Modeling the trajectory of CD4 cell count and its effect on the risk of AIDS progression and TB infection among HIV-infected patients using a joint model of competing risks and longitudinal ordinal data

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ABSTRACT

Background: This study was conducted to better understand the influence of prognostic factors and the trend of CD4 cell count on the risk of progression to acquired immunodeficiency syndrome (AIDS) and tuberculosis (TB) infection among patients with human immunodeficiency virus (HIV) in a developing country.
Methods: The information of 1530 HIV-infected patients admitted in Behavioral Diseases Counseling Centers, Tehran, Iran, (2004-2014) was analyzed in this study. A joint model of ordinal longitudinal outcome and competing events is used to model longitudinal measurements of CD4 cell count and the risk of TB-infection and AIDS-progression among HIV patients, simultaneously.
Results: The results revealed that the trend of CD4 cell count had a significant association with the risk of TB-infection and AIDS-progression ($p<0.001$). Higher ages ($p<0.001$), the history of being in prison ($p=0.013$), receiving antiretroviral therapy (ART) ($p<0.001$) and isoniazid preventive therapy (IPT) ($p<0.001$) were associated with the positive trend of CD4 cell count. Higher ages were also associated with higher risks of TB ($p<0.001$) and AIDS-progression ($p<0.001$). Furthermore, ART ($p=.0009$) and IPT ($p<0.001$) were associated with a lower risk of TB-infection. In addition, ART ($p<0.001$) was associated with a lower risk of AIDS-progression. Moreover, individuals being imprisoned ($p=0.001$) and abusing alcohol ($p=0.012$) were more likely to have TB-co-infection.
Conclusions: The used joint model provided a flexible framework for simultaneous studying of the effects of covariates on the level of CD4 cell count and the risk of progression to TB and AIDS. This model also assessed the effect of CD4 trajectory on the hazards of competing events.

Keywords: HIV/AIDS, Tuberculosis (TB), Competing Risk, Ordinal Longitudinal, Joint Model, Survival

INTRODUCTION

The human immunodeficiency virus (HIV) has remained a major public health issue. About 37.9 million people were living with HIV by the end of 2018 and 1.7 million people were newly infected in 2018, worldwide. HIV is considered as the first cause of infectious disease-related death globally. The most advanced stage of HIV infection, which can cause serious damages to the immune system, is called acquired immunodeficiency syndrome (AIDS) [1]. HIV patients have a weakened immune system, so they are at higher risk of opportunistic infections. Mycobacterium tuberculosis (TB) is the most common opportunistic illness and cause of death among these patients [2]. On the other hand, HIV infection is known as one of the major factors that can increase the risk of progressing to active TB, such that HIV-infected people are 20 to 30 times more likely to progress TB. At least one-third of HIV-infected patients are co-infected with TB [3, 4].

CD4 cell count is affected by both HIV and TB infections [5], such that, CD4 cell count has been reported to be low in TB patients, even if they are not HIV-infected [6-8]. Among patients with HIV, the incidence of active TB increases exponentially as the CD4 cell count decreases and patients with CD4 cell count less than 200 were at higher risk of developing TB [9, 10]. On the other hand, it has been shown that the time of progression to AIDS is affected by the number of CD4 cell count and having less CD4 cell count at baseline causes rapid disease-progression to AIDS [11, 12].

Although, there is no cure for HIV, antiretroviral therapy (ART) can slow down the progression of the HIV virus in the body [13]. It has been reported that early initiation of ART can improve the survival of HIV-infected patients even with low CD4 cell count [14]. ART also provides protection against TB incidence, among HIV-infected patients [15]. While ART reduces the risk of TB, it is not known to be sufficient in controlling HIV-related TB [16, 17]. Isoniazid preventive therapy (IPT) is the primary treatment that can prevent TB in people who live with HIV and reduces its incidence significantly [18]. According to the World Health Organization (WHO), IPT should be a part of HIV care even in HIV-infected patients who are unlikely to develop active TB. However, despite encouraging progress, less than 50% of people who live with HIV receive ART [19] and less than 25% of HIV-infected patients who are in care receive IPT [20].

