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Joint modeling of longitudinal CD4 cell counts and time-to-default from HAART treatment: a comparison of separate and joint models

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In HAART and other follow-up clinical trials, both longitudinal and survival data are generated. Joint models are used to describe the joint behaviour of such data. This study has discussed Bayesian joint modeling approaches using a five years HAART data obtained from Jimma University Specialized Hospital HIV Outpatient Clinic, Ethiopia. The objective is to compare separate and joint models of longitudinal CD4 cells counts and default time processes of HIV/AIDS patients. A linear mixed effects model, assuming homogenous and heterogenous CD4 variances, is used for modeling the CD4 counts and a Weibull survival model is used for describing the default times. Then, both processes are linked using unobserved random effects through the use of a shared parameter model. The analysis of both the separate and the joint models reveal that the assumption of heterogenous (patient-specific) CD4 variances brings a substantial improvement in the mode fit. The parameter estimates of both the separate and joint models are consistent. However, the joint model is parsimonious and fits the data better. The final joint model relates the hazard of defaulting to two characteristics of the repeated CD4 counts; patient-specific slopes and CD4 variability.

keywords: Bayesian Analysis, Deviance Information Criteria (DIC), HAART Data, Joint Modeling, Longitudinal Data Analysis, Survival Data Analysis.

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1 Introduction

1.1 HAART

Highly active antiretroviral therapy (HAART) is a lifetime treatment given for HIV/AIDS patients in order to suppress the progression of the disease. It is a combination of at least three treatment regimens from two or more classes of antiretroviral drugs with different mechanisms of action to treat the virus (Boskey, 2010).

Currently, because of the wide availability and free service of HAART, HIV/AIDS related morbidity and mortality has decreased significantly. But, the critical issue to the success of HAART is retention to the treatment regime as HAART is a lifelong commitment that requires patients to adhere diligently to daily medication, dosing schedules and make frequent clinic visits for care.

Many patients are defaulting from HAART due to the regime side effects or due to their poor health conditions like having small CD4 counts. For example, patients with serious HIV disease may tend to die or withdraw from the treatment earlier compared to the healthier patients, leading to fewer CD4 counts and to have sharper rates of CD4 decline (Wu and Carroll, 1988; Hogan and Laird, 1997).

Patients who defaulted from HAART treatment will develop drug resistance virus and ultimately results drug failure (Poppa et al., 2003). As a result, such defaulter patients are at high risk of illness and death because of AIDS related conditions. Therefore, defaulting remains a public health problem which needs to be addressed so that the maximum benefit from HAART can be obtained.

1.2 Joint Models

Many clinical trials generate both longitudinal (repeated measures) and survival (time-to-event) data. For example, in many medical studies, blood pressures are often collected repeatedly over time and one may be interested in the time to recovery or recurrence of a disease. In HAART treatment, the number of CD4 cell counts is measured repeatedly over time and the time to event could be time to viral rebound, time to dropout, or time to death, depending on the research objectives. Such time to event may be associated with the longitudinal trajectories.

The association between the longitudinal and survival process can arise in two ways, one is through common explanatory variables and the other is through stochastic dependence between subject-specific random effects (Guo and Carlin, 2004). When association between the two processes exists, less biased and more efficient inferences will be obtained by using joint model (Guo and Carlin, 2004) and unbiased statistical inferences are more likely to be obtained via a joint model (Tsiatis et al., 1995; Wulfsohn and Tsiatis, 1997).

A joint model consists of two submodels, which Henderson et al. (2000) referred to as the measurement model for the longitudinal process, and the intensity model for the survival process, and a latent association function of the random effects in which the two submodels are linked. Moreover, these two processes are assumed to be conditionally independent given unobserved random effects (Wulfsohn and Tsiatis, 1997; Rizopoulos, 2010; Sousa, 2011).

The approach that this study has used to build a joint model is the simultaneous modeling of the longitudinal CD4 counts and the default time processes and linking them using unobserved random effects through the use of a shared parameter model. The main focus is on modeling the survival data; modeling the longitudinal data is secondary. In other words, focus is given to the correct specification of the survival submodel of the shared parameter joint model and the longitudinal submodel is simplified to reduce the number of nuisance parameters and avoid potential parameter non-identifiability (Wu, 2010).

The paper is organized as follows. Section 2 describes the materials and methods. The basic findings of the study are presented and discussed in Section 3. Finally, concluding remarks are provided in Section 4.

2 Materials and Methods

2.1 Description of the HAART Data

The HAART data used for this study were obtained from Jimma University Specialized Hospital HIV Outpatient Clinic, South West of Ethiopia. The study population consists of all HIV+ patients who were 18 years old and older, and started the HAART treatment any time in between 1st January 2007 to 31st December 2011. Of the total 3500 registered patients at the hospital, only 1464 of them satisfy these inclusion criteria and hence are included in study.

Both the longitudinal and survival data are extracted from the patient's chart which contains epidemiological, laboratory and clinical information of all patients under follow-up. The two outcome variables considered in this study are defined as follows. The longitudinal response variable is the number of CD4 cell counts per mm^3 of blood which were measured approximately every 6 months; at the study entry, and again at the 6-, 12-, 18-, 24-, 30-, 36-, 42-, 48- and 54-month visits (so that $n_i \leq 10$), hence a common measuring (observation) time is used for all patients. The sample sizes at these ten time points are (1464, 1108, 843, 563, 348, 184, 97, 34, 11, 3) which show a sharply increasing degree of missing data over time due to deaths, dropouts, missed clinic visits and transferring to other hospital. The average number of baseline CD4 counts is 197.79 per mm^3 of blood with standard deviation 171.66.

On the other hand, the survival endpoint of interest is defaulting from HAART treatment. Defaulters are patients that did not come back at least one year after their last

medical contact till the data was censored (31 December 2011) or patients that are away for more than a year at anytime during the five years treatment period. A defaulter could be as a result of death, transferring to other hospital and loss-to-follow. Therefore, defaulting is assumed to be the outcome of interest for the survival analysis and censoring is considered when the patient is still on the treatment. From our data, 329 (22.5%) patients were defaulted while the remaining 1135 (77.5%) patients were actively following the treatment. The survival response, default time in months, is created by subtracting the date of HAART entry from the date of the last visit (default date). The estimated median defaulting time in the five years follow up time was about 97.69 months.

Also, seven potential explanatory variables were considered in this study. The descriptions of these covariates are presented in Table 1 below.

