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Original Article

A Comparative Study of Different Joint Modeling Approaches for HIV/AIDS Patients in Southern Iran

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Abstract

Background: The prevalence of HIV/AIDS has been increasing in Iran, especially amongst the young population, recently. The joint model (JM) is a statistical method that represents an effective strategy to incorporate all information of repeated measurements and survival outcomes simultaneously. In many theoretical studies, the population under the study were heterogeneous. This study aimed at comparing three approaches by considering heterogeneity in the patients.

Methods: This study was conducted on 750 archived files of patients infected with HIV in Fars Province, southern Iran, from 1994 to 2017. Proposed Approach (PA), Joint Latent Class Models (JLCM), and Separated Approach (SA) were compared to evaluate the influence covariates on the longitudinal and time-to-event outcomes in the heterogeneous HIV/AIDS patients.

Results: Gender (P<0.001) and HCV (P<0.01) were two significant covariates in the classification of HIV/AIDS patients. Time had a significant effect on CD4 (P<0.001) in both classes in the three approaches. In PA and SA, females had higher CD4 than males (P<0.001) in the first class. In JLCM, females had higher CD4 than males (P<0.01) in both classes. The patients with higher Hgb had also higher CD4 (P<0.001) in both classes in the three approaches. HCV reduced the CD4 significantly in both classes in PA (P<0.05) and SA (P<0.001). Within the survival sub-model, HCV reduced survival rate significantly in the second class in PA (P<0.05), JLCM (P<0.01) and SA (P<0.001).

Conclusion: PA was an appropriate approach for joint modeling longitudinal and survival outcomes for this heterogeneous population.

Keywords: Longitudinal studies; Survival analysis; HIV; Iran

Introduction

Acquired Immune Deficiency Syndrome (AIDS) is a chronic disease that can affect various aspects of the people's life. In 2016 approximately 36.7 million people lived with HIV/AIDS worldwide (1). The prevalence of AIDS in Iran in 2014 was estimated 0.14%, and the number of related deaths was 5,530. About 45.7% of HIV infected cases were 25-34 yr old, and the same age group had the highest number of people with AIDS in Iran (2). Due to recent advances in HIV/AIDS treatment, it has transformed from an acute and deadly disease to a manageable chronic condition (3, 4).

In patients with HIV-infection, CD4 cell count is the main sign and a strong predictor of disease progression and survival of patients (5, 6). In

studies on AIDS, the associated factors such as CD4 are repeatedly measured over time (7, 8). In biomedicine, these longitudinal measurements and the time to event data are known to be correlated, hence, modeling longitudinal and survival outcomes separately for analyzing this type of data can lead to biased results (7, 8). In recent years, several statistical methods, including Joint model (JM), have been used for modeling the longitudinal and time-to-event outcomes, simultaneously (8, 9).

JM framework is a method used for longitudinal and time-to-event data, instead of separate modeling of longitudinal and survival outcomes (10-12). The motivation behind these JMs is to connect the repeated measurements in the longitudinal process with an appropriate model for survival. The existing JMs only allow the individuals to follow a unique pattern, however, these methods are not appropriate when there are underlying groups based on the response profiles. Thus, we need to consider a subset of longitudinal and survival outcomes that may have different patterns (13, 14).

In this regard, the potential subtypes of the longitudinal and survival outcomes are considered for the joint latent class model (JLCM) (14) .This model considers the population as heterogeneous and assumes that it consists of homogeneous latent subgroups or latent classes of subjects that share the same longitudinal outcome trajectory and the same risk of event (15).

The conditional independence (CI) assumption, as a fundamental assumption of JLCM shows that the entire association between the longitudinal and survival processes is captured by the latent classes' structure. Hence, given these latent classes, two types of data (the longitudinal measurements and time-to-event) are independent (8, 15-17). In addition, a JLCM limitation is that the number of latent classes cannot be directly identified and has to be selected according to a criterion, commonly best (lower) Bayesian information criterion (BIC) (17).

In a simulation-based study, For large sample size and considerable association, PA was preferred (18).

In this study, we compared the three approaches of PA, JLCM and SA on a real AIDS/HIV Iranian dataset, to identify the influential covariates associated with the longitudinal and time-to-event outcomes.

