}$$

$$\begin{cases} y_i(j) & = m_i(j) + \varepsilon_i(j) \\ \sqrt{CD4_{ij}} & = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2\text{M.indicus}_i + \beta_3\big(\text{M.indicus}_i \times t_{ij}\big) + \beta_4 ART_{ij} \\ +\beta_5\big(\text{M.indicus}_i \times ART_{ij}\big) + \beta_6\text{agegrp}_i + \beta_7\text{TBmed}_i + \beta_8\text{gender}_i + \epsilon_{ij}, & \\ h_i(t) = & h_0(t)\exp\{\beta_1\ \text{M.indicus}_i + \beta_2 ART_i + \beta_3(\text{M.indicus}_i \times ART_i) + \beta_4\text{agegrp}_i\} \\ \times\exp\big\{\beta_5\ \text{TBmed}_i + \beta_7\ \text{gender}_i + \alpha_1\mu_i(j) + \alpha_2\mu_i^{'}(j)\big\}. & \end{cases} \tag{A.2}$$

$$\begin{cases} y_i(j) & = m_i(j) + \varepsilon_i(j) \\ \sqrt{CD4_{ij}} & = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2\ \text{M.indicus}_i + \beta_3\big(\ \text{M.indicus}_i \times t_{ij}\big) + \beta_4 ART_{ij} \\ +\beta_5\big(\ \text{M.indicus}_i \times ART_{ij}\big) + \beta_6\ \text{agegrp}_{\ i} + \beta_7\ \text{TBmed}_{\ i} + \beta_8\ \text{gender}_{\ i} + \epsilon_{ij}, & \\ h_i(t) = & h_0(t)\exp\{\beta_1\ \text{M.indicus}_i + \beta_2 ART_i + \beta_3(\ \text{M.indicus}_i \times ART_i) + \beta_4\ \text{agegrp}_{\ i}\} \\ \times\exp\left\{\beta_5\ \text{TBmed}_{\ i} + \beta_7\ \text{gender}_{\ i} + \alpha_3\dfrac{\int_0^j \mu_i(u)du}{j}\right\}, 0 \le u < j. \Bigg\}. & \end{cases} \tag{A.3}$$

$$\begin{cases} y_i(j) & = m_i(j) + \varepsilon_i(j) \\ \sqrt{CD4_{ij}} & = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2\ \text{M.indicus}_i + \beta_3\big(\text{M.indicus}_i \times t_{ij}\big) + \beta_4 ART_{ij} \\ +\beta_5\big(\ \text{M.indicus}_i \times ART_{ij}\big) + \beta_6\ \text{agegrp}_{\ i} + \beta_7\ \text{TBmed}_{\ i} + \beta_8\ \text{gender}_{\ i} + \epsilon_{ij} & \\ h_i(t) = & h_0(t)\exp\{\beta_1\ \text{M.indicus}_i + \beta_2 ART_i + \beta_3(\text{M.indicus}_i \times\ \ \text{ART}_{\ i}) + \beta_4\ \text{agegrp}_{\ i}\} \\ \times\exp\left\{\beta_5\ \text{TBmed}_{\ i} + \beta_7\ \text{gender}_{\ i} + \alpha_1\mu_i(j) + \alpha_2\mu_i^{'}(j) + \alpha_3\dfrac{\int_0^j \mu_i(u)du}{j}\right\} & \end{cases} \tag{A.4}$$

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