Table 1: Covariates used in the Separate and Joint Analysis of the HAART Data

No.	Variable	Description
1.	Gender	0 = Female, 1 = Male
2.	Age	Years
3.	Weight	Kilograms
4.	Marital Status	0 = Never Married, 1 = Married, 2 = Others
5.	Clinical Stage	1 = Stage I, 2 = Stage II, 3 = Stage III, 4 = Stage IV
6.	Functional Status	0 = Working, 1 = Ambulatory, 2 = Bedridden
7.	Education Level	0 = No Education, 1 = Primary, 2 = Secondary, 3 = Tertiary

Out of the total 1464 patients included in the study, 536 (36.65%) were male. More than half of the patients 873 (59.63%) were married while 296 (20.22%) were never married and 295 (20.15%) were in the other (divorced/widowed) group. Regarding the clinical stage of patients, 347 (23.70%) were at clinical stage I, 514 (35.10%) at clinical stage II, 497 (33.90%) at clinical stage III and the rest 106 (7.20%) were at clinical stage IV when they started HAART. There were 1003 (68.51%) patients who were able to work, 404 (27.60%) ambulatory and 57 (3.89%) bedridden patients. Only 297 (20.29%) of the patients were not educated while most of the patients have completed at least primary education.

Regarding the two continuous covariates, the means of the baseline age and weight are 34.04 years and 51.90 kilograms with standard deviations 9.16 years and 10.24 kilograms, respectively. These variables are standardized to have a mean 0 and variance 1 in the remainder of this paper for facilitating parameter convergence. As such, their coefficients

in the regression models represent the effect per one standard deviation change.

2.2 Methods of Data Analysis

2.2.1 Longitudinal Data Modeling

In the linear mixed effects model, the sequence of the longitudinal measurements $y_{i1}, ..., y_{in_i}$ for the i^{th} subject at times $s_{i1}, ..., s_{in_i}$ is modeled as:

$$\begin{aligned} \boldsymbol{y}_i &= \mu_i(s) + W_{1i}(s) + \boldsymbol{\varepsilon}_i \\ &= \boldsymbol{X}_{1i}^T(s)\boldsymbol{\beta}_1 + \boldsymbol{Z}_{1i}^T(s)\boldsymbol{b}_i + \boldsymbol{\varepsilon}_i \\ \boldsymbol{b}_i &\sim N(\boldsymbol{0}, \boldsymbol{\Psi}), \boldsymbol{\varepsilon}_i \sim N(\boldsymbol{0}, \sigma_\varepsilon^2 \boldsymbol{I}) \end{aligned} \tag{1}$$

where $\boldsymbol{y}$ is an n_i dimensional vector of observed responses, $\boldsymbol{\beta}_1$ is a p dimensional vector of fixed effects, $\boldsymbol{b}_i$ is a q dimensional vector of random effects, $\boldsymbol{X}_{1i}^T(s)$ is a matrix of (size $n \times p$) fixed effects possibly time-varying covariates, $\boldsymbol{Z}_{1i}^T(s)$ is a matrix of (size $n \times q$ random effects covariates and $\boldsymbol{\varepsilon}_i$ is an n_i dimensional vector of within group errors with a Gaussian distribution.

In this model, $\mu_i(s) = \boldsymbol{X}_{1i}^T(s)\boldsymbol{\beta}_1$ is the mean response and $W_{1i}(s) = \boldsymbol{Z}_{1i}^T(s)\boldsymbol{b}_i$ incorporates random effects. The term $W_{1i}(s)$ can be viewed as the true individual level CD4 trajectories after they have been adjusted for the overall mean trajectory and other fixed effects. The random effects covariates, $\boldsymbol{Z}_{1i}$, is usually a subset of the fixed effects covariates, $\boldsymbol{X}_{1i}$.

2.2.2 Survival Data Modeling

The Cox Proportional Hazards (PH) model is the most widely used semi-parametric survival regression model in which the hazard at time t can be expressed as:

$$\begin{aligned} h_i(t) &= h_0(t)\mu_i(t) \\ &= h_0(t)\exp(\boldsymbol{X}_{2i}^T(s)\boldsymbol{\beta}_2) \end{aligned} \tag{2}$$

where $h_0(t)$ is the baseline hazard function, $\boldsymbol{X}_{2i}^T(s)$ is a vector of (possibly time-dependent) covariates and $\boldsymbol{\beta}_2$ is a vector of parameters of fixed effects.

The baseline hazard function, $h_0(t)$, corresponds to the reference levels for all covariates (or it is the hazard when all covariates are zero). The vectors $\boldsymbol{X}_{2i}$ and $\boldsymbol{\beta}_2$ may or may not have elements in common with $\boldsymbol{X}_{1i}$ and $\boldsymbol{\beta}_1$, respectively, in the longitudinal model. In this model, no distributional assumption is made for the survival data, the only assumption is that the hazards ratio $\psi = \dfrac{h_i(t)}{h_0(t)}$ does not change over time (i.e., proportional hazards).

In addition to the Cox PH model, parametric survival models are also available. The most common parametric model is the Weibull model, in which the survival time for

the i^{th} subject is assumed to follow a Weibull distribution, $t_i \sim \text{Weibull}(\mu_i(t), \rho)$ where $\mu_i(t) = \exp(\boldsymbol{X}_{2i}^T(s)\boldsymbol{\beta}_2)$ and $\rho > 0$. The corresponding baseline hazard function is given by $h_0(t) = \lambda\rho t^{(\rho-1)}$ where λ is the scale parameter and ρ is the shape parameter. The hazard function for this distribution varies monotonically with time. The hazard decreases with time if ρ is less than 1 and it increases with time if ρ is greater than 1. If ρ equals 1, the hazard function is constant with time and is equivalent to an exponential distribution with parameter λ. The general Weibull hazard model for the event intensity (or hazard) at time t can be written as:

$$h_i(t) = \lambda\rho t^{(\rho-1)}\exp(\boldsymbol{X}_{2i}^T(s)\boldsymbol{\beta}_2) \tag{3}$$

2.2.3 The Joint Models Structure

This study combines two joint modeling approaches proposed by Guo and Carlin (2004), and Gao et al. (2011). Guo and Carlin (2004) investigated the approach proposed by Henderson et al. (2000) from a Bayesian perspective and relying on Markov Chain Monte Carlo (MCMC) algorithms. They add a frailty term to the survival submodel in order to accommodate any effect that cannot be explained by the shared random effects. The joint modeling approach proposed by Gao et al. (2011) directly relates the impact of biomarker (longitudinal response) variability to the survival outcome.

The Longitudinal Submodel Specification

In most joint models studied in the past decade, longitudinal data are delineated by a conventional linear mixed model assuming homogeneous within subject variance. However, such a homogeneity assumption automatically precludes the assessment of the research question "whether individuals with different levels of CD4 variability have different susceptibility to defaulting from HAART treatment". Consequently, the joint model proposed in this study combines both approaches; that is, it relates the variability of longitudinal CD4 counts to defaulting and also adds a frailty to the survival submodel.