Methods

Data collection

This study was conducted on individuals infected with HIV in Fars Province, the fourth most populous province in Iran. Fars is situated in southern region of the country and Shiraz is the capital. Data were collected from the archive of voluntary counseling and testing (VCT) center in Shiraz from Sep 1994 to Mar 2017.

Overall, 1251 cases were studied and HIV infection had been confirmed by ELISA and Western blot tests. Then, the patients were introduced from the laboratory to the health facility close to their place of residence so that the VCT center could cover the patient and carry out the necessary tests and follow-ups. The medical records consisted of demographic characteristics such as gender, marital status and age. Moreover, clinical characteristics such as CD4 cell count have recorded from baseline to maximum 10 times afterward, time-to-death (time from onset to study until to death), co-infection with hepatitis B virus (HBV), co-infection with hepatitis C virus (HCV), prophylaxis for tuberculosis (TB), antiretroviral (ARV) drug, and baseline hemoglobin (Hgb) level.

The study protocol was approved by the code number of IR.SUMS.REC.1395.S198 through the ethics committee of Shiraz University of Medical Sciences.

Inclusion and exclusion criteria

Amongst 1,251 patients in the VCT dataset, those who died through accident, suicide, murder, and hanging were excluded. This data included a highly unbalanced longitudinal dataset. However, HIV-positive patients with three or more measurements of CD4 in their records were included for statistical analysis. Consequently, the

analysis was performed on 750 patients who complied with the inclusion criteria in this study.

Methods for analysis of HIV/AIDS dataset from VCT

PA on VCT center dataset

In PA, to analyze this dataset, according to gender, Hgb, HBV and HCV covariates, the probability of belonging to the latent classes for patient *i* was identified, so based on their highest posterior class membership probabilities, the patients were divided into two latent classes (g=2). The number of classes was chosen such that there were enough observations in each class and easier interpretation according to the researcher' comments (19).

The latent class framework:

The logistic model showed which covariates (gender, Hgb, HBV and HCV) were significant in the classification of the subjects.

$$logit(p_{ig}) = \lambda_{0g} + \lambda_{1g}Gender + \lambda_{2g}Hgb + \lambda_{3g}HBV + \lambda_{4g}HCV$$

That λ_{0g} is intercept and λ_{ig} s are the class-specific coefficients.

After classifying the subjects into two latent classes, we fitted JM for each class; due to the skewed distribution of CD4 cell level, we used log ($CD4_{ij}$) as the longitudinal outcome for patient *i* at *j*th time. The longitudinal and survival sub-models are indicated as follows:

The longitudinal sub-model**:**

$$\log(CD4_{ij}) \mid c_i = g = \beta_{0g} + \beta_{1g}Time + \beta_{2g}Gender + \beta_{3g}Hgb + \beta_{4g}HBV + \beta_{5g}HCV + b_{ig} + \varepsilon_{ij,g} = Z^*_{ig} + \varepsilon_{ij,g}$$

When $Z^*_{ig} = \beta_{0g} + \beta_{1g}Time + \beta_{2g}Gender + \beta_{3g}Hgb + \beta_{4g}HBV + \beta_{5g}HCV + b_{ig}$ as total trajectory of longitudinal measurement of $CD4_{ij}$ for g=1 and 2. b_{ig} is random intercept in class g. Class-specific random error term, $\varepsilon_{ij,g}$ is usually assumed to be normally distributed.

The survival sub-model:

$$h_i(t \mid c_i = g) = h_{0g}(t_i)exp(\gamma_{1g}Gender + \gamma_{2g}Hgb + \gamma_{3g}HBV + \gamma_{4g}HCV + \alpha_g Z^*_{ig})$$

$h_{0g}(t_i)$ is class-specific baseline hazard function and was estimated by Weibull distribution. γ_{ig} is class-specific covariate effect on survival. α_g is the association parameter between the longitudinal and the survival processes in class g.

JLCM on VCT center dataset

JLCM with a range of latent classes from one to three was estimated. Longitudinal measurements of log (CD4) and time-to- death were two outcomes. We used Gaussian quadrature with 50 quadrature points to estimate the parameters. The model with the best (lower) BIC and satisfactory of CI assumption was selected (7, 18). A score test was used to evaluate this assumption (8). Gender, Hgb, HCV and HBV were included as predictors to the latent class membership.

