**Joint modelling of longitudinal CD4 counts and survival of HIV-infected patients initiated on antiretroviral therapy in sub-Saharan Africa.**

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**Aims**

In clinical research, one of the main interests is to investigate the survival of patients and to identify which factors could affect the survival. In the vast majority of published studies, investigators explore the effect of baseline data on survival, but less frequently explore the effect of longitudinal markers on survival. One of the main reasons for this is the lack of simple and comprehensive methods to deal with the complexity of modelling these two processes at the same time. We present here a method to estimate the effect of a change in longitudinal trajectory on survival using a joint modelling approach and we apply it to explore the effect of gender on survival in HIV-infected patients independently of CD4 cell count evolution over time.

**Methods**

A latent class mixed model was fitted to identify two or more typical trajectories of the CD4 counts over time [1]. Throughout this model, posterior membership probabilities to each latent class were estimated for each patient and patients were thus assigned to one of the estimated trajectory. Then, this latent structure was integrated into a Cox proportional-hazards model along with potential other risk factors. Using the hypothesis of conditional independence given the latent classes, individual contributions to the likelihood were imputed and parameters were estimated using maximum likelihood method with Marquardt iterative algorithm. Estimations of latent trajectories of CD4 counts, and hazard ratios of these latent trajectories and other risk factors on survival were obtained at the same time from the model. Analysis was performed with the lcmm package of R [2]. This package provides functions for the estimation of different extensions of the mixed models including latent class and joint latent class mixed models and mixed models for curvilinear univariate and multivariate longitudinal outcomes, using maximum likelihood estimation method. The package also provides various post fit functions.

**Results**

We applied this method to a cohort of patients supported by Médecins sans Frontières in Kenya, Malawi and Uganda. A total of 33,600 patients followed for a median time of 40 months [IQR 21 - 62] after antiretroviral therapy (ART) start were included in the analysis. We have fitted a joint latent class model with a second degree polynomial of time on ART with 2 latent classes for the longitudinal sub-model, and a Cox proportional-hazards model with an M-splines constant baseline

risk function with three nodes for the survival model. We found that 72% of patients followed a low CD4 trajectory compared to 28% following a high CD4 trajectory. Patients following a low CD4 trajectory on ART (aHR 5.11, 95%CI 3.94 - 6.64) and men (aHR 1.56, 95%CI 1.41 - 1.71) were independently associated with a higher risk of death.

**Conclusion**

Joint modelling of longitudinal and survival data with a latent structure approach provides a powerful tool to estimate independently and at the same time the effect of a longitudinal marker and other risk factors on survival. This method is useful when information collected is rich and when the population is heterogeneous but requires special attention for model building. This method should be considered with interest in clinical research since longitudinal markers can affect the survival of patients.

**References**

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