In the proposed model, the CD4 trajectory was described by both the conventional linear mixed model (1) and by the linear mixed effects model that incorporates subject-specific variances (Lyles et al., 1999).

$$\begin{aligned} \boldsymbol{y}_i &= \mu_i(s) + W_{1i}(s) + \boldsymbol{\varepsilon}_i \\ &= \boldsymbol{X}_{1i}^T(s)\boldsymbol{\beta}_1 + \boldsymbol{Z}_{1i}^T(s)\boldsymbol{b}_i + \boldsymbol{\varepsilon}_i \\ \boldsymbol{b}_i &\sim N(\boldsymbol{0}, \boldsymbol{\Psi}), \boldsymbol{\varepsilon}_i \sim N(\boldsymbol{0}, V_i\boldsymbol{I}), \log(V_i) \sim N(\mu_v, \sigma_v^2) \end{aligned} \tag{4}$$

This model incorporates subject-specific variances, that is, the within group errors, $\boldsymbol{\varepsilon}_i$, may not have homogeneous variances. Thus, here, V_i represents the "true" within-subject variability which follows a log-normal distribution with mean μ_v and variance σ_v^2.

The Survival Submodel Specification

As shown before, both of the separate and the joint models assume that the longitudinal submodel has the form similar to the conventional linear mixed effects model (1), while the survival model (3) in the joint model includes a latent association function $W_{2i}(t)$. Thus, the survival submodel is specified in the form as:

$$h_i(t) = h_0(t)\exp(\boldsymbol{X}_{2i}^T(s)\boldsymbol{\beta}_2 + W_{2i}(t)) \tag{5}$$

The form of the association function, $W_{2i}(t)$, is similar to $W_{1i}(s)$, including subject-specific covariate effects and an intercept (often called a frailty). When $W_{2i}(t) = 0$, the association induced is only via shared baseline covariates. Specifically, the joint model links the linear mixed effects model (4) that incorporates subject-specific variance and model (5) by taking:

$$W_{1i}(s) = b_{0i} + b_{1i}s + b_{2i}s^2 \tag{6}$$

and

$$W_{2i}(t) = \gamma_0 b_{0i} + \gamma_1 b_{1i} + \gamma_2 b_{2i} + \gamma_3 \log(V_i) + b_{3i} \tag{7}$$

The longitudinal model (6) is of the usual form as proposed by Laird and Ware (1982), with each patient receiving random intercept, linear and quadratic slope terms. The form in model (6) is quadratic in s, which is motivated while exploring the longitudinal data. The parameters γ_0, γ_1, γ_2 and γ_3 in the survival model (7) measure the association between the two submodels induced by the random intercepts, linear slope, quadratic slope and the CD4 variability, respectively. As mentioned before, the triple latent variables $\boldsymbol{b}^T = (b_{0i}, b_{1i}, b_{2i})^T$ have a zero mean trivariate Gaussian distribution $N(\boldsymbol{0}, \boldsymbol{\Psi})$, and the subject-specific variances V_i's have a lognormal distribution distribution $\log V_i \sim N(\mu_v, \sigma_v^2)$ while the b_{3i}'s are independent frailty terms, modeled as iid $N(0, \sigma_3^2)$, independent of $(b_{0i}, b_{1i}, b_{2i})^T$.

2.2.4 Bayesian Estimation and Inference

The proposed joint models are estimated under a Bayesian framework using Markov chain Monte Carlo (MCMC) methods with Gibbs sampling using the non-commercial software WinBUGS (http://www.mrcbsu.cam.ac.uk/bugs/).

Given the random effects, the longitudinal process is assumed to be independent from the event times. So that the full joint distribution of the longitudinal continuous response, $\boldsymbol{y}$, and time to event, $\boldsymbol{T}$, can be specified in the form of:

$$f(\boldsymbol{y}, \boldsymbol{T}, \boldsymbol{\delta}|\boldsymbol{\Theta}_1, \boldsymbol{\Theta}_2) = \prod_{i=1}^{N} \int f(\boldsymbol{y}|\boldsymbol{\Theta}_1, \boldsymbol{\eta}_i) f(\boldsymbol{T}, \boldsymbol{\delta}|\boldsymbol{y}, \boldsymbol{\Theta}_2, \boldsymbol{\eta}_i) f(\boldsymbol{\eta}_i) d\boldsymbol{\eta}_i$$

with the corresponding likelihood function being

$$L(\boldsymbol{y}, \boldsymbol{T}, \boldsymbol{\delta}|\boldsymbol{\Theta}_1, \boldsymbol{\Theta}_2) = \prod_{i=1}^{N} \int f(\boldsymbol{y}|\boldsymbol{\Theta}_1, \boldsymbol{\eta}_i) f(\boldsymbol{T}, \boldsymbol{\delta}|\boldsymbol{y}, \boldsymbol{\Theta}_2, \boldsymbol{\eta}_i)^{\delta_i} (1 - F(\boldsymbol{T}, \boldsymbol{\delta}|\boldsymbol{y}, \boldsymbol{\eta}_i, \boldsymbol{\Theta}_2)^{(1-\delta_i)} f(\boldsymbol{\eta}_i) d\boldsymbol{\eta}_i$$

where $\boldsymbol{\eta}_i = \{\boldsymbol{b}_i, V_i\boldsymbol{I}\}$ represents the shared underlying process, $\boldsymbol{\Theta}_1 = \{\boldsymbol{\beta}_1, \boldsymbol{\Psi}, \mu_v, \sigma_v^2\}$ and $\boldsymbol{\Theta}_2 = \{\boldsymbol{\beta}_2, \boldsymbol{\gamma}, \sigma_3^2\}$ are the population parameters as given in the mixed and survival models respectively, $f(.)$ and $F(.)$ denote density and distribution functions, respectively.

For Bayesian analysis, inference is based on the posterior distribution given the observed data. Baye's theorem is used to construct the posterior distribution which is given as:

$$f(\boldsymbol{\theta}|\boldsymbol{y}) = \frac{f(\boldsymbol{y}|\boldsymbol{\theta})f(\boldsymbol{\theta})}{f(\boldsymbol{y})} = \frac{f(\boldsymbol{y}|\boldsymbol{\theta})f(\boldsymbol{\theta})}{\int f(\boldsymbol{y}|\boldsymbol{\theta})f(\boldsymbol{\theta})d\boldsymbol{\theta}}$$

where $f(\boldsymbol{\theta}|\boldsymbol{y})$ is the posterior distribution of $\boldsymbol{\theta}$, $f(\boldsymbol{y}|\boldsymbol{\theta})$ is the likelihood and $f(\boldsymbol{\theta})$ is the prior distribution of $\boldsymbol{\theta}$.

Hence, Bayesian analysis combines priors with the likelihood. In this paper, the choice of priors is aided by Guo and Carlin (2004) paper. Specifically, in the longitudinal submodel multivariate normal and inverse gamma priors are used for the main effects vector $\boldsymbol{\beta}_1$ and the error variance σ_ε^2, respectively. Similarly normal and inverse gamma priors are used for $\boldsymbol{\beta}_2$ and σ_3^2 in the survival submodel. Finally, for the parameters common to both models multivariate gamma are used and for the association parameters, γ_h's, normal priors are used.