SA on VCT center dataset

The probability of belonging to the latent classes for each patient was identified based on the latent class framework, as described before. The patients were divided into two latent classes. Moreover, SA contains a linear mixed-model for longitudinal log(CD4) measures and an extended Cox model (for modeling the influence of effective covariates on time-to-death) (18). Log (CD4), as a time-varying covariate, was included to extended Cox model.

Software

The approaches were implemented using the following packages in R ver. 3.2. *lcmm* package for JLCM and *JM* package for JM.

Results

Demographic and clinical characteristics

Median of baseline CD4 cells was 243 and its interquartile range (IQR) was 241.50 cells/mm^3. We also considered gender, Hgb, HCV and HBV covariates. We included time (in months) since study onset as a covariate to study the temporal trend of CD4 levels. The censoring rate was

about 67.20%. The median follow-up time was 88 months. Demographic and clinical characteristics of the patients are summarized in Table 1.

Table 1: Demographic and clinical characteristics of patients in the study (n=750)

Age (yr) (mean ± SD)	***40.7 1± 10.02***
Gender	No (%)
Female	227 (30.30)
Male	523 (69.70)
Marital status	No (%)
Temporary marriage	18 (2.40)
Married	346 (46.13)
Single	187 (24.94)
Widowed	71 (9.47)
Divorced	121 (16.13)
Unknown	7 (0.93)
ARV	No (%)
Yes	731 (97.47)
No	19 (2.53)
TB prophylaxis	No (%)
Yes	382 (50.93)
No	368 (49.07)
HBV test	No (%)
Positive	55 (7.33)
Negative	652 (86.93)
HCV test	No (%)
Positive	420 (56.00)
Negative	301 (40.13)
Baseline Hemoglobin mg/dL (mean ± SD)	12.42 ± 1.63
Baseline CD4 cells/mm3 (mean ± SD)	280.82 ± 199.11

PA results for VCT center dataset

The probability of belonging to the latent classes was significantly associated with gender (P<0.001) and HCV (P<0.01). Hgb (P=0.51) and HBV (P=0.64) were not significant covariates in the classification.

Based on the classification, 49.10% of the patients were in the first class. In the second class, about 70% of them were co-infection with HCV, and the proportion of females in this class (43.30 %) was more than the first class (27.40%). The Kaplan-Meier survival plot is shown in Fig. 1. Patients in the first class had a better survival rate. The parameter estimates for our two latent classes in longitudinal and survival sub-models of PA are shown in Table 2. There was a significant decrease in CD4 count over the time study in both classes (95% CI, -0.011– -0.012: the first class, 95% CI, -0.011– -0.007: the second class) (Fig. 2). Gender was a significant covariate on the CD4 longitudinal outcome in the first class (95% CI, 0.169–0.290). Hgb had a significant positive effect on CD4 values in the first class (95% CI, 0.060–0.061). Co-infection with hepatitis C significantly reduced CD4 cell count in both classes (95% CI, -0.197– -0.060: the first class, 95% CI -0.028- -0.009: the second class).

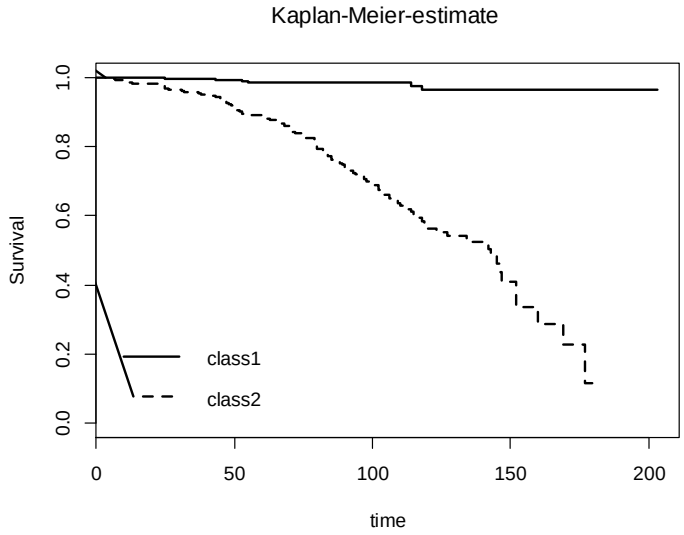

Fig. 1: Kaplan-Meier survival plot for the two latent classes on the HIV/AIDS patients in VCT center based on the latent class framework

