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Adherence to antiretroviral therapy, virological response, and time to resistance in the Dakar cohort

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Abstract

In 1998, with the launch of the Senegalese Initiative for Antiretroviral Access (ISAARV), Senegal became one of the first African countries to propose an antiretroviral access program. Our objective in this paper is to study the time to any first drug resistance, as well as predictors of the time to resistance. We propose a joint model to study the effect of adherence to the HAART therapy, and virological response on the time to resistance mutations. A logistic mixed model is used to model the time-dependent adherence process; and a Markov model is used to study the virological response. Given the presence of missing data in the adherence process and in the virological response, the latent adherence and virological states are then included in the linear predictor of the time to resistance model. The proposed time to resistance model takes into account interval-censored data as well as null hazard periods, during which the viral replication is very low. A Bayesian approach is used for accommodating with missing data and for prediction. We also propose model checking tools to study model adequacy.

Keywords

joint models; virological failure; adherence to antiretroviral therapy; resistance mutations; Bayesian prediction

1. Introduction

In 1998, with the launch of the Senegalese Initiative for Antiretroviral Access (ISAARV), Senegal became one of the first African countries to propose an antiretroviral access program. The emergence of HIV-resistance mutations in the viral protease and reverse transcriptase genes is a major cause of failure of antiretroviral therapy. Despite the relatively recent introduction of HAART in many developing countries, some limited and sparse data on the prevalence of ART resistance are available. WATCH, a worldwide surveillance program, found the prevalence of resistance (to any antiretroviral drug) among treatment naive individuals to be 5.5 per cent in Africa [1]. The main goal of this paper is to study the time to resistance to any antiretroviral drug resistance, as well as the predictors of the time to resistance, in the Dakar cohort. A second objective is to predict for a new patient the

adherence profile, the virological response, and the time to first drug resistance, according to the patient disease history (adherence and virological response) up to the last visit time. These analyses should provide us with a more complete understanding of the relationship between adherence, virological response, and time to resistance mutation.

Obtaining complete data may be particularly challenging in clinic-based cohorts in resource-poor settings. In the Dakar cohort, adherence to antiretroviral therapy was measured every month as the proportion of pills actually taken of the number of pills prescribed. The median proportion of missing adherence values per patient was 66 per cent, mainly because the systematic recording of adherence data began a while after the inclusion in the cohort for many patients. Viral load was intended to be measured at entry and every 6 months thereafter; however, the median proportion of missing viral load measurements per patient was 20 per cent. Below, we discuss strategies for handling the high degree of missing data.

The patients with genotypic resistance tests did not represent a random sample from the cohort. Indeed, present guidelines recommend that a viral load of at least 500–1000 copies/mL be achieved before resistance testing is undertaken [2]. Hence, as recommended, tested patients had viral load levels above 500–1000 copies/mL, which may reflect either transient ‘blips’ or actual virological failure. Hence, the viral load level is a strong predictor of the probability of resistance testing. Below, we discuss strategies to include viral load in the resistance model, in order to avoid selection bias [3].

Joint models have been widely used to model a longitudinal biomarker (continuous or dichotomous) and the elapsed time to an event ([4–6] among others). Such models are useful in that they accommodate missing observations and measurement error in the longitudinal biomarker. Given the level of missing data in the adherence process and in the virological response, and the necessity of including the virological response as a covariate in the time to resistance model, joint models of the adherence process, the virological response and the time to first resistance mutation will be considered. Joint models are also useful in the context of individual prediction. Yu *et al.* [7] proposed a joint model for the prostate-specific antigen (PSA) and the time to prostate cancer recurrence. The model provides individual predictors for both future PSA values and the predicted probability of recurrence up to four years in the future. In our setting, we condition on the adherence process and the virological response of a patient up to a certain time point, and then use the joint model to predict the future adherence process, the future virological response, and the time to the first resistance mutation.

Huang *et al.* [8] proposed a highly flexible model that allows for abrupt variation in the virological response. They considered three periods in the virological response: an ‘on-track’ period (the disease is under control—the patient presents a good response to the therapy), a possible ‘rebound’ or virological failure (a sharp increase in the viral load), and a possible ‘off-track’ period (period following the rebound, a high level viral load plateau). To study the virological response Huang *et al.* used an autoregressive linear model; the coefficients of the model were allowed to vary according to the track. Because in this model, the track is itself determined from the virological response and thereafter treated as a known covariate in the virological response model, it is not appropriate in our context. To avoid cyclic relationships (variable A influences variable B, at the same time B influences A), we propose a Markov model for the virological response.

The development of drug resistance requires the concurrence of two antagonistic factors: antiretroviral drug exposure and ongoing viral replication [9]. Hence, when the patient’s viral load is below the detection level, the hazard of resistance may be assumed to be null.

Moreover, time-to-resistance-data are interval censored. Hence the proposed time to resistance model takes into account null hazard periods and interval-censored data.

Both EM algorithms and Monte Carlo Markov Chain techniques have been developed to fit joint models [4]. Our analyses make use of bayesian inference because it efficiently deals with missing data, and is a natural framework for prediction. The bayesian model takes into account model uncertainty via the likelihood of the new observation, and the parameters uncertainty via the posterior distribution.

Section 2 proposes a joint model to investigate the effect of adherence to treatment, and virological response, on the time to first resistance mutation. Model checking tools and predictions are also described. The proposed method is applied to the Senegal cohort data in Section 3. Discussion and potential extensions are presented in Section 4.

2. Methods

2.1. Models

2.1.1. Adherence data model—Several studies ([10–13] among others) have demonstrated that adherence greater than 95 per cent is associated with virological success. Although, it is not possible to identify an optimal threshold effect for adherence, we defined two adherence states according to whether adherence is above or strictly below 95 per cent. Adherence data are intended to be recorded every month.

Each adherence state, $S_{i,t}$ for patient $i = 1 \dots N$ at time $t = 0 \dots T_i$ (time in months since the inclusion in the cohort) can be either observed $S_{i,t} = S_{i,t}^{\text{obs}}$ or missing $S_{i,t} = S_{i,t}^{\text{miss}}$. The data are assumed to be missing at random. A logistic mixed model is used to study the adherence process, with the following linear predictor:

$$\text{logit}(p(S_{i,t}=1|S_{i,t-1}, S_{i,t-2}, \text{PI}_{i,t-1})) = \mu_{i,t}^S \\ = \beta_0 + u_{0,i} + S_{i,t-1}(\beta_1 + u_{1,i}) + S_{i,t-2}(\beta_2 + u_{2,i}) + \beta_3 \text{PI}_{i,t-1} + \beta_4 \text{PI}_{i,t-1} \times S_{i,t-1} + \beta_5 I(12 < t \leq 24) + \beta_6 I(t > 24)$$

where $I(x) = 1$ if x is true, $S_{i,t} = 1$ if the patient i is non-adherent at time t , and $\text{PI}_{i,t-1} = 1$ if the patient has a protease inhibitor (PI) in its therapy at time $t-1$.

The random effects $u_{0,i}$, $u_{1,i}$, $u_{2,i}$ are assumed to follow a multivariate normal distribution with zero mean and variance covariance matrix Σ . Apart from the previous ($S_{i,t-1}$) and the penultimate ($S_{i,t-2}$) adherence state effect, the model also includes an effect of PI in the therapy, and an effect of time since HAART initiation. Indeed, a PI in the therapy has been already reported to be associated with poorer adherence to antiretroviral therapy (see [10, 14, 15]). This might be due to adverse side effects of the treatment, or to the recommendations that PI tablets be taken according to the timing of meals and with sufficient hydration. In a first study on a subsample of the cohort, Etard *et al.* [10] found a time effect; hence, these two covariates are included in the adherence model.

2.1.2. Virological response model—Viral load is intended to be measured every 6 months. Each viral load measurement, $\text{VL}_{i,t}$ for patient i at time $t = 0, 6, 12, \dots, T_i$ (biannual measurement time since inclusion in the cohort) can be observed $\text{VL}_{i,t} = \text{VL}_{i,t}^{\text{obs}}$ or missing $\text{VL}_{i,t} = \text{VL}_{i,t}^{\text{mis}}$. The data are again assumed to be missing at random.