2.2.5 Joint Model Selection

The precise nature of the two submodels (i.e., the exact form of $W_{1i}(s)$ and $W_{2i}(t)$ and their association are selected via the DIC (Deviance Information Criterion); (Spiegelhalter et al., 2002), a hierarchical modeling generalization of the AIC (Akaike Information Criterion). The DIC approach mimics AIC by setting $DIC = \bar{D} + pD$. The first term is the posterior expectation (mean) of the deviance function, $\bar{D}$, and measures the goodness-of-fit. The second term pD is the effective number of parameters and measures model complexity. Since a smaller $\bar{D}$ indicates a better fit and a smaller pD indicates a parsimonious model, small value of the sum (DIC) indicates preferred model.

In general, the DIC facilitates an easy comparison among the various complex but realistic models that do not need to be nested. For example, the DIC is used for determining the random effects to be included in the longitudinal model and to select the best model among several candidate joint models.

3 Results and Discussion

3.1 Results Using the Classical Models

In order to fully specify the mean responses, both the longitudinal and survival data are analyzed separately using the classical models reviewed in sections 2.2.1 and 2.2.2.

3.1.1 Separate Analysis of the Longitudinal Data

To check the normality of the longitudinal data, boxplots of the CD4 counts over time are shown below in Figure 1. The left side of the plot shows a high degree of skewness toward high CD4 counts, suggesting some transformation. After a square root transformation, right side plot, the data attained normality.

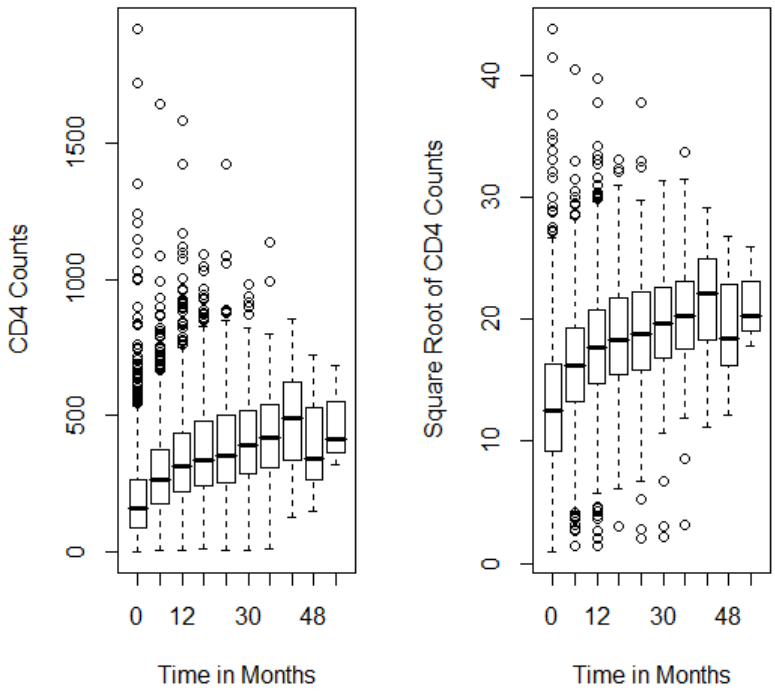

Figure 1: Boxplots of the actual CD4 counts and the square root CD4 counts over time

Exploring the Mean Structure

To understand the possible relationships among the CD4 means over time, the plot of the mean structure is shown in Figure 2. The circled points in the plot show the actual CD4 means at each observation time. Since the data is not balanced, loess smoothing technique is used instead.

The plot suggests that the mean of the square root CD4 profiles have a quadratic relationship over time. In other words, both the linear and quadratic time effects may be included as fixed-effects in the longitudinal model.

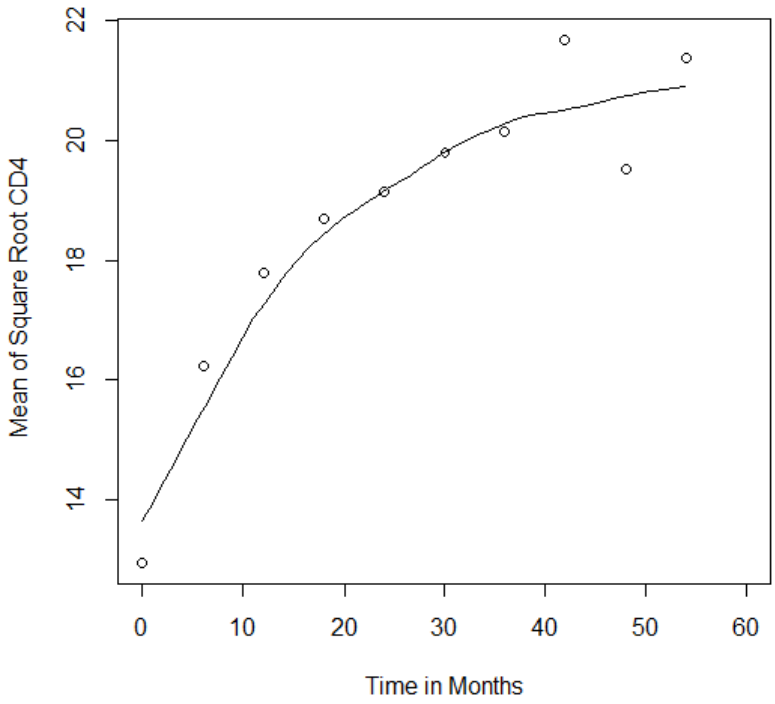

Figure 2: Loess smoothing plot of the mean of the square root CD4 counts over time

The Linear Mixed Effects Model Results

Taking advantage of the fact that the conventional linear mixed effects model (1) described by Laird and Ware (1982); and the linear mixed effects model (4) that incorporates subject-specific (heterogeneous) variances, produce almost identical estimates for fixed effects (Manatunga et al., 2005), initially, the repeated CD4 counts are analyzed using model (1). These data analyses were conducted using R software to avoid intensive computation of MCMC methods.

In many longitudinal studies, much of the systematic variation between subjects may be explained by covariates such as age and gender (Wu, 2010). So, only Age and Gender are included in the linear mixed effects models of this study. The results show that among these two covariates, Gender is only statistically significant. Also the results reveal that adding quadratic time can significantly improve the model fit ($\chi^2 = 121.26$, $df = 1$, $p < 0.001$).