According to WHO, HIV and TB combination can always be lethal and each can speed up the progress of the other one [4]. As the burden of HIV-related TB infection is high in low-income countries, conducting research in this area is becoming more useful to provide information for the integration of TB and HIV services [21]. The CD4 cell count plays a fundamental role in both HIV progression and TB infection. However, based on our knowledge, there is no any study to assess the effect of the trajectory of CD4 cell count on AIDS progression and TB infection simultaneously among HIV-infected patients as a joint of competing risks and longitudinal outcomes. So, in the present study, a joint model of longitudinal outcome and competing events was used to identify the effect of potential risk factors as well as the trajectory of CD4 cell count on the risk of progression to TB infection and AIDS, among HIV-infected patients.

METHODS

Data Sources

The information of patients who are infected with HIV is used in this study. The database was not frozen. It is still ongoing. However, we collected the data from April 2004 to March 2014 for another study that has been already published by Poorolajal et al. in 2015 [22]. The main dataset contained the information of 2473 patients, of them 593 were diagnosed with AIDS and 157 were developed AIDS within the first week. Moreover, the longitudinal CD4 measurements were not recorded for 193 patients. The analysis was based on the data from the remaining 1530 patients. Each HIV-seropositive patient, regardless of clinical stage confirmed by laboratory criteria according to country definitions and requirements, is defined as an HIV-positive patient [23]. In the Islamic Republics of Iran, an individual is an HIV-positive patient if two sequential enzyme-linked immunosorbent assay (ELISA) tests and western blot test be positive [24]. According to World Health Organization, an AIDS case is defined by clinical diagnosis, including a presumptive or definitive diagnosis of stage 4 and/or CD4 cell count of less than 200 cells/mm3 [23]. Patients were followed and those diagnosed with AIDS/TB were ascertained through a clinical follow-up by the original investigators and the times of these events were recorded. The time from HIV diagnosis to TB/AIDS progression (in month) was considered as the failure time response variable. It should be noted that a subject who had not experienced any of these events was defined as a censor. In addition, the collected information involved demographic information (age at diagnosis, gender, level of education, and marital status), behavioral information (being in prison, alcohol/drug abuse), receiving ART and IPT. It should be noted that in the Islamic Republic of Iran, ART is started for HIV-positive people with the following criteria: [1] stage 3 or 4 conditions; [2] CD4 cell count less than 350 per mm3; [3] coinfection with hepatitis B (HB) virus; [4] HIV-induced nephropathy; [5] having malignancy; [6] age over 60 years; or [7] HIV viral load above 100,000 copies [25]. The CD4 cell count was also measured over time since the time of HIV diagnosis. The frequency of CD4 measurements for each subject would depend on his or her survival time. Moreover, the CD4 measurement times varied irregularly from subject to subject. Patients who their CD4 has measured at least two

times were enrolled in the study. We categorized CD4 cell count based on the World Health Organization. So, the categories included less than 200, 200-349, 350-500, and more than 500 cells/mm3 [23].

Joint Model

The joint model consists of two sub-model, including: [1] a proportional odds model which incorporates subject-specific random effects for ordinal repeated measurements of CD4 cell count and [2] a cause-specific hazard model for failure time in the presence of competing risks, including the TB infection or AIDS progression, that are linked by latent random variables.

Longitudinal sub-model

For each individual i, i=1,2,…,n, there is n_i repeated measures. Let $Y_i=(Y_{i1},...,Y_{in_i})$ denotes the vector of n_i longitudinal measures at times $t_{i1},...,t_{in_i}$, where Y_{ij} ($j=1,...,n_i$) takes values in $\{1,...,k\}$ for $k \geq 2$. Here, the longitudinal ordinal response variable, the level of CD4 cell count, has four ordinal categories (k=4). To modeling these longitudinal ordinal repeated measurements, a proportional odds sub-model, which incorporates subject-specific random effects for multiple observations on each subject, was used. The proportional odds model is written as follows:

$$\log\left(\frac{P_{ijk}}{1-P_{ijk}} \mid X_{ij},W_{ij},\theta,\beta,\alpha,b_i\right)=\theta_k-X_{ij}^T\beta-W_{ij}^Tb_i \quad (1)$$

where $P_{ijk}=P(Y_{ij}\leq k)$ and $q=(q_1,...,q_{K-1})^T$ is the intercept of each response categories, $k=1,...,K-1$, with $k=1,...,K-1$, $\theta_1<\cdots<\theta_{K-1}$, β is a $p\times1$ parameter vector of fixed effects of predictors X_{ij}, and W_{ij} is a $q\times1$ vector of predictors for random effects. Moreover, $b_i\sim N_q(0,\Sigma_b)$ denotes the vector of random effects for ith subject.