A Markov model with three states is used to study the virological response. Let $Y_{i,t}$ represent the observed or missing state for patient i at time $t = 0, 6, 12, \dots, T_i$.

$$\begin{aligned}
 Y_{i,t} &= 1 && \text{if } VL_{i,t} \leq 500 \text{ copies/mL} \\
 Y_{i,t} &= 2 && \text{if } 500 < VL_{i,t} \leq 10000 \text{ copies/mL} \\
 Y_{i,t} &= 3 && \text{if } VL_{i,t} > 10000 \text{ copies/mL}
 \end{aligned}$$

The first virological state corresponds to full suppression of viral replication: viral load below the detection level. The second state corresponds to an intermediate level of viral load: incomplete suppression of viral replication. This state is clinically relevant because the best strategy for patients with detectable viral load below 10000 copies is still a matter of debate. Finally, the third level corresponds to virological failure.

The Markov model is written as a multinomial logistic model. Let $p_{i,t,m,n}$ be the transition probability from state $m = \{1, 2, 3\}$ to state $n = \{1, 2, 3\}$ for the patient i at time t :

$$\begin{aligned}
 p(Y_{i,t}=n|Y_{i,t-6}=m, A_{i,t}, PI_{i,0}) &= p_{i,t,m,n} \\
 \eta_{i,t,m,n} &= \log\left(\frac{p_{i,t,m,n}}{p_{i,t,m,1}}\right) \\
 &= \gamma_0^{m,n} + \gamma_1^{m,n} PI_{i,0} + \gamma_2^{m,n} I(t \geq 24) + \gamma_3^{m,n} I(0 < A_{i,t} \leq 2) + \gamma_4^{m,n} I(A_{i,t} = 3) \quad (2) \\
 p_{i,t,m,n} &= \frac{\exp(\eta_{i,t,m,n})}{\sum_{l=1}^3 \exp(\eta_{i,t,m,l})}
 \end{aligned}$$

where $A_{i,t} = S_{i,t} + S_{i,t-1} + S_{i,t-2}$ is the number of non-adherent states during the 3 last months before time t for patient i , and $PI_{i,0} = 1$ if there is a PI in patient i 's initial therapy. Unlike the adherence model, the virological response model takes into account the presence of PI in the initial therapy. In fact, PI treatment changes were of short duration (PI were stopped during 1, or 2 months) and resulted from adverse effects of treatment or treatment shortage. Unlike adherence, virological response is measured every 6 months, and a PI treatment change can occur anytime within a 6 months interval. Given that $PI_{i,t-1}$ cannot be directly included in the virological response model, a covariate that captures a treatment change between two virological measurements was tested. This variable is not included in our final model, however, because of small interest and for parsimony reasons. Finally, we model the effect of time since inclusion as a binary covariate; however, this model may be generalized to include more covariates.

State 1 is chosen to be the reference state; for identifiability of the multinomial logistic model, the following constraints are imposed: $\gamma_0^{m,1} = \gamma_1^{m,1} = \gamma_2^{m,1} = \gamma_3^{m,1} = \gamma_4^{m,1} = 0$, for all $m = \{1, 2, 3\}$.

2.1.3. Time to resistance model—The time to resistance, R_i , is assumed to be discrete; and resistance status is available on a monthly visit: $R_i \in 1, \dots, T_i$. Resistance data are interval-censored and there was no set schedule for resistance testing. Physicians could request resistance tests when they judged it as necessary. This decision was usually driven by an elevated viral load in association with good adherence. Hence, it was assumed that the resistance test timing only depends on the virological response and the adherence data. A discrete logistic failure time model is used to study the time to resistance. The proposed model assumes that the hazard of resistance at time t is strictly positive only if the viral load at time t is above 500 copies/mL (virological state 2 or 3), i.e. the hazard of resistance is assumed to be null, when the patient's viral load is below detection. The proposed model can be written

$$h_{i,t} = p(R_i = t | R_i \geq t, \tilde{Y}_{i,t}, \tilde{A}_{i,t}, \text{PI}_{i,0}) = I(\tilde{Y}_{i,t} \geq 2) \frac{\exp(\mu_{i,t}^R)}{1 + \exp(\mu_{i,t}^R)} \quad (3)$$

where $h_{i,t}$ is the hazard of resistance at time t for patient i , $\tilde{Y}_{i,t}$ the assumed virological exposure, $\tilde{A}_{i,t}$ the assumed adherence exposure, and $\mu_{i,t}^R$ is the linear predictor of the time to resistance model:

$$\mu_{i,t}^R = I(\tilde{Y}_{i,t} = 2)(\delta_0^1 + \delta_1^1 \text{PI}_{i,0} + \delta_2^1 I(\tilde{A}_{i,t} \geq 2) + \delta_3^1 I(t > 12)) + I(\tilde{Y}_{i,t} = 3)(\delta_0^2 + \delta_1^2 \text{PI}_{i,0} + \delta_2^2 I(\tilde{A}_{i,t} \geq 2) + \delta_3^2 I(t > 12))$$

The linear predictor includes an effect of the presence of a PI in the therapy. PI-containing regimens are generally believed to have higher genetic barrier (number of mutations required to confer resistance) to resistance than do Nucleosidic Reverse Transcriptase Inhibitors (NRTIs) or Non-Nucleosidic Reverse Transcriptase Inhibitors (NNRTIs), especially when low-dose ritonavir (RTV) is used to boost levels of another PI [16].

Given that $Y_{i,t}$ is only measured at biannual visits, and that we want to measure the combined effect of $Y_{i,t}$ and $A_{i,t}$, $\tilde{Y}_{i,t}$ and $\tilde{A}_{i,t}$ are assumed to be piecewise constant:

$$\begin{aligned} \tilde{Y}_{i,0} &= \tilde{Y}_{i,1} = Y_{i,0} & \tilde{A}_{i,0} &= \tilde{A}_{i,1} = 0 \\ \tilde{Y}_{i,j} &= Y_{i,6} & \tilde{A}_{i,j} &= A_{i,6} & 2 \leq j \leq 9 \\ \tilde{Y}_{i,6k+j} &= Y_{i,6k} & \tilde{A}_{i,6k+j} &= A_{i,6k} & \forall k \geq 2 \in \mathbb{N}, -2 \leq j \leq 3 \end{aligned}$$

Although, $A_{i,t}$ is known at every time t , $\tilde{A}_{i,t}$ is introduced in linear predictor $\mu_{i,t}^R$. To study the combined effect of the adherence and the virological response on the time to resistance, we include in the time to resistance model, the adherence level that corresponds to the assumed virological response. For example, if we assume that $\mu_{i,4}^R$ depends on $\tilde{Y}_{i,4} = Y_{i,6}$ and that $Y_{i,6}$ depends on $A_{i,6}$, then it is necessary to include both $\tilde{Y}_{i,4}$ and $\tilde{A}_{i,4}$ in the time to resistance model at time $t = 4$ months.

The probability that the resistance mutation occurs at time t is then:

$$f_{i,t} = p(R_i = t | \tilde{Y}_i, \tilde{A}_i, \text{PI}_{i,0}) = h_{i,t} \prod_{l=1}^{t-1} (1 - h_{i,l}) \quad (4)$$

where $\tilde{Y}_i = (\tilde{Y}_{i,0}, \dots, \tilde{Y}_{i,t})$ and $\tilde{A}_i = (\tilde{A}_{i,0}, \dots, \tilde{A}_{i,t})$.

The probability that the resistance mutation occurs up to time t is:

$$F_{i,t} = p(R_i \leq t | \tilde{Y}_i, \tilde{A}_i, \text{PI}_{i,0}) = 1 - \prod_{l=1}^t (1 - h_{i,l}) \quad (5)$$

2.2. Inference

In the absence of missing or censored data, the complete likelihood of the joint model can be

written as: $\mathcal{L} = \prod_{i=1}^N \mathcal{L}_i$, where N is the number of patients. Suppose patient i has a resistance test after the inclusion; we let LN_i be the time of the last negative resistance test, FP_i be the time of the first positive resistance test, if patient i was tested positive during the

follow-up, and v_i an indicator of censoring, i.e. $v_i = 1$ if patient i was tested positive during the follow-up. If patient i was never tested positive, $FP_i = \infty$ and $v_i = 0$.