Let y_{ij} denote the square root of j^{th} CD4 count of the i^{th} patient at time s_{ij}, $j =$

$1, 2, ..., n_i$ and $i = 1, 2, ..., N$. Hence, the linear random effects model for square root CD4 counts is specified as:

$$y_{ij} = \beta_{10} + \beta_{11}s_{ij} + \beta_{12}s_{ij}^2 + \beta_{13}\text{Gender} + \beta_{14}\text{Age} + W_{1i}(s_{ij}) + \varepsilon_{ij} \tag{8}$$

where $W_{1i}(s_{ij}) = b_{10} + b_{11}s_{ij} + b_{12}s_{ij}^2$. Here, $W_{1i}(s_{ij})$ includes the random effects for intercept, linear and quadratic time slopes, where the $\boldsymbol{b}^T = (b_{0i}, b_{1i}, b_{2i})^T \sim N(\mathbf{0}, \boldsymbol{\Psi})$. This specification allows different subjects to have different baseline CD4 counts, different linear and quadratic time trends for CD4 counts during the treatment period.

Table 2: Posterior Means and 95% Credible Intervals for Population Parameters of the Conventional Linear Mixed Effects Model (1) and for Model (4) that incorporates Patient-Specific Variances

Parameter	Without Patient-Specific Variances		With Patient-Specific Variances	
	Posterior Mean	95% CI	Posterior Mean	95% CI
Fixed Effects				
Intercept	13.6100	(13.320, 13.910)	13.4500	(13.1600,13.73000)
Time	0.4406	(0.4046, 0.4779)	0.4543	(0.4190, 0.49020)
$Time^2$	-0.0072	(-0.0089,-0.0054)	-0.0076	(-0.0089,-0.00540)
GenderMale	-1.2140	(-1.6790,-0.7492)	-1.1690	(-1.6790,-0.74920)
Age	0.1427	(-0.0840, 0.3699)	0.1069	(-0.0840, 0.36990)
σ_ε^2	13.20	(12.42, 14.01)	-	-
Random Effects				
$Var(b_0)$	10.8700	(9.5930,12.2300)	10.1500	(9.5930, 12.2300)
$Var(b_1)$	0.0126	(0.0040, 0.0231)	0.0155	(0.0040, 0.0231)
$Var(b_2)$	0.0001	(0.00009, 0.00012)	0.0001	(0.00008, 0.00011)
μ_v	-	-	2.2910	(2.200, 2.381)
σ_v^2	-	-	0.6586	(0.5287, 0.8064)
DIC	26622.7		25539.1	

Table 2 presents the posterior means and 95% credible intervals for the population parameters of two models; for the conventional linear mixed effects model and for the model incorporating patient specific CD4 variances. Here the results of the two models are quite similar to each other. In both models both the linear and quadratic time effects, and Gender are statistically significant at 0.05 level of significance (in the Bayesian sense; 95% posterior credible interval excludes 0). The table also shows, the estimated subject-specific variance is $\sigma_v^2 = 0.6586$ with 95% credible interval (0.5225,0.7965). Hence, it supports the assumption of heterogeneous variance for the repeated CD4 counts. Also,

the reduction in the DIC for the model incorporating subject-specific variances is an evident that subject-specific CD4 variances must be considered in the analysis.

3.1.2 Separate Analysis of the Survival Data

Turning to the separate analysis of the survival data, the variables to be included in the survival model are determined using an automatic variable selection method (`stepAIC` in R). Regardless of the survival time distributions, of the seven covariates only two of them (weight and marital status) were not significant. Four parameteric models (Weibull, Exponential, Loglogistic and Lognormal) and also the Cox PH models were explored and then compared using AIC in order to select the appropriate survival time distribution. Then, the Loglogistic model was having the smallest AIC value but there was not substantial difference (less than 5) with the AIC of the Weibull model. Thus, we have decided to use the Weibull survival model because of two reasons; firstly, its parameters are easily interpretable as compared to the other parametric models and secondly, it is the only model having both a proportional hazards and accelerated failure time properties.

Because none of the covariates are time-varying, the regression equation for the log-relative hazard in the absence of random effects is:

$$\begin{aligned}\log(\mu_i) = \beta_{20} &+ \beta_{21}\text{Gender} + \beta_{22}\text{Age} \\ &+ \beta_{23}\text{Stage I} + \beta_{24}\text{Stage II} + \beta_{25}\text{Stage II} \\ &+ \beta_{26}\text{Working} + \beta_{27}\text{Ambulatory} \\ &+ \beta_{28}\text{No Education} + \beta_{29}\text{Primary} + \beta_{2,10}\text{Secondary}\end{aligned} \tag{9}$$

This is the parameterization used in WinBUGS for Weibull model. The Cox proportional hazards model uses parameterization (9), except that the intercept is modeled as part of the (nonparametric) baseline hazard. Parameter estimates of both the full Weibull and Exponential models are very similar to each other, but the estimated Weibull shape parameter ρ is 0.8131 with 95% CI (0.7391, 0.8897) which is significantly less than 1 indicating that default rate decreases over time. The estimated median defaulting time is about 97.69 months with 95% CI (81.87, 116.57).

3.2 Results Using Joint Models

After the separate analysis of the data, two types of joint models with a variety of latent processes are investigated. In the first type of joint models, the longitudinal submodel of the joint model assumes homogenous variances (using model (1)) while in the second type of joint models, the longitudinal submodel assumes heterogenous CD4 variances (using model (4)). In other words, the longitudinal submodel is described by both the usual linear mixed effects model and by the linear mixed effects model incorporating patient-specific variances. On the other hand, the survival submodel is fitted using a full Weibull distribution, and the two sub-models are linked via shared covariates and

patient-specific random effects.

Hence, several joint models with and without incorporating subject-specific variances and with a variety of latent processes are explored. In all cases, the results are based on three parallel MCMC sampling chains of 50,000 iterations each, following a 25,000 iteration burn-in period. Each model required approximately 3-4 hours when using 3 parallel chains with different starting values.

By default, WinBUGS provides the components of DIC for the two submodels (that is, the terms in the loglikelihood arising from longitudinal and survival model components) to evaluate their relative contributions to the total DIC score; hence the DIC for the longitudinal and survival submodels are denoted as DIC_1 and DIC_2, respectively.

3.2.1 Joint Models With Homogenous Within-Patient CD4 Variances

Table 3 below reports $\bar{D}$, pD and DIC scores for thirteen joint models with different random effects and different forms of the latent processes $W_1(s)$ and $W_2(t)$. In these models, the longitudinal submodel is described by the conventional linear mixed effects model (1) which assumes homogenous patient-specific CD4 variances.

As joint modeling starts with simple model, first, a simple joint model (Model I) is fitted with no random effects in the two submodels. This model has extremely large (poor) total DIC score. In Model II, a frailty term b_3 is added in the survival submodel, $W_2(t)$, and this does seem to improve the total DIC. A similar relationship exists between Models III and IV, and Models V and VI. In these cases in which the models differ only in the addition of the frailty term b_3, the frailty term brings an improvement, that is, the frailty term decreases the total DIC score of the joint model. As such, the frailty term b_3 is considered in subsequent models.