Proportional hazards sub-model

A proportional cause-specific hazards model with the subject-specific random effects is used to analyze competing risks failure time data. Let us define $C_i=(T_i,D_i)$ as the survival data, where T_i is the survival time, and D_i denotes the type of failure, $D_i\in\{0,1,...,g\}$. It should be noted that $D_i=0$ indicates a censoring event and $D_i=d$ ($d=1,...,g$) shows that subject i failed from the dth type of failure and g is the number of event type. This model is defined as follows

$$\lambda_d^i(t\mid Z_i(t),u_i,g,h)=\lambda_{0d}(t)\exp\{Z_i^T(t)g_d+h_du_i\} \qquad d=1,...,g \quad (2)$$

where $\lambda_d(t\mid.)$ is the hazard of failure due to event type d at time t, $\lambda_{0d}(t)$ is the baseline hazard function for dth type of failure, $Z_i(t)$ is the $l\times1$ vector of potential time-dependent predictors, $\gamma=(\gamma_1,...,\gamma_g)^T$ is the vector of regression coefficients for different types of events, and $\eta=(\eta_1,...,\eta_g)^T$ presents the coefficients of the frailty u_i for the g competing risks. The random effects u_i represent all unobservable traits of subject i which are shared in all g failure processes and induce correlation between all types of failure. It is assumed that the random effects b_i and u_i jointly have a multivariate normal distribution $v_i=(b_i,u_i)^T\sim N(0,\Sigma)$, where $\Sigma=(\Sigma_b,\Sigma_{bu}^T;\Sigma_{bu},s_u)$. It is further assumed that the two processes are conditionally independent given the covariates and random effects v_i.

An EM algorithm proposed by [26] was used to estimate the parameters of this joint model. All statistical analyses were performed at a significance level of 0.05 using the JMcmprsk library from the R software, version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria, RC Team. URL http://www. R-project. org).

RESULTS

Of 1530 HIV-infected patients, 149 patients developed TB and 711 patients progressed to AIDS, during the follow-up. The mean and the median of follow-up time were 64.76 and 40.01 months, respectively. The first CD4 cell count was measured at the time of diagnosis, known as baseline CD4 cell count. Other occasions for assessing CD4 cell counts were different across patients. The frequency of CD4 measurements varied between 2 to 31 times over the follow-up period. However, the CD4 cell count of most of the patients (about 89%) was measured at most 12 times. So, the CD4 trajectories of the first twelve CD4 measurements for patients infected with TB and progressed to AIDS were shown in Figure 1 (a) and (b), respectively. In both parts of Figure 1, the top sections show that the patients'CD4 cell count decreased linearly (dark to light colors), the middle sections showed that the patients' CD4 cell count increased linearly (light to dark colors), and the bottom sections showed the patients'CD4 cell count did not change over time.

The mean (SD) age of the patients at the time of diagnosis was 33.72 (10.04) years with a range of 1 to 74 years. The characteristics of these patients are given in Table1. The majority of the patients were male (76.53%), married (59.55%) (including married, divorced, and widowed individuals), with a low educational level (92.94%) and without the history of being in prison (59.34%). Only 4.58% of patients were alcohol abusers, while 51.44% of them were drug abusers. About 47.72% of patients received ART and only 18.24% of them were enrolled in IPT (Table1).

The cumulative incidence curves of AIDS progression and TB infection for different trajectories of CD4 cell count were given in Figure 2. This Figure suggested that lower

TABLE 1. The characteristics of HIV-infected patients (n=1530)

VARIABLE	FREQUENCY	PERCENTAGE (%)
Gender		
Male	1171	76.53
Female	359	23.47
Marital Status		
Never married	619	40.45
Married	911	59.55
Educational Level		
High (academic)	108	7.06
Low (school)	1422	92.94
Being in Prison		
No	908	59.34
Yes	622	40.66
Drug Abuse		
No	743	48.56
Yes	787	51.44
Alcohol Abuse		
No	1460	95.42
Yes	70	4.58
Antiretroviral Therapy		
No	800	52.28
Yes	730	47.72
Isoniazid Preventive Therapy		
No	1251	81.76
Yes	279	18.24
Baseline CD4 cell/mm3		
<200	526	34.38
200-349	368	24.05
350-500	271	17.71
>500	365	23.86

CD4 cell counts were associated with a shorter time of AIDS progression and a shorter time of TB infection.