Patient i 's contribution to the complete likelihood is

$$\begin{aligned} \mathcal{L}_i &= p(Y_{i,6}, \dots, Y_{i,T_i}, S_{i,1}, S_{i,2}, \dots, S_{i,T_i}, LN_i, FP_i | Y_{i,0}, S_{i,0}, \mathbf{PI}_i, v_i, \beta, u_{0,i}, u_{1,i}, u_{2,i}, \gamma, \delta) \\ \mathcal{L}_i &= p(LN_i < R_i \leq FP_i | \tilde{Y}_i, \tilde{A}_i, \mathbf{PI}_{i,0}, \delta)^{v_i} p(R_i > LN_i | \tilde{Y}_i, \tilde{A}_i, \mathbf{PI}_{i,0}, \delta)^{1-v_i} \\ &\times \prod_{t=6 \dots T_i} p(Y_{i,t} | Y_{i,t-6}, A_{i,t}, \mathbf{PI}_{i,0}, \gamma) \prod_{t=1}^{T_i} p(S_{i,t} | S_{i,t-1}, \mathbf{PI}_i, \beta, u_{0,i}, u_{1,i}, u_{2,i}) \\ \mathcal{L}_i &= \left(\sum_{j=LN_i+1}^{FP_i} f_{i,j} \right)^{v_i} (1 - F_{i,LN_i})^{1-v_i} \\ &\times 1 \prod_{t=6 \dots T_i} (p_{i,t,Y_{i,t-6},1})^{I(Y_{i,t}=1)} (p_{i,t,Y_{i,t-6},2})^{I(Y_{i,t}=2)} (p_{i,t,Y_{i,t-6},3})^{I(Y_{i,t}=3)} \\ &\times \prod_{t=1}^{T_i} \left(\frac{\exp(\mu_{i,t}^S)}{1 + \exp(\mu_{i,t}^S)} \right)^{S_{i,t}} \left(\frac{1}{1 + \exp(\mu_{i,t}^S)} \right)^{1-S_{i,t}} \end{aligned} \quad (6)$$

where $\beta = \{\beta_0, \beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6\}$ are the fixed effect parameters of the adherence model (equation (1)), $\gamma = \{\gamma_0^{m,n}, \gamma_1^{m,n}, \gamma_2^{m,n}, \gamma_3^{m,n}, \gamma_4^{m,n}\}$ with $m = 1, 2, 3$ and $n = 1, 2, 3$ are the parameters of the virological response model (equation (2)), $\delta = \{\delta_0^1, \delta_1^1, \delta_2^1, \delta_3^1, \delta_0^2, \delta_1^2, \delta_2^2, \delta_3^2\}$ are the parameters of the resistance model (equation (3)), and $\mathbf{PI}_i = \mathbf{PI}_{i,0} \dots \mathbf{PI}_{i,T_i}$. In absence of missing data, and conditionally to the random effects, the three parts of the previous likelihood can be maximized separately.

The part of the complete likelihood corresponding to the resistance model is

$\left(\sum_{j=LN_i+1}^{FP_i} f_{i,j} \right)^{v_i} (1 - F_{i,LN_i})$ (see equation (6) above). If patient i presents a last negative resistance test at month 3 (i.e. $LN_i = 3$) and a first positive test at month 11 (i.e. $FP_i = 11$ and $v_i = 1$), the contribution of patient i to the resistance model likelihood is $\sum_{j=4}^{11} f_{i,j}$. If patient i has a last negative resistance test at month 2 (i.e. $LN_i = 2$ and $v_i = 0$), the contribution of patient i to the resistance model likelihood is $1 - F_{i,2}$. If patient i is never tested for resistance mutations, $LN_i = 0$, $v_i = 0$, and $F_{i,0} = 0$; hence patient i does not contribute to the resistance model likelihood.

Inference was performed in a Bayesian framework. Let $\Phi = (\beta, \Sigma, \gamma, \delta)$ be the whole set of parameters. Independent prior distributions were assumed for the parameters. Normal priors $N(0, 1000)$ were used for β_k , $0 \leq k \leq 6$, for $\gamma_k^{m,n}$, $0 \leq k \leq 4$, $1 \leq m \leq 3$, $2 \leq n \leq 3$, and for δ_k^j , $j = 1, 2$ and $k = 0, 1, 2, 3$.

Finally, a Wishart(R, ρ) prior was specified for Σ^{-1} the 3×3 precision matrix of the random effects. The degrees of freedom, ρ , was set at the minimum value 3 to represent vague prior knowledge. The scale matrix R was a diagonal matrix with diagonal elements equal to 1; it represents our prior guess of the covariance matrix Σ .

The posterior distribution of interest is $p(\Phi | \mathbf{Y}^{\text{obs}}, \mathbf{S}^{\text{obs}}, \mathbf{LN}, \mathbf{FP})$.

Gibbs sampling [17, 18] is used to approximate drawing from $p(\Phi, \mathbf{Y}^{\text{miss}}, \mathbf{S}^{\text{miss}}, u_0, u_1, u_2 | \mathbf{Y}^{\text{obs}}, \mathbf{S}^{\text{obs}}, \mathbf{LN}, \mathbf{FP})$. The empirical marginal distribution of Φ is then summarized to obtain an approximation of $p(\Phi | \mathbf{Y}^{\text{obs}}, \mathbf{S}^{\text{obs}}, \mathbf{LN}, \mathbf{FP})$. On a given iteration of the Gibbs sampler, we sample in turn from the posterior conditional distribution of each unknown parameter, random effect, or missing covariate given the observed data and the current values of all other parameters, random effects, and missing/censored covariates. Appendix A gives some

details on how to write the posterior conditional distribution of each parameters, taking β_1 as an example. WinBUGS [19] was used for the Gibbs sampling; parameter estimates were based on 20 000 iterations and the first 2500 iterations were discarded. Convergence was assessed using the Gelman–Rubin convergence statistics, as modified by Brooks and Gelman [20]. For each parameter, posterior mean and 95 per cent central credible interval [18] will be reported.

2.3. Model checking

2.3.1. Adherence model—We first check the posterior distribution of the random effects $u_{0,i}$, $u_{1,i}$ and $u_{2,i}$, $i = 1 \dots N$. The distribution of the posterior expectations of the random effects is compared with a Normal distribution. The posterior expectation $E(u_{0,i} |$

$\mathbf{Y}^{\text{obs}}, \mathbf{S}^{\text{obs}}, \mathbf{LN}, \mathbf{FP}$) of $u_{0,i}$ is approximated by $(1/m) \sum_{k=1}^m u_{0,i}^k$, with $u_{0,i}^k$ obtained from the k th iteration of the Gibbs sampling of length m . We obtain $E(u_{1,i} | \mathbf{Y}^{\text{obs}}, \mathbf{S}^{\text{obs}}, \mathbf{LN}, \mathbf{FP})$ and $E(u_{2,i} | \mathbf{Y}^{\text{obs}}, \mathbf{S}^{\text{obs}}, \mathbf{LN}, \mathbf{FP})$ in the same way.

Posterior predictive checks permit detection of systematic differences between the model and the observed data, by generating replicated data sets from the posterior predictive distribution of the model under consideration. These replicated data sets are then compared with the observed data set with respect to features of interest [18].

We replicate the data set using exactly the same number of patients N , of adherence states per patient, as well as the same matrix of predictors as in the observed data set. Simulation of replicated data for a new patient is performed sequentially. For each iteration k of the Gibbs sampling, for each patient i , and for each time $t = 1 \dots T_i$:

- compute the following linear predictor:

$$\mu_{i,t}^{S,k} = \beta_0^k + u_{0,i}^k + S_{i,t-1}^{\text{repl},k} (\beta_1^k + u_{1,i}^k) + S_{i,t-2}^{\text{repl},k} (\beta_2^k + u_{2,i}^k) + \beta_3^k \text{PI}_{i,t-1} + \beta_4^k \text{PI}_{i,t-1} \times S_{i,t-1}^{\text{repl},k} + \beta_5^k I(12 < t \leq 24) + \beta_6^k I(t > 24)$$

where $S_{i,t-1}^{\text{repl},k}$ is the previous replicated states and $S_{i,t-2}^{\text{repl},k}$ is the penultimate replicated states for patient i at time t

- draw $S_{i,t}^{\text{repl},k} \sim \text{Bernouilli}(\exp(\mu_{i,t}^{S,k}) / (1 + \exp(\mu_{i,t}^{S,k})))$

Four test quantities are computed to evaluate quality of model fit:

- the mean of the proportion of time a patient is not adherent:

$$T_1(S) = \frac{1}{N} \sum_{i=1}^N \frac{1}{T_i} \sum_{l=1}^{T_i} S_{i,l}$$

- the variance of the proportion of time a patient is not adherent:

$$T_2(S) = \frac{1}{N} \sum_{i=1}^N \left(\frac{1}{T_i} \sum_{l=1}^{T_i} S_{i,l} - T_1(S) \right)^2$$

- the mean of the proportion of adherence state changes per patient:

$$T_3(S) = \frac{1}{N} \sum_{i=1}^N \frac{1}{T_i-1} \sum_{l=2}^{T_i} I(|S_{i,l} - S_{i,l-1}|=1)$$

- the variance of the proportion of adherence state changes per patient:

$$T_4(S) = \frac{1}{N} \sum_{i=1}^N \left(\frac{1}{T_i-1} \sum_{l=2}^{T_i} I(|S_{i,l} - S_{i,l-1}|=1) - T_3(S) \right)^2$$

Given that the observed test quantities $T_1(S)$, $T_2(S)$, $T_3(S)$, and $T_4(S)$ can only be computed on the subset of observed data (S^{obs}), the replicated statistics are computed on the corresponding subset of replicated data. For each iteration of the Gibbs sampler, we obtain a replicated data set, and then compute the test quantities on these replicated data set:

$T_1(S^{\text{repl}})$, $T_2(S^{\text{repl}})$, $T_3(S^{\text{repl}})$, and $T_4(S^{\text{repl}})$. The distribution of each observed test quantity is compared with the posterior predictive distribution of each test quantity. The statistical significance of the test is summarized by a p -value: $p(T(S^{\text{repl}}) > T(S) | S^{\text{obs}}) = \int p(T(S^{\text{repl}}) > T(S) | S^{\text{obs}}, \beta, u_0, u_1, u_2) p(\beta, u_0, u_1, u_2 | S^{\text{obs}}) d\beta du_0 du_1 du_2$. The last quantity can

be approximated from the Gibbs sampling simulations by $1/K \sum_{k=1}^K I(T(S^{\text{repl},k}) > T(S))$, where $S^{\text{repl},k}$ is the k th replicated data set.

2.3.2. Virological model—To evaluate the fit of the virological response model, we replicate the data set using exactly the same number of patient N , of adherence states per patient, of virological states per patient, as well as the same matrix of predictors as in the observed data set. Simulation of replicated data for a new patient is performed sequentially. For each iteration k of the Gibbs sampling, for each patient i , and for each time $t = 6, 12, \dots, T_i$:

- compute the following linear predictors, $n = 1, 2, 3$ and $m = Y_{i,t-6}^{\text{repl},k}$:

$$\eta_{i,t,m,n}^k = \gamma_0^{m,n,k} + \gamma_1^{m,n,k} \text{PI}_{i,o} + \gamma_2^{m,n,k} I(t \geq 24) + \gamma_3^{m,n,k} I(0 < A_{i,t}^k \leq 2) + \gamma_4^{m,n,k} I(A_{i,t}^k = 3)$$

where $A_{i,t}^k$ equals to $A_{i,t}^{\text{obs}} = S_{i,t}^{\text{obs}} + S_{i,t-1}^{\text{obs}} + S_{i,t-2}^{\text{obs}}$ if the three states $S_{i,t}$, $S_{i,t-1}$, and $S_{i,t-2}$ are observed or to the imputed value from its posterior distribution, obtained from the k th iteration of the Gibbs sampler.

- compute the corresponding probabilities, $n = 1, 2, 3$:

$$p_{i,t,m,n}^k = \frac{\exp(\eta_{i,t,m,n}^k)}{\sum_{l=1}^3 \exp(\eta_{i,t,m,l}^k)}$$

- sample $Y_{i,t}^{\text{repl},k}$ from a Multinomial distribution with vector of probabilities $(p_{i,t,m,1}^k, p_{i,t,m,2}^k, p_{i,t,m,3}^k)$.

Nine test quantities are computed: $T_1(Y) = \sum_{i=1}^N \sum_{t=6,12,\dots,T_i} I(Y_{i,t-6}=1 \text{ and } Y_{i,t}=1)$, the number of transitions from state 1 to state 1, $T_2(Y) = \sum_{i=1}^N \sum_{t=6,12,\dots,T_i} I(Y_{i,t-6}=1 \text{ and } Y_{i,t}=2)$, the number of transitions from state 1 to state 2, etc.

As previously described, each observed test quantity is compared with its posterior predictive distribution, and the corresponding p -values are computed.

2.3.3. Resistance model—We also perform evaluation of fit of the resistance model. For all the patients in the cohort with at least one resistance test, we replicate the resistance time, using for each patient, the observed adherence pattern, the observed virological response, and the observed matrix of predictors. For each iteration k of the Gibbs Sampling, for each patient i with at least one resistance test, and for each time $t = 1 \dots T_i$:

- compute the following linear predictor:

$$\mu_{i,t}^{R,k} = I(\tilde{Y}_{i,t}^k = 2)(\delta_0^{1,k} + \delta_1^{1,k} \text{PI}_{i,0} + \delta_2^{1,k} I(\tilde{A}_{i,t}^k \geq 2) + \delta_3^{1,k} I(t > 12)) + I(\tilde{Y}_{i,t}^k = 3)(\delta_0^{2,k} + \delta_1^{2,k} \text{PI}_{i,0} + \delta_2^{2,k} I(\tilde{A}_{i,t}^k \geq 2) + \delta_3^{2,k} I(t > 12))$$

where $\tilde{A}_{i,t}^k$ and $\tilde{Y}_{i,t}^k$ (resp.) are set equal to the observed $\tilde{A}_{i,t}^{\text{obs}}$ and $\tilde{Y}_{i,t}^{\text{obs}}$ (resp.) if observed, or, if missing, to the imputed value from their posterior distribution, obtained from the k th iteration of the Gibbs Sampling.

- compute the corresponding hazard of resistance:

$$h_{i,t}^k = p(R_i^k = t | R_i \geq t, \tilde{Y}_{i,t}^k, \tilde{A}_{i,t}^k, \text{PI}_{i,0}) = I(\tilde{Y}_{i,t}^k \geq 2) \frac{\exp \mu_{i,t}^{R,k}}{1 + \exp \mu_{i,t}^{R,k}}$$

- sample $R_i^{\text{repl},k}$, the replicated time to resistance for patient i , from the vector of hazards $h_{i,t}^k$.

For each iteration of the Gibbs Sampling procedure, we fit a Kaplan–Meier replicated survival curve using the replicated time to resistance for each patient. Finally, the replicated survival curves are compared with the observed survival. Given that the observed time to resistance are interval censored, a non-parametric Turnbull estimator [21] is used to study the observed survival.

2.4. Predictions

If a large amount of information were available, the proposed model could be used for prediction for a new patient. We assume here that partial data on such a patient has been previously observed but not used for parameter estimation. For illustration, we present results for a hypothetical patient, for whom we assume an adherence and a virological response profile up to a given time point, and a resistance status. In particular, this new patient is assumed to have a biannual follow-up visit at time t_b , resistance status at time t_b denoted $R_{t_b}^*$, virological response at time t_b denoted $Y_{t_b}^*$, and adherence history up to time t_b (included) denoted $S_{t_b-}^*$ are assumed to be known. We predict the adherence states up to time $t_b + 6$ denoted $S_{t_b+1}^*, \dots, S_{t_b+6}^*$, the virological response at time $t_b + 6$ denoted $Y_{t_b+6}^*$, and the resistance status at time $t_b + 6$ denoted $R_{t_b+6}^*$. Let data = $\{Y^{\text{obs}}, S^{\text{obs}}, \text{LN}, \text{FP}\}$ be the set of observed data. The posterior predictive distribution of $R_{t_b+6}^*, Y_{t_b+6}^*, S_{t_b+1}^*, \dots, S_{t_b+6}^*$ is:

$$\begin{aligned}
p(R_{t_b+6}^*, Y_{t_b+6}^*, S_{t_b+1}^*, \dots, S_{t_b+6}^* | \text{data}, R_{t_b}^*, Y_{t_b}^*, S_{t_b-}^*) &= p(R_{t_b+6}^* | \text{data}, R_{t_b}^*, Y_{t_b+6}^*, S_{t_b+6}^*, S_{t_b+5}^*, S_{t_b+4}^*) \\
&\times p(Y_{t_b+6}^* | \text{data}, Y_{t_b}^*, S_{t_b+6}^*, S_{t_b+5}^*, S_{t_b+4}^*) \\
&\times p(S_{t_b+6}^* | \text{data}, S_{t_b+5}^*, S_{t_b-}^*) \\
&\times \dots \times p(S_{t_b+1}^* | \text{data}, S_{t_b-}^*)
\end{aligned}$$