In Model III and IV, random intercepts are allowed in the longitudinal submodel, $W_1(s)$, which results in a dramatic improvement in DIC_1, but the total DIC score for the joint model is worth it if the frailty term is not included.

Next, the association between $W_1(s)$ and $W_2(t)$ is introduced through the common random intercept b_0 in Model V, which leads to a substantial decrease in DIC for both submodels, and hence the total DIC for the joint model when the frailty term is added. Models VII-XIII further allow both random intercepts and slopes in the longitudinal submodel, and introduce association between the two submodels in different ways. For example, Model IX introduce the association between the two submodels through random intercepts, Model XI through random slopes, Model XIII through both random intercepts and slopes with frailty term. The introduction of both the random intercepts and slopes in the longitudinal submodel substantially decreases DIC_1 but does not seem to improve the total DIC except for Model XII when the association is induced due to the linear time slopes, b_1, and a frailty term is added.

Table 3: Model Selection for thirteen candidate Joint Models when the Conventional Linear Mixed Effects Model (1) is used for the Longitudinal Submodel, and a Weibull Survival Model is used for the Survival Submodel

Model	$W_1(s)$	$W_2(t)$	DIC_1	DIC_2	$\bar{D}$	pD	DIC
No random effects							
I	0	0	28326.8	3694.69	32000.7	20.8360	32021.5
II	0	b_3	28326.7	2196.17	30069.0	453.911	30522.9
Random intercepts							
III	b_0	0	26910.4	3694.88	29672.4	932.942	30605.3
IV	b_0	b_3	26909.7	2137.06	27668.6	1378.17	29046.7
V	b_0	$\gamma_0 b_0$	26882.4	3649.45	29581.8	950.053	30531.8
VI	b_0	$\gamma_0 b_0 + b_3$	26909.3	2120.71	27634.0	1395.98	29030.0
Random intercepts and slopes							
VII	$b_0 + b_1 s$	0	26381.5	3695.10	28805.8	1270.77	30076.6
VIII	$b_0 + b_1 s$	b_3	26383.2	3106.02	27971.4	1517.78	29489.2
IX	$b_0 + b_1 s$	$\gamma_0 b_0$	26349.9	3649.37	28714.4	1284.84	29999.2
X	$b_0 + b_1 s$	$\gamma_0 b_0 + b_3$	26358.4	2832.34	27607.5	1583.25	29190.7
XI	$b_0 + b_1 s$	$\gamma_1 b_1$	26399.1	3584.85	28706.3	1277.63	29983.9
XII	$b_0 + b_1 s$	$\gamma_1 b_1 + b_3$	26378.9	2005.25	26783.4	1600.78	28384.2
XIII	$b_0 + b_1 s$	$\gamma_0 b_0 + \gamma_1 b_1 + b_3$	26619.7	3694.97	28719.3	1595.31	30314.7

Therefore, among these candidate joint models when the conventional linear mixed effects model is used for the longitudinal submodel, Model XII seems to be good as it has the smallest total DIC score. But, on the contrary the model has the largest effective number of parameters (largest complexity) as compared to the other models. Under this model, it appears that a patients survival is related to only the rate of CD4 increase.

3.2.2 Joint Models Incorporating Patient-Specific CD4 Variances

Similar to Table 3, Table 4 also reports $\bar{D}$, pD and DIC score for a variety of joint models, where the linear mixed effects model that incorporates patient-specific CD4 variability is used for the longitudinal submodel. These joint models relate the variability of longitudinal CD4 counts to defaulting. Such approach is relatively straightforward to interpret, that is, if the proportional hazards assumption is holding, for example, the effect of the longitudinal response variability on survival outcome can be readily quan-

tified as hazard ratio (Gao et al., 2011).

Like the previous case, a simple joint model (Model XIV) with no random effects is fitted first, which has a large (poor) total DIC. But, the incorporation of subject-specific CD4 variances in the longitudinal submodel improves DIC_1 and also the total DIC when it is compared with Model I which does not take into account the patient-specific CD4 variability. Also in Model XV, the addition of a frailty term b_3 in $W_2(t)$ improves DIC_2 as well as the total DIC. Next, random intercepts are introduced in the longitudinal submodel.

Models XVI-XX allow random intercepts in $W_1(s)$, which results in a dramatic improvement in DIC_1 for the longitudinal submodel and the total DIC scores. Then, different latent associations through the random intercepts b_0, and random variances are introduced. Models XXI-XXX have both random intercepts and slopes in the longitudinal submodel which results in a substantial decrement in DIC_1.

Generally, Model XXVII emerges with the smallest effective number of parameters (less complex or more parsimonious model) among the models that introduce association due to random effects and also it has the smallest total DIC (fits the data well) among all other models. Thus, Model XXVII is selected as a good model among models which incorporate patient-specific CD4 variability. Under this model, it appears that a patients survival is related to two characteristics of driving the patients longitudinal data pattern, namely the rate of CD4 increase and its variability. This is clinically reasonable, since an increase in the CD4 count represents better health status and hence patients are not likely to default from the therapy; and patients with more fluctuation of CD4 would be expected to have poorer survival.

3.3 Comparison of Separate and Joint Models

After selecting the final joint model, the results should be compared with the separate (i.e., ignoring any latent association introduced by W_2) model. In all of the cases, the models which incorporate the patient-specific CD4 variability have smaller total DIC scores than those models which do not assume homogenous CD4 variability. Therefore, both the separate and the joint model to be compared incorporate patient-specific CD4 variability. That is, both the separate and joint models assume the longitudinal submodel has form (4), while the survival model now takes the form:

$$\begin{aligned}\log(\mu_i) = \beta_{20} &+ \beta_{21}\text{Gender} + \beta_{22}\text{Age} \\ &+ \beta_{23}\text{Stage I} + \beta_{24}\text{Stage II} + \beta_{25}\text{Stage II} \\ &+ \beta_{26}\text{Working} + \beta_{27}\text{Ambulatory} \\ &+ \beta_{28}\text{No Education} + \beta_{29}\text{Primary} + \beta_{2,10}\text{Secondary} \\ &+ W_{2i}(t)\end{aligned} \tag{10}$$

Table 4: Model Selection for seventeen candidate Joint Models when the Linear Mixed Effects Model (4) that incorporates Patient-Specific Variances is used for the Longitudinal Submodel and a Weibull Model is used for the Survival Submodel