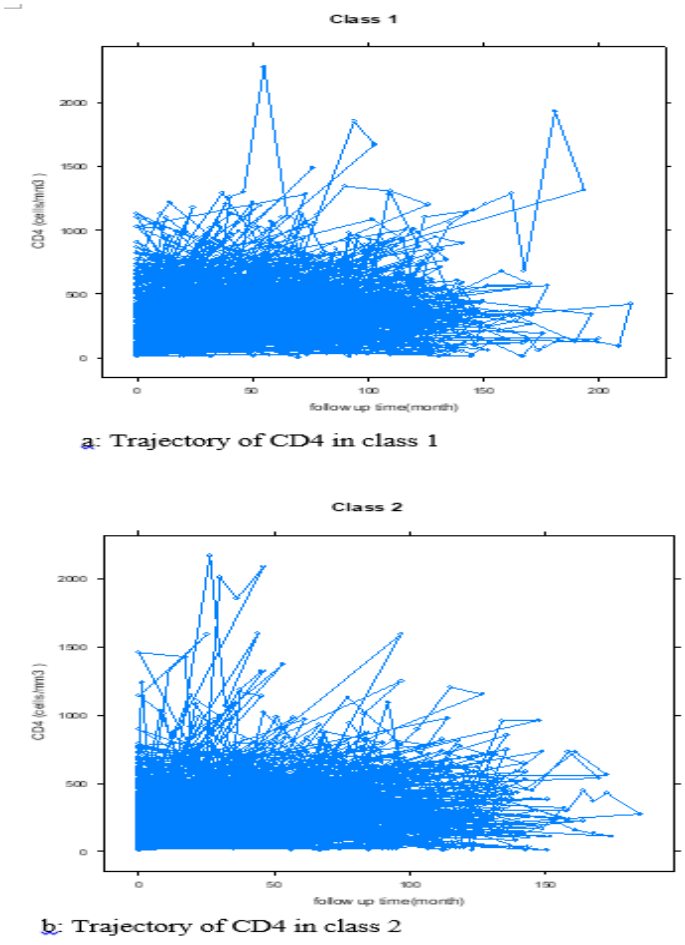

Fig. 2: (a)-(b) Profile plots of CD4 for 2 classes on the HIV/AIDS patients in VCT center based on the latent class framework

Within the survival sub-model, co-infection with hepatitis C reduced survival rate significantly in the second class (95% CI, 0.363–0.508). The estimates of association parameters between CD4 and the time-to-death (α_g) were significant and negative in both classes (95% CI, -0.728– -0.653: the first class, 95% CI, -0.568– -0.557: the second class); that is, CD4 counts had a significant impacted on the survival time.

Table 2: Results of fitting PA in VCT center dataset

	Parameter name	***Estimates***	***SE***	***P-value***
Class 1		Longitudinal sub-model		
	Intercept	1.690	0.121	< 0.001
	Time	-0.012	0.00005	< 0.001
	Gender Female	0.230	0.031	< 0.001
	Hgb	0.061	0.003	< 0.001
	HBV Positive	0.055	0.038	0.158
	HCV Positive	-0.129	0.035	0.044
		Survival sub-model		
	Gender Female	-0.177	0.212	0.590
	Hgb	-0.139	0.098	0.678
	HBV Positive	0.148	0.193	0.679
	HCV Positive	0.539	0.388	0.566
	α_1	-0.691	0.019	< 0.001
Class 2		Longitudinal sub-model		
	Intercept	1.985	0.218	< 0.001
	Time	-0.009	0.00001	< 0.001
	Gender Female	0.318	0.101	0.239
	Hgb	0.014	0.023	0.569
	HBV Positive	0.035	0.049	0.076
	HCV Positive	-0.019	0.005	0.037
		Survival sub-model		
	Gender Female	0.077	0.414	0.063
	Hgb	-0.043	0.150	0.117
	HBV Positive	0.210	0.329	0.084
	HCV Positive	0.436	0.037	0.018
	α_2	-0.563	0.003	< 0.001

HBV = Hepatitis B Virus, HCV = Hepatitis C Virus, Hgb = Baseline Hemoglobin, Alpha = association parameter between CD4 and the time to death.