We first sample $S_{t_b+1}^*, \dots, S_{t_b+6}^*$ from their posterior predictive distribution, then $Y_{t_b+6}^*$ from its posterior predictive distribution $p(Y_{t_b+6}^* | \text{data}, Y_{t_b}^*, S_{t_b+6}^*, S_{t_b+5}^*, S_{t_b+4}^*)$, and finally $R_{t_b+6}^*$ from its posterior predictive distribution $p(R_{t_b+6}^* | \text{data}, R_{t_b}^*, Y_{t_b+6}^*, S_{t_b+6}^*, S_{t_b+5}^*, S_{t_b+4}^*)$. Sampling $Y_{t_b+6}^*$ and $R_{t_b+6}^*$ from their posterior predictive distribution is straightforward. We detail how to sample $S_{t_b+1}^*$ from $p(S_{t_b+1}^* | \text{data}, S_{t_b-}^*)$:

$$\begin{aligned}
p(S_{t_b+1}^* | \text{data}, S_{t_b-}^*) &= \int p(S_{t_b+1}^* | \beta, u_0^*, u_1^*, u_2^*, S_{t_b}^*) p(\beta, u_0^*, u_1^*, u_2^*, \Sigma | \text{data}, S_{t_b-}^*) d\beta du_0^* du_1^* du_2^* d\Sigma \\
p(\beta, u_0^*, u_1^*, u_2^*, \Sigma | \text{data}, S_{t_b-}^*) &= p(\beta, \Sigma | \text{data}) p(u_0^*, u_1^*, u_2^* | \beta, \Sigma, S_{t_b-}^*) \\
p(u_0^* | u_1^*, u_2^*, \beta, \Sigma, S_{t_b-}^*) &= \prod_{j=1}^{t_b} p(S_{t_j}^* | S_{t_{j-1}}^*, u_0^*, u_1^*, u_2^*, \beta) p(u_0^* | \Sigma) \\
p(u_1^* | u_0^*, u_2^*, \beta, \Sigma, S_{t_b-}^*) &= \prod_{j=1}^{t_b} p(S_{t_j}^* | S_{t_{j-1}}^*, u_0^*, u_1^*, u_2^*, \beta) p(u_1^* | \Sigma) \\
p(u_2^* | u_0^*, u_1^*, \beta, \Sigma, S_{t_b-}^*) &= \prod_{j=1}^{t_b} p(S_{t_j}^* | S_{t_{j-1}}^*, u_0^*, u_1^*, u_2^*, \beta) p(u_2^* | \Sigma)
\end{aligned}$$

We use a Gibbs sampler to sample in turn from the posterior distribution of $\beta, \Sigma | \text{data}$, from the conditional posterior predictive distribution of $u_0^* | u_1^*, u_2^*, \beta, \Sigma, S_{t_b-}^*$, from the conditional posterior predictive distribution of $u_1^* | u_0^*, u_2^*, \beta, \Sigma, S_{t_b-}^*$, from the conditional posterior predictive distribution of $u_2^* | u_0^*, u_1^*, \beta, \Sigma, S_{t_b-}^*$ and finally from the model distribution of $S_{t_b+1}^* | \beta, u_0^*, u_1^*, u_2^*, S_{t_b}^*$. The same approach is used to sample from $S_{t_b+2}^* \dots S_{t_b+6}^*$ from their posterior predictive distribution. In practice, the `cut` () function from WinBUGS was used to sample from the posterior predictive distribution of u_0^*, u_1^* and u_2^* .

3. Application

3.1. Description of the Dakar cohort

The Dakar cohort was composed of 404 patients enrolled between 1998 and 2002. The details of the study population, inclusion and exclusion criteria have been previously published [22, 23]. First-line treatment regimens were 2 NRTI (3TC, D4T, DDI, AZT) + 1 NNRTI (NVP, EFZ) or 2 NRTI + PI (IDV, NFV). Follow-up was censored at the first-treatment change maintained for at least 5 months, associated with virological failure (following WHO recommendations [24]). Virological evaluations were carried out at the inclusion and every 6 months thereafter, and the median proportion of missing virological data per patient was 20 per cent. Adherence to antiretroviral therapy was measured every month as the proportion of pills taken among the pills prescribed. However, some patients received their treatment for a two-month period, and only the adherence during the month previous to each two-monthly visit was recorded. Moreover, the systematic recording of adherence data began a while after the inclusion in the cohort for many patients, leading to a high level of missing adherence data. Consequently, the median proportion of missing adherence data per patient after start of the recording was 42 per cent (66 per cent

considering the whole follow-up). Among the 404 patients included in the Dakar cohort, 337 had at least 2 measurements, a virological measurement before 12 months (exclusive) and a follow-up ≥ 6 months. Among these patients, the median follow-up time was 48 months; 135 (40 per cent) of the patients had a PI in the initial therapy. Moreover, 132 patients had at least 1 resistance test. Genotypic resistance interpretation was performed with the ANRS algorithm (www.hivfrenchresistance.org). A patient was considered to be resistant if the ANRS algorithm reported an evidence of drug resistance for one of the drug included in the therapy. The following resistance data were excluded:

- patients tested positive at the inclusion ($N = 4$). These patients were not ART-naïve,
- patients with only one test, negative, at the inclusion ($N = 17$).

As previously mentioned, follow-up was censored at the first treatment change. Consequently:

- nine patients without positive tests were censored before their last negative test (treatment change occurs before their last negative test),
- nine patients with a positive test were censored before their last negative test (treatment change occurs before the last negative test, for patients with a positive test),
- one patient with a positive test was censored before its first positive test (treatment change occurs between the last negative test and the first positive test).

Among the 111 patients considered in the analysis with at least 1 resistance test, 57 (51.3 per cent) patients had a positive resistance test. The median duration between the last negative test and the first positive test among patients with a positive resistance test was 20 months. The median time of the last negative test among patients never tested positive was 24.5 months.

Figure 1 presents observed the virological response, the adherence pattern, and the number of non-adherence states among the 3 last months, according to the time since HAART initiation, for 2 patients. Patient A (left panel) has a last negative resistance test at time $t = 35$ months; this patient received a PI in combination with other drugs during all the entire follow-up period (PI = 1 during all the follow-up); patient B (right panel) has a positive resistance test at time $t = 24$ months, and did not receive a PI during the follow-up period (PI = 0 during all the follow-up). A point in the A -plots (number of non-adherent states among the three last states) is observed at time t only if the three adherence states before time t are observed. However, all the observed adherence states are used to estimate the missing points.

Finally, Figures B1–D1 present respectively summaries of adherence patterns (mean and variance of the proportion of time a patient is non-adherent, and mean and variance of the proportion of state changes per patient), virological response patterns (observed number of transitions from virological state 1,2, and 3 to virological state 1,2 and 3), and non-parametric estimation of the survival time without resistance.

3.2. Adherence to antiretroviral therapy

Posterior distribution features of the parameters are presented in Table I. Within the first year of HAART without PI, the estimated probability of becoming non-adherent was $\text{antilogit}(-2.0) = 0.08$ [0.07;0.10]. The between-patient variance of the current adherence state was high: $\sigma_0^2 = 0.90$ [0.62;1.27]. Indeed, the OR of non-adherence for a patient with a u_0 random effect (random effect of the current adherent states) in the 75th percentile of the u_0

random effect distribution vs a patient with a u_0 random effect in the 25th percentile of the u_0 random effect distribution was 3.61 [2.88; 4.57]. The probability of remaining non-adherent for a patient who was non-adherent during the two previous months was 0.23 [0.16;0.31]. The between-patient variance of the previous state random effect was $\sigma_1^2=0.63$ [0.24;1.19]. The OR of non-adherence for a patient with a u_1 random effect (random effect of the previous adherence state) in the 75th percentile of the u_1 random effect distribution vs a patient with a u_1 random effect in the 25th percentile of the u_1 random effect distribution was 2.92 [1.94; 4.35]. Finally, the between-patient variance of the penultimate state random effect was 0.44 [0.20;0.80]. The OR of non-adherence for a patient with a u_2 random effect (random effect of the penultimate adherence state) in the 75th percentile of the u_2 random effect distribution vs a patient with a u_2 random effect in the 25th percentile of the u_2 random effect distribution was 2.45 [1.82; 3.33]. The inclusion of a PI in the therapy significantly increased the probability of becoming non-adherent: OR = 1.65 [1.22;2.16]. The adherence probability was also significantly associated with the duration of the therapy: the OR of non-adherence for a patient in its second year of treatment vs a patient beginning HAART was 1.74 [1.37;2.19], and the OR of non-adherence for a patient on HAART for more than two years vs a patient beginning HAART was 2.45 [1.98;3.00].