Model	$W_1(s)$	$W_2(t)$	DIC_1	DIC_2	$\bar{D}$	pD	DIC
No random effects							
XIV	0	0	27760.1	3694.56	30958.9	495.724	31454.6
XV	0	b_3	27761.7	2101.56	28973.0	890.346	29863.3
Random intercepts							
XVI	b_0	0	26076.0	3695.27	28476.1	1295.25	29771.3
XVII	b_0	b_3	26074.2	2136.27	26549.2	1661.25	28210.5
XVIII	b_0	$\gamma_0 b_0$	26074.2	2136.27	26549.2	1661.25	28210.5
XIX	b_0	$\gamma_0 b_0 + b_3$	26039.0	2661.10	26546.8	1653.31	28200.1
XX	b_0	$\gamma_3 \log(V) + b_3$	26097.3	2332.21	26786.0	1643.51	28429.6
Random intercepts and slopes							
XXI	$b_0 + b_1 s$	0	25417.7	3694.77	27533.1	1579.39	29112.5
XXII	$b_0 + b_1 s$	b_3	25423.4	2221.28	25672.3	1972.37	27644.7
XXIII	$b_0 + b_1 s$	$\gamma_0 b_0 + b_3$	25379.5	2375.30	25786.8	1967.99	27754.8
XXIV	$b_0 + b_1 s$	$\gamma_1 b_1$	25424.2	3654.70	27466.9	1612.00	29078.9
XXV	$b_0 + b_1 s$	$\gamma_1 b_1 + b_3$	25416.9	2500.17	25980.9	1936.20	27917.1
XXVI	$b_0 + b_1 s$	$\gamma_3 \log(V) + b_3$	26061.3	976.737	26359.0	679.055	27038.0
XXVII	$b_0 + b_1 s$	$\gamma_1 b_1 + \gamma_3 \log(V)$	25492.2	1474.21	25717.7	1248.74	26966.4
XXVIII	$b_0 + b_1 s$	$\gamma_0 b_0 + \gamma_1 b_1$	25410.7	3299.88	27299.7	1410.80	28710.5
XXIX	$b_0 + b_1 s$	$\gamma_0 b_0 + \gamma_1 b_1 + b_3$	25377.0	2228.88	25669.8	1936.08	27605.9
XXX	$b_0 + b_1 s$	$\gamma_0 b_0 + \gamma_1 b_1 + \gamma_3 \log(V) + b_3$	25395.9	2347.29	25790.6	1952.66	27743.2

where

$$W_{2i}(t) = \begin{cases} 0, & \text{(Separate)} \\ \gamma_1 b_1 + \gamma_3 \log(V), & \text{(Joint)} \end{cases}$$

The posterior estimates of the regression coefficients $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$ together with their 95% confidence intervals are summarized below in Table 5. Here, the results from the separate and joint analyses are quite similar to each other.

In the longitudinal submodel, both the linear and quadratic time effects and Gender are statistically significant at 0.05 level of significance whereas Age is significant in neither the separate nor the joint model. Turning to the survival submodel of the joint model, all covariates included are significantly associated with the hazard of defaulting. But, Clinical Stage is not significant in the separate model. Also, the estimated shape parameter of the Weibull distribution ρ is significantly less than 1 in both analyses indicating the rate of defaulting decreases over time.

The parameter estimates of the separate and joint models are quite similar to each other but not identical. However, the posterior estimates of the association parameters in the joint analysis are significantly different from zero, providing strong evidence of association between the two submodels. The estimate of the association parameter due to the slope (trend) of CD4 is negative ($\gamma_1 = -3.836$). This means that the slope of CD4 count is negatively associated with the hazard of defaulting. On the other hand, the estimate of the association parameter due to the CD4 variability is positive ($\gamma_3 = 0.5077$) indicating that the higher CD4 fluctuation is associated with the higher hazard of defaulting.

In general, the joint model is preferred as it has a smaller total DIC than the separate model. Also, the statistical significance of both the association parameters is also another evidence that the joint model is better than the separate models.

To check the convergence of this final joint model, time series plot of the history of iterations is used. The plot (not shown here) shows a reasonable degree of randomness between iterations indicating that Gibbs Sampler has converged to the target density. The estimated hazard ratios (HRs) and 95% posterior credible intervals for the survival submodel of this joint model are presented in Table 6.

4 Conclusions

In this study, a full Bayesian approach to jointly model the CD4 fluctuations of HIV/AIDS patients under HAART follow-up and time-to-default from the treatment is discussed. The results of both the separate and joint analyses are consistent. However, the joint model is the simplest model compared to the separate model as its effective number of parameters is smaller. In other words, this reduction in the effective number of parameters ensures that the joint model is more parsimonious (less complex). Also, the joint model has much smaller posterior mean of the deviance function which indicates that

Table 5: Comparison of the Separate and Joint Models of Longitudinal CD4 Counts and Time-to-Default from HAART Treatment

Parameter	Separate Models		Joint Model	
	Posterior Mean	95% CI	Posterior Mean	95% CI
Longitudinal Submodel				
Fixed Effects				
$Intercept$	13.5100	(13.220,13.8000)	13.5500	(13.270, 13.840)
$Time$	0.4354	(0.4051, 0.4665)	0.4276	(0.3942, 0.4594)
$Time^2$	-0.0068	(-0.0078,-0.0058)	-0.0068	(-0.0078,-0.0058)
$GenderMale$	-1.1990	(-1.6500,-0.7496)	-1.1920	(-1.6320,-0.7327)
Age	0.1014	(-0.1181, 0.3247)	0.1136	(-0.1030, 0.3270)
Random Effects				
$Var(b_0)$	10.0900	(8.8430,11.4200)	9.8530	(8.5920, 11.200)
$Var(b_1)$	0.0228	(0.0178, 0.0285)	0.0236	(0.0183, 0.0295)
$Var(b_2)$	0.0001	(0.00009, 0.00012)	0.0001	(0.00008, 0.00011)
μ_v	2.2990	(2.2150, 2.3830)	2.3450	(2.2560, 2.4280)
σ_v^2	0.6538	(0.5259, 0.7927)	0.6360	(0.5026, 0.7705)
Survival Submodel				
Fixed Effects				
$Intercept$	-3.4750	(-4.1390,-2.7970)	-4.8350	(-6.0300,-3.7940)
$GenderMale$	0.5301	(0.2913, 0.7673)	0.5641	(0.0315, 0.8189)
Age	-0.2827	(-0.4115,-0.1568)	-0.3144	(-0.4587,-0.1741)
Clinical Stage				
$StageI$	-0.4904	(-0.9570, 0.0114)	-0.6294	(-1.1470,-0.1006)
$StageII$	-0.3452	(-0.7607, 0.1215)	-0.3545	(-0.8162, 0.1334)
$StageIII$	-0.3209	(-0.7162, 0.1230)	-0.3618	(-0.8067, 0.1089)
$StageIV$	-	-	-	-
Functional Status				
$Working$	-0.9630	(-1.3840,-0.5264)	-1.1050	(-1.5960,-0.6093)
$Ambulatory$	-0.6416	(-1.0540,-0.2097)	-0.7355	(-1.2160,-0.2493)
$Bedridden$	-	-	-	-
Education Level				
$NoEducation$	0.4984	(0.0459, 0.9785)	0.4803	(0.0169, 0.9637)
$Primary$	0.4193	(-0.0053, 0.8854)	0.4008	(-0.2839, 0.8613)
$Secondary$	0.1537	(-0.2833, 0.6338)	0.1374	(-0.3164, 0.6140)
$Tertiary$	-	-	-	-
γ_1	-	-	-3.8360	(-6.5180,-1.4760)
γ_3	-	-	0.5077	(0.2238, 0.8506)
ρ	0.8136	(0.7377, 0.8895)	0.8668	(0.7789, 0.9690)

