JOINT MODELING OF TREATMENT MODIFICATION AND MARKERS DYNAMICS IN HIV INFECTION

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Keywords: Joint modeling, longitudinal data, HIV infection
Topic area of the submission: Outcome dependent treatment in AIDS studies (J Sterne)

Abstract

Background
Joint modeling of longitudinal evolution of markers and survival time is useful to correct the estimations of longitudinal marker model in case of informative missing data and to estimate the effect of marker evolution on event occurrence as well [1].
In HIV infection, when evaluating the markers response to antiretroviral treatment, follow-up may be censored at the time of treatment modification. This censoring may generate informative missing data that would compromise the maximum likelihood estimations. In this case, a joint model of markers evolution and time to treatment modification allows studying the effect of markers response on time to treatment modification and also provides corrected estimations of markers evolution. However, the association between longitudinal and event time components may vary according to causes of treatment modification (lack of efficacy, side effects...).

Objective
To study the association between markers dynamics (plasma HIV RNA and CD4+ cell count) and antiretroviral treatment modification in HIV infected patients through a joint model.

Methods
The model is a joint model including a linear model for repeated measures of a marker $Y_i$ in subject $i=1,\ldots,N$ and a survival model for the time until treatment modification or end of study.

**Longitudinal model**

The number of measurements may be different for each subject. A linear mixed model could be written as follow:

$$Y_i \sim X_i ? Z_i ? \sim N(0, \sigma_i^2)$$

$X_i$ is a $n_i \times p$ design matrix of explanatory variables, $\beta_i$ is a $p$-vector of fixed effects, $Z_i$ is a $n_i \times q$ design matrix which is usually a subset of $X_i$, $\gamma_i$ is a $q \times 1$-vector of individual random effects with $q \leq p$. The covariance matrix of measurement errors is a diagonal matrix, denoted by $\sigma_i^2 I_n$. With the assumption that $\beta_i$ and $\gamma_i$ are mutually independent, we obtain $\text{var}(Y_i) = V_i \approx Z_i G Z_i^T \gamma_i^2.$

**Survival model**

An accelerated failure time model may be used to fit the process of treatment modification:

- The event was the occurrence of treatment modification $\delta_i = 1$?
- Patients followed until the end of the study without treatment modification were censored $\delta_i = 0$?

Let $C_i$ the time (or a transformation of the time) from baseline to the scheduled end of follow-up, $T_i$ is the time (or a transformation of the time) from baseline to the date of treatment modification. For each patient, we observed the pair $(T_i, C_i)$.

We assume that $T_i$ is correlated to the random effects $\gamma_i$ through the covariance matrix $B$ such that:

$$\begin{pmatrix} T_i \\ T_i \end{pmatrix} \sim N(0, B)$$

**Likelihood**

The likelihood of the joint model could be written:
with \( F_{ij}, \gamma_i \) the cdf of the univariate normal distribution: \( f_{ij}, \gamma_i \).

Other joint model may be used, relaxing distribution hypotheses or the link between longitudinal and survival model [1].

**Application**

Data came from the APROCO-COPILOTE study; a French prospective cohort of HIV-1 infected patients treated with Highly Active Antiretroviral Therapy. The study sample included 537 patients with at least one measurement of both markers plasma viral load and CD4+ lymphocytes T cell count and without history of treatment before the initiation of antiretroviral regimen. The median number of CD4+ and HIV RNA measurements was 5 (interquartile range [IR]: 2-8) during a median follow-up before treatment modification of 16 months (IR: 5-33).

During the study period, the antiretroviral treatment was modified in 432 subjects. The causes of treatment modifications were collected in 391 patients and varied from personal, lack of efficacy and side effects.

To assume model hypotheses, logarithm, squared root and cubic root transformations were used for HIV RNA, CD4+ count and time to treatment modification, respectively. The longitudinal model was a piecewise linear model including one intercept and two slopes. The change point of slope was common for all subjects and estimated at 1.6 months. In average, CD4+ initial level was of 13.6 square root cells/mm\(^3\) (standard error [se] 0.24), increasing by 2.5 (se 0.11)/month during the first 1.6 months and 1.7/month thereafter. The covariance between the time to treatment modification and individual intercept, first slope and second slope were 0.17 (se 0.12), 0.12 (se 0.049) and -0.0080 (se 0.090), respectively. So, when evaluating the link between CD4+ evolution and time to treatment modification through a joint model, the covariance was significant with the first slope. This means that the better was the short response in CD4+ (increasing slope) after treatment initiation; the longer was the duration of this treatment without modification. Moreover, taking into account the censoring due to treatment modification allowed to correct CD4+ evolution parameters. For HIV RNA, the estimations of fixed parameters taking into account undetectable measures of HIV RNA
[2-3] were: 4.37 (0.038), -1.63 (0.036) and -0.35 (0.089) for the baseline, first slope and second slope, respectively. The covariance between the time to treatment modification and individual intercept, first slope and second slope were –0.068 (se 0.11), -0.11 (se 0.065) and –0.23 (se 0.093), respectively. Thus, the better was the long-term HIV RNA response (steeper decline) after treatment initiation; the longer was the duration of this treatment without modification.

Further analyses will be presented to study the association between marker evolution and time to treatment modification according to the informed cause of treatment modification.

References