The effects of the various predictors on the cause-specific hazards of AIDS progression and TB infection as well as the trend of CD4 cell count based on the joint model were given in Table 2. Table 2 (A) represents the results of the longitudinal model for the CD4 cell count. According to the results, having higher ages (OR=2.17; 95% CI: 1.39 to 3.41 and; p<0.001), and being in prison (OR=1.81; 95% CI: 1.13 to 2.89 and; p=0.013) were associated with a decreased the level of CD4 cell count significantly. Moreover, receiving antiretroviral therapy (OR=0.28; 95% CI: 0.18 to 0.44 and; p<0.001), and isoniazid preventive therapy (OR=0.56; 95% CI: 0.41 to 0.77 and; p<0.001) were associated with an increasing level of CD4 cell count. Moreover, the interaction term between ART and time was significant (OR= 0.89; 95% CI: 0.85 to 0.92 and; p<0.001), which revealed that the effect of antiretroviral therapy on the trend of CD4 cell count changes over time, The results of the likelihood ratio test, which was used to assess the proportional odds assumption in the longitudinal part of the joint model,

TABLE 2. The results of the joint model for competing events (AIDS/TB) and longitudinal measurements (CD4 cell count)

(A) LONGITUDINAL ENDPOINT

Variable	Ref	Parameter (SE)	OR (95% CI)	P-value
Age (Year)	-	0.78 (0.23)	2.17 (1.39, 3.41)	<0.001*
Gender	Male	-0.40 (0.34)	0.67 (0.34, 1.30)	0.234
Marital Status	Married	-0.08 (0.27)	0.92 (0.54, 1.56)	0.764
Education	High	0.33 (0.44)	1.39 (0.59, 3.29)	0.451
Being in prison	No	0.59 (0.24)	1.81 (1.13, 2.89)	0.013*
Drug Abuse	No	0.11 (0.31)	1.11 (0.60, 2.03)	0.737
Alcohol Abuse	No	0.42 (0.47)	1.52 (0.61, 3.81)	0.372
ART	No	-1.28 (0.23)	0.28 (0.18, 0.44)	<0.001*
IPT	No	-0.58 (0.16)	0.56(0.41, 0.77)	<0.001*
Time (Month)	-	0.10 (0.06)	1.11 (0.99, 1.25)	0.083
ART×time†	-	-0.12 (0.02)	0.89 (0.85, 0.92)	<0.001*
IPT×time†	-	0.01 (0.01)	1.01 (0.98, 1.02)	0.764

(B) SURVIVAL ENDPOINT

RISK1: TB INFECTION

Variable	Ref	Parameter (SE)	HR (95% CI)	P-value
Age (Year)	-	0.99 (0.18)	2.69 (1.89, 3.83)	<0.001*
Gender	Male	-0.33 (0.35)	0.72 (0.36,1.42)	0.344
Marital Status	Married	0.06 (0.21)	1.07 (0.71, 1.59)	0.759
Education	High	-0.09 (0.38)	0.91 (0.43,1.92)	0.798
Being in prison	No	1.02 (0.30)	2.77 (1.52, 4.99)	0.001*
Drug Abuse	No	0.05 (0.26)	1.05 (0.64, 1.74)	0.832
Alcohol Abuse	No	0.65 (0.26)	1.91 (1.15, 3.18)	0.012*
ART	No	-0.94 (0.36)	0.39 (0.19, 0.79)	0.009*
IPT	No	-2.89 (0.06)	0.06 (0.02, 0.19)	<0.001*