Figure 2 presents quantile–quantile plots of the distribution of the posterior means of the current adherence state (u_0), previous adherence state (u_1), and penultimate (u_2) random effects against the normal distribution. There was no evidence of departure of the distribution of the posterior means of the intercept random effects from normality. The distribution of the previous and penultimate random effects appeared to have a heavier tail than expected. A small proportion of patients had particularly long sequences of consecutive adherent or non-adherent states. The posterior predictive distributions of the four test quantities (T_1 , T_2 , T_3 , T_4) were also computed; there was no evidence to suggest discrepancy between the model and observed data (see Appendix B, Figure B1).

3.3. Virological response

Table II presents posterior mean and 95 per cent credible intervals of the virological model parameters (equation (2)), and Figure 3 presents the transition probabilities from state $m=1,2,3$ to state $n=1,2,3$ according to the presence of a PI in the initial therapy, the time since inclusion in the cohort, and the adherence to antiretroviral therapy. The presence of a PI in the initial therapy significantly increased the transition probabilities from state 1 to state 2 and 3, and the probability of remaining in 3; the odds of transition from state 1 to 2 vs staying in state 1 were multiplied by 2.44 [1.52;3.77] for a patient with a PI vs a patient without PI in the initial therapy. A longer time since inclusion in the cohort significantly decreased the transition probabilities from state 1 to 2 and 3, and significantly increased the transition probabilities from state 3 to state 2 or 3. The odds of staying in state 1 vs transition from state 1 to 3 were multiplied by 3.83 [2.02;6.89] for a patient who has been followed for more than 2 years vs a patient who has been followed for less than 2 years. On the contrary, the odds of staying in state 3 vs transition from state 3 to 1 were multiplied by 18.42 [9.89;32.49] for a patient who has been followed for more than 2 years vs a patient who has been followed for less than 2 years. Finally, non-adherence to antiretroviral therapy significantly increased the transitions from state 1 to 2 and 3, and significantly decreased the transitions from state 2 and 3 to state 1. The odds of transition from state 1 to 3 vs staying in state 1 were multiplied by 66.65 [9.76;267.74] for a patient never adherent during the 3 months preceding the virological measurement vs a patient perfectly adherent during the 3 months preceding the virological measurement.

The posterior predictive distributions of the nine tests quantities were computed; there was no evidence of discrepancy between the model and data (see Appendix C, Figure C1).

3.4. Time to resistance

Table III presents the posterior distribution features (mean, median and 95 per cent credible intervals) of the hazard rate (per month) of resistance at time t according to the virological state, the adherence, the presence of a PI in the therapy, and the effect of time since HAART initiation (within or after the first year of treatment) for patients in virological state 3. Effect of time since HAART initiation for patients in virological state 2 was not significant and removed for parsimony reasons ($\delta_3^1 = 0.34 [-1.98; 4.19]$ cf. equation (3)). By contrast, the effect of time since HAART initiation for patients in virological state 3, although not significant, was large in magnitude: the odds of the hazard of resistance (i.e. $h_{i,t}(1 - h_{i,t})$) for a patient in their first year of therapy were multiplied by 2.92 [0.89; 47.66] vs a patient under treatment for more than 1 year. The presence of a PI in the therapy significantly decreased the hazard of resistance at time t for patients in virological state 2 (viral load between 500 and 10000 copies/mL); the odds of the hazard of resistance were multiplied by 4.19 [1.27; ∞] for a patient without a PI in the therapy vs a patient with a PI in the therapy. Although not significant, non-adherent patients with detectable viral load had a lower risk of resistance than did adherent patients ($\delta_2^1 = -7.31 [-22.32; 2.74]$ and $\delta_2^2 = -2.77 [-17.12; 2.47]$).

The replicated time to resistance survival curves and the time to resistance survival estimated with the Turnbull non-parametric estimator are presented in Figure D1 (Appendix D). Although the Turnbull estimated survival appears higher than the replicated survival in the beginning, this can be explained by the limitation of the data. Intervals are wide in the beginning, and therefore provide no basis for inference. Hence, there is no evidence of discrepancy between the model and data.

3.5. Predictions

Figure 4(a) presents the predicted adherence process, the predicted virological response, and the predicted resistance status for a new patient whose therapy did not include a PI and who was perfectly adherent for 12 months and was in virological state 1 at 12 months. Figure 4(b) differs in that the new patient is assumed to be never adherent for the first 12 months. Predicted adherence profiles and predicted virological response differed sharply; at time $t = 66$ months, the predicted probability to be in virological state 3 was 10.1 per cent and 53.9 per cent for patient (a) and patient (b), respectively. By contrast, the predicted resistance status was very similar: the predicted probability for patient (a) or patient (b) to have a resistance mutation at time $t = 66$ months was around 33 per cent. This absence of difference can be explained by the fact that although patient (b) had a poor virological response, the patient was poorly adherent and hence not exposed to antiretroviral therapy.

Patient (c) was assumed to be perfectly adherent for 30 months, and in virological state 3 at 30 months, whereas patient (d) was assumed to be never adherent for 30 months, but also in virological state 3 at 30 months. As expected, these patients had different predicted adherence profiles and virological responses. The predicted probability of resistance at $t = 66$ months was higher for patient (c) (54.7 per cent) than for patient (d) (44.3 per cent) because patient (c) combined good adherence and bad virological response at 30 months.

Patient (e) was assumed to be perfectly adherent for 12 months, whereas patient (f) was assumed to be never adherent for 12 months. Both patients were assumed to have no PI in their therapy, and to be in virological state 2 at 12 months. Because the estimated hazard of resistance in state 2 was high (Table III), the predicted probabilities for these 2 patients to have a resistance mutation at time $t = 66$ months was very high: 72 per cent.

The same adherence and virological status assumptions were made for patient (g) and patient (h) but they were assumed to have a PI in their therapy. As expected, the predicted probability for these two patients to have a resistance mutation at time $t = 66$ was much lower: 33 per cent.

4. Discussion

In this article, we propose a joint model to study adherence to the HAART therapy, virological response, and time to development of at least one resistance mutation. The joint model allows investigation of two intermittently observed time-dependent covariates: the adherence state process, and the virological response. A logistic mixed model was used for the time-dependent adherence process and a Markov model for virological response. The autoregressive linear model proposed by Huang *et al.* [8] relies on the definition of the track, i.e. ‘on-track’ for suppression of HIV-RNA levels below the limits of detection, and ‘off-track’ for deviation from this response. It would be difficult to identify the track in the Dakar cohort, given the high level of missing viral load measurements, and occasional episodes of poor adherence. In our study, model checking did not reveal discrepancy between the virological Markov model and observed data. Another advantage of the Markov model was that it did not require specific modeling tools to handle-censored data, i.e. viral load measurements below the detection level. The latent adherence and virological states were then included in the linear predictor of the time to resistance model. Resistance tests were not available for all the patients in the cohort; and adherent patients with high viral load levels were more likely to be tested than other patients. Hence, it was necessary to include these two confounders in the time to resistance model.

Since emergence of drug resistance requires ongoing of viral replication, the proposed time to resistance model assumes a null hazard when the viral load is below the detection level. The proposed model assumes no delay between exposure and emergence of resistance mutations. It would be interesting to study this delay, using for example time-promotion-based models ([25, 26]); however, this would require more frequent virological measurements and drug resistance tests. Given that resistance tests were not necessarily performed during biannual visits, the hazard of resistance had to be modeled monthly. Hence, the virological response was included as a piecewise constant covariate in the time to resistance model. To evaluate the sensitivity to this hypothesis, we performed an additional analysis in which patients were assumed to be exposed to the previous virological state level until the next biannual visit; results were qualitatively the same.