JLCM results for VCT center dataset

In JLCM, BIC calculated from the two latent classes was 2625.95, which was smaller than the one class (2919.35), and three classes (3134.80), Also, the CI assumption was not rejected (P=0.17) for this model, hence the model with two latent classes was preferred. The probability of belonging to the latent classes was significantly associated with gender (P<0.01) and HCV (P<0.05).

In the longitudinal sub-model, time had a small but significant, negative effect in two latent classes (95% CI, -0.002– -0.001: the first class, 95% CI, -0.003–-0.002: the second class). In both classes, the gender variable was a significant covariate on the longitudinal outcome (95% CI, 0.066–0.215: the first class, 95% CI, -0.540– -0.129: the second class). Hgb was a significant covariate affecting the CD4 values in the first class (95% CI, 0.223–0.0537). Co-infection with hepatitis B in-

creased CD4 cell counts significantly in the second class (95% CI, 0.015–0.309).

In the survival sub-model, female gender (95% CI, 0.024–2.145) and co-infection with hepatitis C (95% CI, 0.326–1.883) were significantly associated with the risk of death for HIV patients in the second class (Table 3).

Table 3: Results of fitting JLCM in VCT center dataset

	Parameter name	*Estimates*	*SE*	*P-value*
Class 1		Longitudinal sub-model		
	Intercept	1.831	0.110	< 0.001
	Time	-0.002	0.000002	< 0.001
	Gender Female	0.141	0.038	< 0.001
	Hgb	0.038	0.008	< 0.001
	HBV Positive	0.061	0.042	0.148
	HCV Positive	-0.063	0.035	0.072
		Survival sub-model		
	Gender Female	0.317	0.713	0.952
	Hgb	-0.197	0.126	0.120
	HBV Positive	0.118	0.990	0.962
	HCV Positive	0.544	0.587	0.353
Class 2		Longitudinal sub-model		
	Intercept	2.410	0.311	< 0.001
	Time	-0.003	0.000005	< 0.001
	Gender Female	-0.335	0.105	< 0.001
	Hgb	0.008	0.021	0.712
	HBV Positive	0.162	0.075	0.031
	HCV Positive	-0.074	0.115	0.481
		Survival sub-model		
	Gender Female	1.085	0.541	0.044
	Hgb	-0.088	0.104	0.395
	HBV Positive	0.620	0.471	0.188
	HCV Positive	1.105	0.397	0.005

HBV = Hepatitis B Virus, HCV = Hepatitis C Virus, Hgb = Baseline Hemoglobin

SA results for VCT center dataset

In our estimated class-specific linear mixed effect models, time covariate reduced CD4 cell count significantly in both classes (95% CI, -0.002–-0.001: the first class, 95% CI, -0.015–-0.003: the second class). Gender (95% CI, 0.033–0.182) and Hgb (95% CI, 0.021–0.044) were the effective covariates on the longitudinal outcome in the first class. In both classes, co-infection with hepatitis C reduced CD4 cell count significantly (95% CI, -0.198–0.061: the first class, 95% CI, -0.166–0.115: the second class).

In the extended Cox model, the survival rates among patients with HCV comparing to those without HCV were lower and significantly significant in the second class (95% CI, 0.322–0.805). The effect of CD4 cell count on the time-to-death was statistically significant in both classes (95% CI, -0.669– -0.508: the first class, 95% CI, -0.739–-0.366: the second class) (Table 4).

Overall, the average SE of parameter estimation for the longitudinal sub-model was 0.052, 0.072 and 0.305 for the PA, JLCM, and SA, respectively. Furthermore, the average SE of parameter estimation for the survival sub-model among the three approaches was 0.184, 0.491 and 1.437 for the PA, JLCM, and SA, respectively.