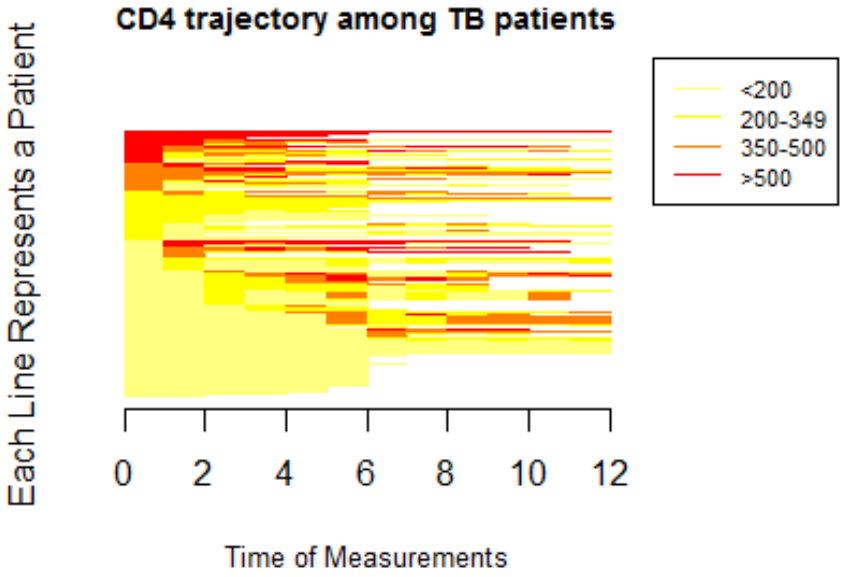
RISK2: PROGRESSION TO AIDS

Age (Year)	-	0.58 (0.09)	1.79 (1.49, 2.13)	<0.001*
Gender	Male	0.17 (0.14)	1.19 (0.90,1.57)	0.224
Marital Status	Married	-0.06 (0.12)	0.94 (0.75,1.18)	0.598
Education	High	0.22 (0.20)	1.24 (0.83, 1.85)	0.280
Being in prison	No	0.36 (0.28)	1.44 (0.83, 2.48)	0.198
Drug Abuse	No	-0.07 (0.13)	0.93 (0.71, 1.21)	0.599
Alcohol Abuse	No	0.08 (0.22)	1.08 (0.69, 1.67)	0.733
ART	No	-0.50 (0.11)	0.60 (0.49, 0.75)	<0.001*
IPT	No	-0.16 (0.13)	0.85 (0.66, 1.10)	0.223

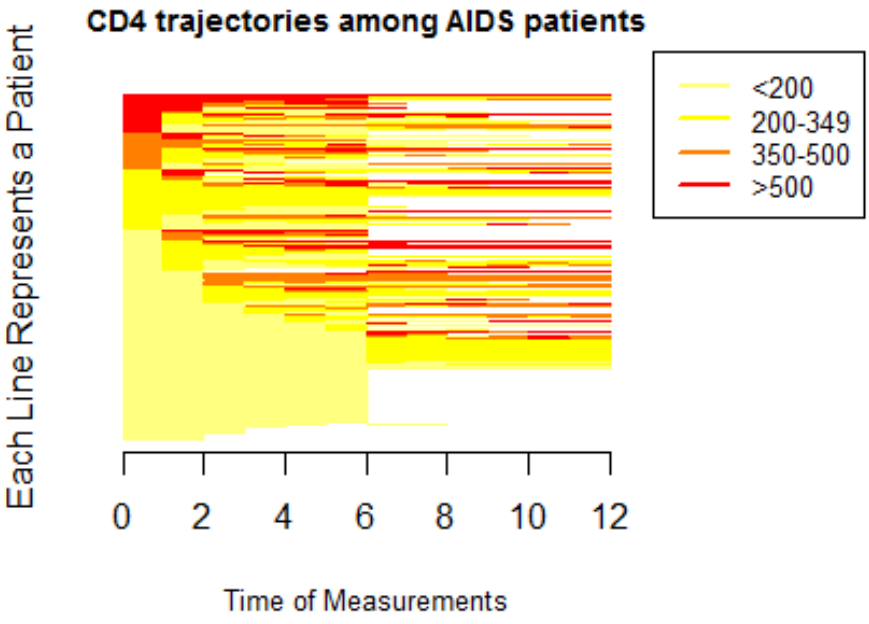
(C) RANDOM EFFECTS

		Parameter (SE)	P-value	
ρ_{bu}		1.75 (0.24)	<0.001*	
η_2		1.14(0.18)	<0.001*	

FIGURE 1. The trajectories of CD4 cell count in HIV-infected patients who a) Infected with TB and b) Progressed to AIDS.