We used a Bayesian approach for the joint model inference. In the Bayesian framework missing variables and random effects are treated as parameters, requiring no special missing data techniques. We proposed posterior predictive model checks for the adherence, the virological response, and the time to resistance models. Model evaluation did not reveal major problems with fit. We also performed predictions for new patients, given their disease history up to the last visit. Such predictions would be helpful in clinical practice, because the optimal timing of resistance testing or changes in antiretroviral therapy has not been established, especially in resource-limited countries. However, given the limitations of available data, we do would not consider our fitted model to be a practical prognostic tool. In the present context, predictions are more useful to illustrate the relationships among virological response, adherence and emergence of resistance mutation. It would be necessary to have a larger independent data set with more resistance data to validate this model more extensively. Cross-validation is a useful way to estimate the prediction error, when no independent validation data set is available. Although theoretically feasible, it is particularly computationally intensive to perform cross-validation in a Bayesian framework. Moreover, the proposed model is not a classification model with a binary outcome, but instead a

longitudinal model with three outcomes. Hence, there is no obvious way to summarize a patient outcome.

Adherence to the Dakar cohort was fairly high: within the first year of HAART without PI, the probability of becoming non-adherent for an adherent/on-track patient was 0.08 [0.07;0.10]; however, the between-patient variability was also very high. As previously shown by Etard *et al.* [23], the adherence probability was significantly associated with presence of a PI in the therapy, and the duration of the therapy. There was no evidence of discrepancy between the Markov model and the observed virological profiles. Transition probabilities were associated with time since inclusion in the cohort. After two years of treatment, patients in virological state 1 (undetectable viral load) are more likely to stay in state 1 than patients treated for less than 2 years. By contrast, after 2 years of treatment patients in virological state 3 (viral load > 10 000 copies/mL) have a higher probability of staying in state 3 than patients treated for less than 2 years. There was also an association between virological transition probabilities and adherence to treatment. As expected, poor adherence to antiretroviral therapy significantly increased the transition probabilities from virological state 1 to 2, and from virological state 3 to 2 or 3.

The estimated hazard rate of resistance for a patient in virological state 2 ($500 < \text{viral load} < 10000 \text{ copies/mL}$) not treated with a PI was 0.21 [0.08;0.39] per month. The presence of PI in the therapy significantly decreased the hazard of resistance. As proposed by Friedland and Williams [27], the relationship is thought to be ‘bell shaped’, implying that complete adherence and total non-adherence to HAART are associated with low probabilities of resistance, whereas intermediate levels of adherence increase the risk of resistance. In the Dakar cohort, poor adherence seemed to decrease the hazard of resistance, although the effect is not statistically significant. However, it was not possible to investigate further the relationship between time to resistance, adherence and virological response due to the sparseness of the data.

Hu and De Gruttola [6] modeled jointly the progression of HIV resistance mutations and failure time data. In particular, they used a hidden Markov model to fit the viral genetic process, and included the uncertain genetic state as a time-dependent covariate in a Cox model for failure time. In contrast, we included the latent virological state as a time-dependent covariate in a discrete logistic failure time model for the time to first resistance mutation. Consequently, the proposed model did not include the effect of emerging resistance mutations on the virological response; this should be taken into account when interpreting predictions. Both relationships are of interest. However, it would require much more genetic and virological data to study simultaneously both relationships in a model that included cyclic relationships.

Finally, we used a Missing At Random assumption, which allows the missingness to depend on the covariates included in the model. As such, our approach is valid under a broader set of assumptions than would be the case for a Missing Completely At Random assumption; in fact, it is the best one could do in this setting. In the virological model, the probability of a missing viral load at time t is allowed to depend on the previous viral load measurement, the adherence pattern within the three last months, the time since inclusion in the cohort, and the presence of a PI in the therapy. Although not verifiable, it appears reasonable that these covariates include the major drivers of the probability of having a missing viral load. Adherence data can be missing for two main reasons: late recording of adherence data and having the adherence schedule reduced to every 2 months for stable patients treated for a long time. Given that time effect is included in the adherence, the MAR assumption appears reasonable here as well. Another possible extension of our approach would be to model the missingness and the censoring processes. Our approach could be extended to allow for joint

modeling of adherence to treatment, virological response, time to resistance, and the missingness and censoring process, but attaining convergence of the relevant algorithms would require a great deal more data.

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Appendix A: Posterior conditional distributions for GIBBS sampling

The Gibbs Sampling requires the posterior conditional distributions of unknown parameters, random effect, or missing covariate given the observed data and the current values of all other parameters, random effects, and missing/censored covariates. Here, β_1 is taken as an example. Let $N, Y^{obs}, Y^{miss}, S^{obs}, S^{miss}, LN, FP, u_0, u_1, u_2$, and $\Phi^{-\beta_1}$ be, respectively, the number of patients, the observed virological states, the missing virological states, the observed adherence states, the missing adherence states, the vector of last negative resistance times, the vector of first positive resistance times, the vector of the current adherence states random effects, the vector of previous adherence states random effects, the vector of penultimate adherence states random effects, and the vector of all the model parameters except for β_1 . The posterior conditional distribution of β_1 can be written:

$$\begin{aligned}
 p_{\text{Post-Cond}}(\beta_1) &= p(\beta_1 | Y^{obs}, Y^{miss}, S^{obs}, S^{miss}, LN, FP, u_0, u_1, u_2, \Phi^{-\beta_1}) \\
 p_{\text{Post-Cond}}(\beta_1) &= \frac{p(\beta_1, Y^{obs}, Y^{miss}, S^{obs}, S^{miss}, LN, FP, u_0, u_1, u_2, \Phi^{-\beta_1})}{p(Y^{obs}, Y^{miss}, S^{obs}, S^{miss}, LN, FP, u_0, u_1, u_2, \Phi^{-\beta_1})} \\
 &\propto p(\beta_1, Y^{obs}, Y^{miss}, S^{obs}, S^{miss}, LN, FP, u_0, u_1, u_2, \Phi^{-\beta_1}) \\
 &\propto p(Y^{obs}, Y^{miss}, S^{obs}, S^{miss}, LN, FP | \beta_1, \Phi^{-\beta_1}, u_0, u_1, u_2) \times p(\beta_1, \Phi^{-\beta_1}, u_0, u_1, u_2) \\
 &\propto p(Y^{obs}, Y^{miss}, S^{obs}, S^{miss}, LN, FP | \beta_1, \Phi^{-\beta_1}, u_0, u_1, u_2) \times p(u_0, u_1, u_2 | \Sigma) p(\beta_1) p(\Phi^{-\beta_1}) \\
 &\propto p(Y^{obs}, Y^{miss}, S^{obs}, S^{miss}, LN, FP | \beta_1, \Phi^{-\beta_1}, u_0, u_1, u_2) p(\beta_1) \\
 &\propto \prod_{i=1}^N \prod_{t=1}^{T_i} \left(\frac{\exp(\mu_{i,t}^S)}{1 + \exp(\mu_{i,t}^S)} \right)^{S_{i,t}} \left(\frac{1}{1 + \exp(\mu_{i,t}^S)} \right)^{1 - S_{i,t}} p(\beta_1)
 \end{aligned}$$

The posterior conditional distribution of all the parameters, random effects, and missing/censored covariates can be written in an analogous manner. Then, the derivative-free adaptive rejection sampling [28] can be used to sample the parameter/random effect/missing covariate, when the posterior conditional distribution is log-concave; if not it is possible to use the adaptive rejection metropolis sampling to accommodate non-concavity in the log density [29]. As previously mentioned, we used WinBUGS as a Gibbs Sampler.

Figure B1.

Posterior predictive distribution of test quantities T_1 (mean of the proportion of time a patient is not adherent), T_2 (variance of the proportion of time a patient is not adherent), T_3 (mean of the proportion of adherence state changes per patient), and T_4 (variance of the proportion of adherence state changes per patient). Vertical lines represents the observed value of each test quantity.

Appendix B: Adherence model checking

Figure B1. The posterior predictive distributions of the four test quantities were computed and is shown in Figure B1.

Appendix C: Virological model checking

Figure C1. The posterior predictive distributions of the nine tests quantities were computed; there was no evidence of discrepancy between the model and data as shown in Figure C1.