Table 4: Results of fitting SA in VCT center dataset

	Parameter name	*Estimates*	*SE*	*P-value*
Class 1		Linear mixed-effect model		
	Intercept	1.985	0.093	< 0.001
	Time	-0.001	0.000003	< 0.001
	Gender Female	0.108	0.038	< 0.010
	Hgb	0.033	0.006	< 0.001
	HBV Positive	-0.033	0.049	0.503
	HCV Positive	-0.130	0.035	< 0.001
		Extended Cox model		
	Gender Female	0.215	0.330	0.427
	Hgb	-0.159	0.142	0.263
	HBV Positive	0.167	0.391	0.545
	HCV Positive	1.649	1.072	0.124
	CD4	-0.589	0.041	< 0.01
Class 2		Linear mixed effect model		
	Intercept	2.014	0.143	< 0.001
	Time	-0.009	0.003	< 0.001
	Gender Female	2.120	3.128	0.315
	Hgb	0.033	0.106	0.431
	HBV Positive	-0.033	0.049	0.503
	HCV Positive	-0.141	0.013	< 0.001
		Extended Cox model		
	Gender Female	-0.411	0.662	0.370
	Hgb	-8.627	11.164	0.440
	HBV Positive	0.271	0.353	0.440
	HCV Positive	0.564	0.123	< 0.001
	CD4	-0.553	0.095	< 0.001

HBV = Hepatitis B Virus, HCV = Hepatitis C Virus, Hgb = Baseline Hemoglobin, Alpha = association parameter between CD4 and the time to death

Discussion

The present study compared three statistical approaches of PA, JLCM and SA for the analysis of CD4 cell counts and time-to-death factors, accounting for individual patient's heterogeneity. The CD4 longitudinal measurements were taken at different time points clinically related in individuals infected with HIV. In addition, heterogeneity among patients may arise.

Classification of the patients into two latent class showed that, in the second class, there were patients with poorer clinical conditions. Moreover, the proportion of patients who died in this class was significantly higher than the first class. Many factors affect patients' survival with HIV in each class. This means that to reduce the rate of HIV transmuting into AIDS, and to delay patients' death, special care to these factors and changing patient's conditions in each class of patients are required.

According to the results of the VCT center dataset, time had a negative significant effect on CD4 longitudinal outcomes for each class in the three stated approaches. CD4 values decreased with time in both classes. The results of this study corroborated the findings of previous works on HIV/AIDS dataset (14, 20). Gender was a significant covariate on CD4 longitudinal outcome in the first class for PA and SA; that is, females had a significantly higher CD4 than males in the first class. This result concurs with those observed in an earlier study (14).

Furthermore, patients with higher Hgb had a higher CD4 in the first class for the three approaches. Our finding is consistent with a similar study (14). In both classes, co-infection with hepatitis C reduced the CD4 counts significantly for PA and SA. This result is in line with the findings

of similar studies (7, 21, 22). Co-infection with hepatitis B significantly increased CD4 cell count in the second class of JLCM. As reported in other studies, co-infection with hepatitis B increases CD4 cell count (7, 23).

Within the survival sub-model, co-infection with hepatitis C significantly reduced the survival in the second class in the three mentioned approaches. Co-infection with hepatitis C is often associated with an increased risk of death for HIV patients. Co-infection with hepatitis C and HIV increased the risk of death for patients by about 35% (24). From a clinical point of view, hepatitis B increased the risk of AIDS or death for newly diagnosed patients, even if it is not statistically significant (25, 26).

According to the findings of JLCM, female gender was a risk factor for HIV patients' survival time in the second class. This result is consistent with that of a similar study on the same data in Shiraz VCT center (27). Similarly, although the mean CD4 count was higher in females compared to males, the mean of survival time was less in females compared to males (28, 29), which confirms the finding of JLCM in our study.

The estimated association parameters between CD4 and time-to-death in SA and, trajectory of CD4 and time-to-death in PA were negative and significant in both classes for PA and SA. A higher CD4 count was associated with a lower death rate (22, 30-32).

Overall, the results of PA in this study confirmed the biomedical literature (8, 14, 22, 33). Moreover, PA enjoyed the smallest average SE of parameter estimation for the longitudinal sub-model that indicates more efficiency than JLCM and SA. In addition, PA had a lower average SE of parameter estimation for the survival sub-model; hence, PA was more efficient than the other two approaches. The results of the three approaches on VCT center data confirmed those of the simulation study when there was a considerable association parameter between the longitudinal outcome and time-to-event in a large sample size (18).

This study with limited availability and quality of data. The data was limited to highly unbalance longitudinal dataset. In addition, having known that all patients were not diagnosed at the early stages of their disease, hence, baseline CD4 count are likely not to be appropriate.

Conclusion

Using the latent class framework in JMs had more advantages than the classic JMs. Indeed, by exhibiting profiles of evolution associated with the clinical event, considering the latent classes in JM is simpler to interpret and an attractive tool in comparison with JMs.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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