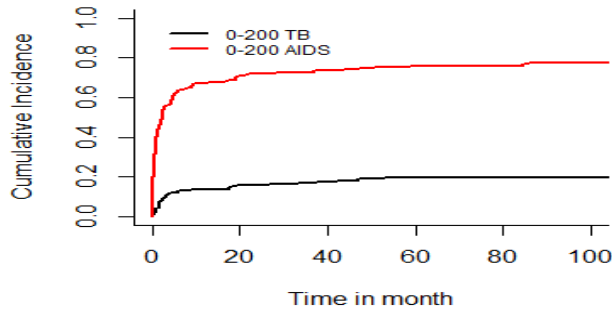


(a)

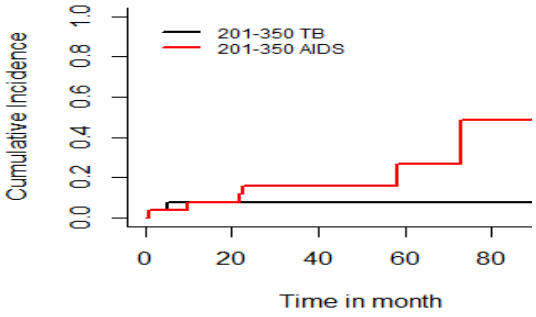


(b)

FIGURE 2. The cumulative incidence curves of AIDS progression and TB infection in based on CD4 cell count a) Less than 200 cells over time, b) Between 201-350 cells over time, c) Between 351 to 500 cells over time, d) More than 500 cells over time, e) Decreasing trend over time for CD4 cell count, and f) Increasing trend over time for CD4 cell count.



(a)



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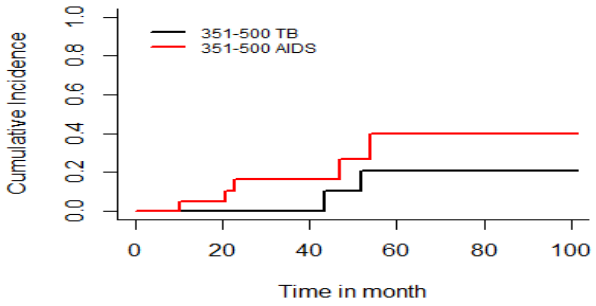
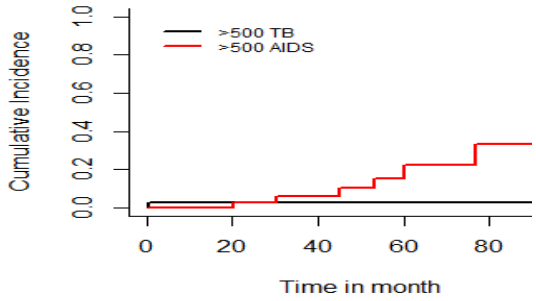
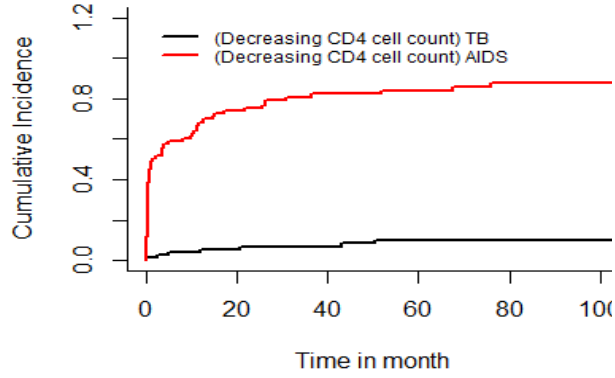


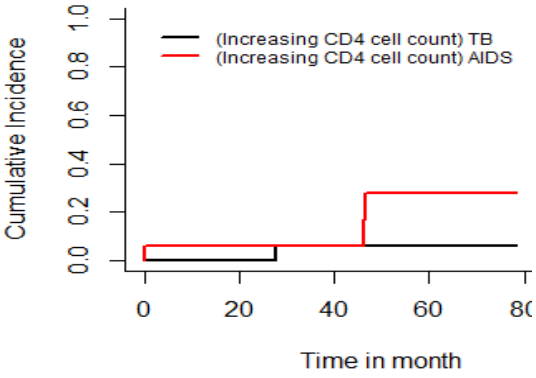
(c)



(d)



(e)



(f)

revealed that all of the variables satisfied the assumption.