Figure C1.

Posterior predictive distribution of test quantities (number of transitions from state $m=1,2,3$ (rows) to state $n=1,2,3$ (columns)). Vertical lines represent the observed values of each test quantity.

Figure D1.

Posterior predicted survival curves (black curves) and Turnbull survival estimation (gray curve).

Appendix D: Resistance model checking

Figure D1. The posterior predicted survival curves (black curves) and Turnbull survival estimation (gray curve) are shown in Figure D1.

Figure 1.

Observed virological response Y , observed adherence pattern S , and observed number of non-adherence states among the three last months A for two patients. An absence of a point (at biannual times for Y and A , and every months for S) indicates missing data. Patient A (left panel) has a last negative resistance test at time $t = 35$ months and has a PI in its therapy during all the follow-up. Patient B (right panel) has a positive resistance test at time $t = 24$ months and has no PI in its therapy during all the follow-up.

Figure 2. QQ-plot of the distribution of the posterior means of the current adherence state random effects, previous adherence state random effects, and penultimate adherence state random effects against the normal distribution.

Figure 3.

Posterior mean (dots) and 95 per cent credible intervals (segments) of transition probabilities from virological state $m=1,2,3$ to state $n=1,2,3$, according to the presence of a protease inhibitor in the initial therapy (PI = 1 if a protease inhibitor is included in the initial therapy and 0 otherwise), time since inclusion in the cohort ($T=1$ if the patient has been followed for more than 2 years), and adherence to antiretroviral therapy. Each graph is divided into three subgraphs (according to a dotted line); the lower subgraph corresponds to perfect adherence during the three months preceding the transition, the middle subgraph to 1 or 2 non-adherence states during the three months preceding the transition, and the upper subgraph to non-adherence during the three months preceding the transition.

Figure 4.

Each subfigure ((a) to (h)) presents predictions for eight new patients: the predictive distribution of the number of non-adherence states during the three last months preceding each biannual visit (bottom graph), of the virological states (middle graph), and of the resistance status (upper graph) for a new patient. At each biannual visit, the number of non-adherence states during the three last months can be 0, 1, 2, 3 (from light to dark gray); the virological state can be 1,2,3 (from light to dark gray); and the resistance status can be 0—non-resistant (light gray) or 1—resistant (dark gray). Patients (a)–(d) were assumed to have no PI in their therapy, and to have no resistance mutation at their last visit. Patients (e) to (h) were assumed to have no resistance mutation at their last visit. Patients (e) and (f) were assumed to have no PI in the therapy, unlike patients (g) and (h). (a) Perfectly adherent for 12 months, and in virological state 1 at 12 months. (b) Never adherent for 12 months, and in virological state 1 at 12 months. (c) Perfectly adherent for 30 months, and in virological state 3 at 30 months. (d) Never adherent for 30 months, and in virological state 3 at 30 months. (e) Perfectly adherent for 12 months, and in virological state 2 at 12 months. (f) Never adherent for 12 months, and in virological state 2 at 12 months. (g) Perfectly adherent for 12 months, and in virological state 2 at 12 months. (h) Never adherent for 12 months, and in virological state 2 at 12 months.

Table I

Posterior features (posterior mean, mean OR, and 95 per cent credible intervals) of the adherence model parameters. The parameters are obtained from a logistic mixed effect model with outcome $S_{i,t} = 1$ (adherence <95 per cent).

Parameters	Posterior mean	95 per cent CI	Posterior mean OR	95 per cent CI
β_0 - Intercept	-2.40	-2.64; -2.15		
$\beta_1 - S_{i,t-1}$	0.71	0.36; 1.07	2.07	1.43; 2.91
$\beta_2 - S_{i,t-2}$	0.48	0.25; 0.70	1.62	1.28; 2.01
$\beta_3 - \text{PI}_{i,t-1}$	0.50	0.20; 0.77	1.65	1.22; 2.16
$\beta_4 - S_{i,t-1} \times \text{PI}_{i,t-1}$	-0.28	-0.73; 0.18	0.77	0.48; 1.20
$\beta_5 - I(12 < t \leq 24)$	0.55	0.32; 0.78	1.74	1.37; 2.19
$\beta_6 - I(t > 24)$	1.02	0.68; 1.10	2.45	1.98; 3.00
σ_0^2	0.90	0.62; 1.27		
σ_1^2	0.63	0.24; 1.19		
σ_2^2	0.44	0.20; 0.80		
$\sigma_{0,1}$	-0.20	-0.61; 0.14		
$\sigma_{0,2}$	-0.21	-0.50; 0.05		
$\sigma_{1,2}$	0.29	0.05; 0.56		

Table II

Posterior mean and 95 per cent credible intervals (in square brackets) of the virological model parameters.

V1	V2	$n=1$	$n=2$	$n=3$
$m=1$	$\gamma_0^{m,n}$ -intercept	0	-3.11 [-3.72; -2.53]	-4.35 [-5.98; -3.27]
	$\gamma_1^{m,n}$ -PI ₀	0	0.87 [0.42;1.33]	0.59 [0.04;1.17]
	$\gamma_2^{m,n}$ - $I(t \geq 24)$	0	-0.55 [-1.06; -0.03]	-1.29 [-1.93; -0.70]
	$\gamma_3^{m,n}$ - $I(0 < A_{i,t} \leq 2)$	0	0.99 [0.26;1.75]	2.45 [1.10;4.24]
	$\gamma_4^{m,n}$ - $I(A_{i,t}=3)$	0	-4.56 [-19.77;1.75]	3.80 [2.28;5.59]
$m=2$	$\gamma_0^{m,n}$ -intercept	0	-0.81 [-1.66;0.00]	-1.98 [-3.13; -0.97]
	$\gamma_1^{m,n}$ -PI ₀	0	-0.01 [-0.81;0.77]	-0.18 [-1.11;0.71]
	$\gamma_2^{m,n}$ - $I(t \geq 24)$	0	0.55 [-0.25;1.39]	1.50 [0.54;2.52]
	$\gamma_3^{m,n}$ - $I(0 < A_{i,t} \leq 2)$	0	-0.13 [-1.21;0.91]	0.15 [-1.12;1.37]
	$\gamma_4^{m,n}$ - $I(A_{i,t}=3)$	0	6.56 [1.38;13.89]	6.30 [0.93;13.68]
$m=3$	$\gamma_0^{m,n}$ -intercept	0	-2.28 [-2.97; -1.69]	-2.16 [-2.78; -1.63]
	$\gamma_1^{m,n}$ -PI ₀	0	0.31 [-0.35;1.02]	0.81 [0.23;1.41]
	$\gamma_2^{m,n}$ - $I(t \geq 24)$	0	1.56 [0.81;2.29]	2.87 [2.29;3.48]
	$\gamma_3^{m,n}$ - $I(0 < A_{i,t} \leq 2)$	0	0.87 [-0.18;1.81]	0.43 [-0.48;1.37]
	$\gamma_4^{m,n}$ - $I(A_{i,t}=3)$	0	-3.26 [20.74;11.34]	11.33 [3.48;25.15]

Posterior features of the hazard rate of resistance (per month) at time t , according to the virological state ($\tilde{Y}_{i,t}$), the number of non-adherent states among the three last states ($\tilde{A}_{i,t}$), the presence of a protease inhibitor in the therapy (PI= 1), and the time since HAART initiation ($t>12$).

Table III

	Hazard	Posterior mean hazard	Posterior median	95 per cent CI
$\tilde{Y}_{i,t}=2$	$\tilde{A}_{i,t}<2$	PI= 0	0.21	0.08; 0.39
		PI= 1	0.05	0; 0.12
	$\tilde{A}_{i,t}=2$	PI= 0	0.06	0; 0.71
		PI= 1	0.01	0; 0.08
$\tilde{Y}_{i,t}=3$	$\tilde{A}_{i,t}<2$	PI= 0	0.11	0.05; 0.20
		PI= 1	0.08	0.02; 0.15
	$\tilde{A}_{i,t}=2$	PI= 0	0.07	0; 0.41
		PI= 1	0.04	0; 0.20
$t>12$	$\tilde{A}_{i,t}<2$	PI= 0	0.04	0; 0.12
		PI= 1	0.03	0; 0.10
	$\tilde{A}_{i,t}=2$	PI= 0	0.02	0; 0.10
		PI= 1	0.01	0; 0.05