Table 6: Posterior Means and Hazard Ratio Estimates with corresponding 95% Credible Intervals for Parameters of the Survival Submodel of the Final Joint Model

Parameter	Parameter Estimates		HR Estimates	
	Posterior Mean	95% CI	HR	95% CI
Intercept	-4.8350	(-6.0300,-3.7940)	0.0079	(0.0024, 0.0225)
GenderMale	0.5641	(0.0315, 0.8189)	1.7579	(1.3703, 2.2680)
Age	-0.3144	(-0.4587,-0.1741)	0.7302	(0.6321, 0.8402)
Clinical Stage				
StageI	-0.6294	(-1.1470,-0.1006)	0.5329	(0.3176, 0.9043)
StageII	-0.3545	(-0.8162, 0.1334)	0.7015	(0.4421, 1.1427)
StageIII	-0.3618	(-0.8067, 0.1089)	0.6964	(0.4463, 1.1150)
StageIV	-	-	-	-
Functional Status				
Working	-1.1050	(-1.5960,-0.6093)	0.3312	(0.2027, 0.5437)
Ambulatory	-0.7355	(-1.2160,-0.2493)	0.4793	(0.2964, 0.7793)
Bedridden	-	-	-	-
Education Level				
NoEducation	0.4803	(0.0169, 0.9637)	1.6166	(1.0170, 2.6214)
Primary	0.4008	(-0.2839, 0.8613)	1.4930	(0.9655, 2.3662)
Secondary	0.1374	(-0.3164, 0.6140)	1.1473	(0.7288, 1.8478)
Tertiary	-	-	-	-
γ_1	-3.8360	(-6.5180,-1.4760)	0.0216	(0.0015, 0.2286)
γ_3	0.5077	(0.2238, 0.8506)	1.6615	(1.2508, 2.3411)

it fits the data better than the separate model. Hence, the joint model is not only the simplest model, but also provides a better fit to the data.

Separate analysis of the longitudinal CD4 counts and also the joint model analysis prove that incorporation of patient-specific CD4 variances brings a significant improvement in the mode fit. Specifically, the assumption of heterogeneous CD4 variances among patients results a reduction in both the effective number of parameters and the posterior mean of the deviance function of the model.

All the covariates; Gender, Age, Clinical Stage, Functional Status and Education Level, included in the survival submodel of the joint model are found to be significantly associated with defaulting. In additon, the results show that the patients survival in the HAART treatment is associated with patient-specific CD4 fluctuations such that a patient with higher CD4 trend is less likely to default from the treatment and an individual with higher CD4 variability is more likely to default than an individual with smaller CD4 variability.

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WinBUGS Codes for Selected Models

The Separate Model - Model XXI

```
model{
  for (i in 1:N) {
for (j in 1:M) {
mu.CD4[i,j] <- beta1[1]+beta1[2]*ss[j]+beta1[3]*s2[j]+
       beta1[4]*sex[i]+ beta1[5]*age[i]+b0.i[i]+
       b1.i[i]*ss[j]

CD4[i,j] ~ dnorm(mu.CD4[i,j], tau.vi[i])
}

log(mu.surv[i])<- beta2[1]+beta2[2]*sex[i]+beta2[3]*age[i]+
      beta2[4]*st1[i]+beta2[5]*st2[i]+beta2[6]*st3[i]+
      beta2[7]*wor[i]+beta2[8]*amb[i]+
      beta2[9]*noe[i]+beta2[10]*pri[i]+
      beta2[11]*sec[i]

       sur.t[i] ~ dweib(p,mu.surv[i])I(cen.t[i],)

tau.vi[i] <- 1/exp(log.vi[i])
log.vi[i] ~ dnorm(mu.v, tau.v)
b0.i[i]~dnorm(0,tau.b0)
b1.i[i]~dnorm(0,tau.b1)
}
var.v <- 1/tau.v
var.b0 <- 1/tau.b0
var.b1 <- 1/tau.b1

 p~dgamma(1,1) # Full Weibull Model
 # p <-1 # Use this for Exponential Model

# Priors
for(k in 1:5){ beta1[k] ~ dnorm(0, 0.01)}
for (h in 1:11) { beta2[h] ~ dnorm(0,0.01) }
mu.v ~ dnorm(0,0.01)
r0 ~ dnorm(0,0.01)
tau.v ~ dgamma(0.1, 0.1)
tau.b0 ~ dgamma(0.1, 0.1)
tau.b1 ~ dgamma(0.1, 0.1)
}
```

The Final Joint Model - Model XXVII

```
model{
      for (i in 1:N) {
              for (j in 1:M)  {
        mu.CD4[i,j] <- beta1[1]+beta1[2]*ss[j]+beta1[3]*s2[j]+
                       beta1[4]*sex[i]+ beta1[5]*age[i]+b0.i[i]+
                       b1.i[i]*ss[j]

        CD4[i,j] ~ dnorm(mu.CD4[i,j], tau.vi[i])
}

    log(mu.surv[i])<- beta2[1]+beta2[2]*sex[i]+beta2[3]*age[i]+
                      beta2[4]*st1[i]+beta2[5]*st2[i]+beta2[6]*st3[i]+
                      beta2[7]*wor[i]+beta2[8]*amb[i]+
                      beta2[9]*noe[i]+beta2[10]*pri[i]+
                      beta2[11]*sec[i]+r1*b1.i[i]+r3*log.vi[i]

        sur.t[i] ~ dweib(p,mu.surv[i])I(cen.t[i],)

        tau.vi[i] <- 1/exp(log.vi[i])
        log.vi[i] ~ dnorm(mu.v, tau.v)
        b0.i[i]~dnorm(0,tau.b0)
        b1.i[i]~dnorm(0,tau.b1)
             }

     var.v <- 1/tau.v
     var.b0 <- 1/tau.b0
     var.b1 <- 1/tau.b1

p~dgamma(1,1) # Full Weibull Model
# p <-1 # Use this for Exponential Model

# Priors
      for(k in 1:5){ beta1[k] ~ dnorm(0, 0.01)}
      for (h in 1:11) { beta2[h] ~ dnorm(0,0.01) }
      mu.v ~ dnorm(0,0.01)
      r1 ~ dnorm(0,0.01)
      r3 ~ dnorm(0,0.01)
      tau.v ~ dgamma(0.1, 0.1)
      tau.b0 ~ dgamma(0.1, 0.1)
      tau.b1 ~ dgamma(0.1, 0.1)
     }
```