The results obtained from fitting the joint model for the competing risks were presented in Table2 (B). As seen, the variables of age (HR=2.69; 95% CI: 1.89 to 3.83 and ; p<0.001), being in prison (HR=2.77; 95% CI: 1.52 to 4.99 and; p=0.001), being an alcohol abuser (HR=1.91; 95% CI: 1.15 to 3.18 and; p=0.012), were positively associated with the cause-specific hazards of progression to TB infection, while receiving antiretroviral therapy (HR=0.39; 95% CI: 0.19 to 0.79 and; p=0.009) and isoniazid preventive therapy (HR=0.06; 95% CI: 0.02 to 0.19 and; p<0.001) were negatively associated with the cause-specific hazards of progression to TB infection.

In addition, the results showed that age (HR=1.79; 95% CI: 1.49 to 2.13 and ; p<0.001) was positively associated with the cause-specific hazards of progression to AIDS, while receiving antiretroviral therapy (HR=0.60; 95% CI: 0.49 to 0.75 and; p<0.001) was negatively associated with the cause-specific hazards of progression to AIDS.

The estimate of $\mathbf{h}_2$ in the random-effects part of the model showed that there was a direct significant association (as the estimate was positive) between AIDS progression and TB infection (p<0.001). This means that, the patients with a higher risk of AIDS progression were more likely to progress to TB infection, as well. In addition, based on the results of the used joint model, the obtained estimation of ρ_{bu} indicated that the patients with a decreasing trend of CD4 cell count tended to have a higher risk of TB infection and AIDS progression (Table2 (C)).

DISCUSSION

In the current study, the effects of several potential risk factors and the trajectory of CD4 cell count on the risk of TB infection and AIDS progression were assessed using a joint model of the longitudinal ordinal outcome and competing risks data. The results of this joint model showed that the patients with a lower CD4 cell count are at a higher risk of TB infection and progression to AIDS. Moreover, it was shown that the HIV-infected patients with a higher risk of TB were more likely to progress to AIDS and vice versa.

Although, the HIV-TB co-infected patients had a wide spectrum of CD4 cell count, it has been shown that most of these patients had a CD4 cell count less than 200 cells per mm3 [27-29]. Furthermore, epidemiological studies have shown that the lower risk of TB-HIV co-infection is related to an increased level of CD4 cell count [23, 29]. In addition, other studies revealed that lower levels of CD4 was associated with a higher risk of progression to AIDS [30, 31]. Our findings of the joint model, which considers the changes in the trajectory of CD4 cell count, showed that the patients with a decreasing trend of CD4 cell count tend to have higher risks of TB infection and progression to AIDS.

Our findings showed that the patients who received ART had an increasing trend of CD4 cell count over time. Based on our results, the odds of having less CD4 cell count in patients who received ART compared to the patients who did not receive ART was 0.28. The findings of a systematic review including randomized controlled trials and observational studies revealed that the onset of receiving ART in patients with lower levels of CD4 cell count (at most 350 cells/mm3) causes an increase in the level of CD4 cell count and stops increasing virus burden [32].

We showed that the level of CD4 cell count had an increasing trend over time among the patients who received IPT. Therefore, the odds of having less CD4 cell count in patients who received IPT compared to the patients who did not receive IPT was 0.56. Although, Golub et al [33] have shown that the levels of CD4 were similar for all patients whether or not received IPT. In addition, our findings showed that there was a negative association between the age of the patients and the level of CD4 cell count. It has been shown that older patients tend to have lower CD4 cell count. Furthermore, an epidemiological study has shown that higher ages were associated with increased levels of CD4 cell count after receiving ART [34].

According to our findings, a substantial proportion (40.66%) of the patients had an imprisoning experience. This might be because of the fact that all prisoners who are intravenous drug users are routinely checked for HIV infection. This issue increased the frequency of HIV-positive patients who were imprisoned. Our findings revealed that the HIV-infected prisoners tended to have a lower CD4 cell count. The other retrospective study also has shown a reduction in CD4 cell count among inmates in the period between release and reincarceration [35].

It has been revealed that ART should be used judiciously for all HIV-infected patients and its clinical efficiency and biomedical benefits have been well authenticated [36, 37]. ART which consists of several antiretroviral drugs can suppress the HIV virus and stop the progression of HIV to the advanced stage of the disease, especially if it starts in the early stages [29]. On the other hand, for people who lived with HIV, ART is known to be (about 70%) protective against TB [15]. Our findings confirmed that ART can considerably reduce the risk of TB infection and progression to AIDS, such that the hazards of TB progression and AIDS progression for the patients who enrolled in ART were 0.39 and 0.60 lower compared with the other patients, respectively.

Several cohort studies have shown that ART is associated with a reduction in TB incidence [38-40], while it has been found that the incidence of TB remains unacceptably high after initiation of receiving ART [38, 41]. According to WHO, IPT leads to a reduction in the burden of TB among HIV-positive people and it should be adopted by policymakers and urgently be implemented

in all health facilities which offer HIV-care services [42]. Based on our findings, IPT can impressively decrease the risk of TB infection among HIV-infected patients; such that the risk of TB progression was 0.06 lower among HIV-infected patients who received IPT. It can be concluded that the patients who received both ART and IPT had a considerably lower risk of TB. In other words, the combination of ART and IPT may have a greater impact on the TB incidence.

Based on our findings, higher ages were strongly associated with increasing risk of progression to AIDS and TB infection. The epidemiological studies have shown that the patients older than 50 years were at a higher risk of AIDS progression as compared with the younger patients [43-45]. Furthermore, other studies have shown that the patients aged 40-49 years were at lower risk of TB compared to the patients aged less than 30 years [46].

The findings indicated that HIV-infected patients who were alcohol abusers were at a higher risk of TB infection. Based on our findings, the cause-specific hazard of progression to TB infection for the patients who were alcohol abusers was 1.91 times greater compared with the patients who were not alcohol abusers. According to WHO, using alcohol increases the risk of TB infection by threefold [47].

According to our findings, the hazard of TB infection was higher among HIV-infected patients who were imprisoned. It was estimated that the cause-specific hazard of progression to TB infection for the patients with the history of being in prison was 2.77 times greater compared with the patients not being imprisoned. A recent systematic review indicated that the risk of developing active TB infection among HIV patients who were in prisons varied among countries. However, in all of the studies who were enrolled in this review, the risk of TB was higher among HIV-positive prisoners. Indeed, lower CD4 count was associated with a higher risk of TB. Therefore, the higher risk of TB may in part be explained by the level of CD4 cell count among HIV-infected prisoners [48].

The results of our joint model revealed that the risks of TB infection and progressing to AIDS were positively correlated. Furthermore, TB has been known as the most profitable clinical indicator for the progression of HIV infection with the severity of immunosuppression or signs and symptoms of AIDS [23]. Since the aim of this study was to assess the factors affecting on time to AIDS and TB progression, we have not considered death event as a competing risk. Although, it is of interest to add death event as a competing risk for future studies. This study had some limitations. For survival analysis, reliable data based on prospective cohort studies are required. However, our data was based on a retrospective study where information was based on the data recorded by registry centers. Therefore, we were unable to assess the accuracy of the data. This issue may introduce information bias. On the other hand, another limitation of this study was that the CD4 cell count was recorded just twice for a proportion of the patients, while it would have been better if recording CD4 cell count was repeated several times. The other limitation was that we considered the diagnosis time as the starting time of follow-up while a number of patients might be diagnosed until late in infection. This limitation (left censorship) can introduce under/overestimate cumulative incidence probabilities for both TB infection and AIDS progression. As our joint model was not able to model the sequence of the events (TB infection and AIDS progression), it is suggested to use a multi-state model in the survival part of the model and to develop R codes for this extended model in future studies. In spite of these limitations, simultaneous examination of several potential predictors on TB infection, AIDS progression, and on the trajectory of CD4 cell count was evident. Such information may be useful for institution of intervention measures to suppress the progression to AIDS and TB infection among HIV-infected patients.

CONCLUSION

The joint model provided a flexible framework for simultaneous studying the effects of different covariates on the level of CD4 cell count as well as the risk of TB infection and AIDS progression. This model also enabled us to assess the effect of CD4 trajectory on competing risks of TB and AIDS progression.

Ethical Approval and 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. This study was approved by the Research Ethics Committee of Hamadan University (No. IR.UMSHA.REC.1396.690).
Written informed consent was obtained from all participants.

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Conflict of interest

The authors declare that there is no conflict of interests.

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