Identifying predictors of progression to AIDS and mortality post-HIV infection using parametric multistate model

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ABSTRACT

Objectives: The human immunodeficiency virus (HIV) has already remained as a major public health problem all over the world. This study aimed to identify the prognostic factors influencing the disease progression in patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) in Iran, using parametric multi-state model to take into account the intermediate event in the analysis.
Methods: The data of the present retrospective cohort study was extracted in Tehran from April 2004 to March 2014. The number of 2473 HIV-infected patients in Behavioral Diseases Counseling Centers was enrolled. The outcomes of interest were the transition times from HIV diagnosis to AIDS and AIDS to death. The effect of several prognostic factors on both transitions was investigated.
Results: Parametric model indicated that AIDS progression was significantly associated with an increase in age (P = 0.017), low education (P = 0.026), and a decreased CD4 cell count (P = 0.001). Furthermore, the AIDS-related death was significantly associated with male sex (P = 0.010), tuberculosis coinfection (P = 0.001), antiretroviral therapy (P = 0.001) and a decreased CD4 cell count (P = 0.035).
Conclusion: The results of this study indicated that CD4 cell count was one of the most important prognostic factors that affected and accelerated both HIV→AIDS and AIDS→DEATH transitions and antiretroviral treatment was found to be an effective measure in decelerating transition of the patients with AIDS to death state. The usual Cox Model was not able to identify some of these prognostic factors.

Key words: HIV/AIDS; highly active antiretroviral therapy; multistate model; survival analysis; tuberculosis; cohort studies.

INTRODUCTION

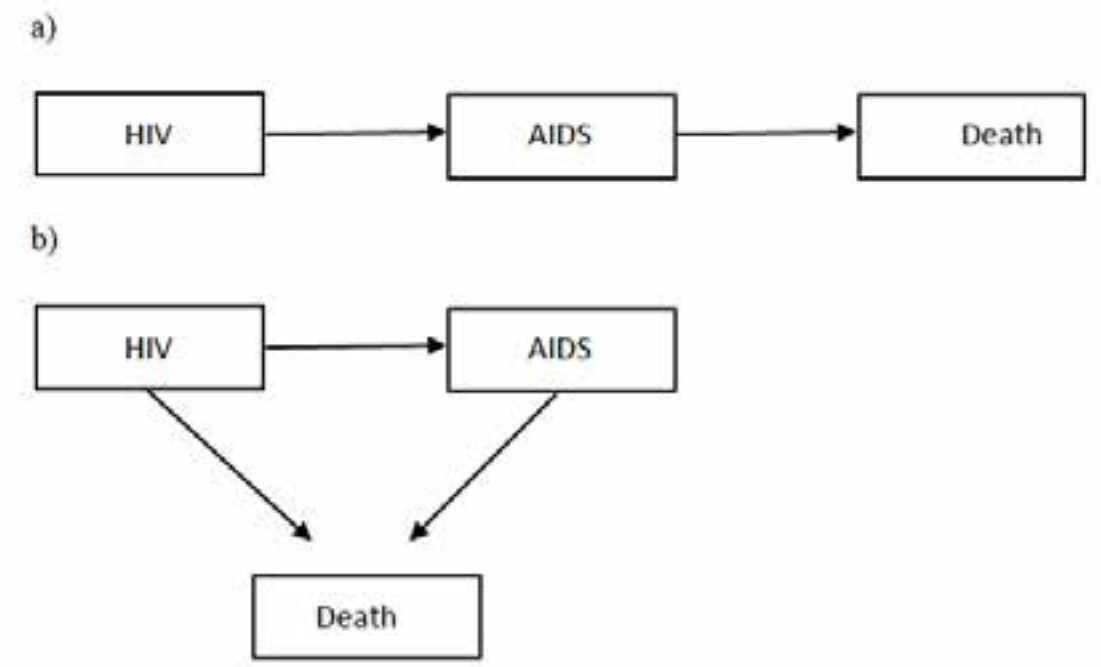
The human immunodeficiency virus (HIV) has already remained as a major public health problem worldwide. The final and the most serious stage of HIV infection is acquired immunodeficiency syndrome (AIDS), which results in sever damages to the body immune system. Since the onset of the epidemic, about 78 million people have been infected with the HIV virus and about 35 million people have died because of AIDS-related diseases. As stated by the World Health Organization (WHO), there was an estimated 36.7 million people worldwide living with HIV/AIDS at the end of 2015 [1].

Currently, no functional cure is available for HIV infection. Nevertheless, antiretroviral treatment (ART) can efficiently control the HIV virus progression and help patients to return to a relatively healthy and productive lives [2]. In addition, several prognostic factors including chronic pathologies associated with immunodeficiency, chronic viral and bacterial infections can complicate treatment. There are some evidences that show life span can be prolonged and quality of life can be improved significantly by suppressing the levels of HIV and remaining the CD4 count high (above 200) [3]. The risk of opportunistic infections, especially co-infection with tuberculosis (TB) is a life-threatening issue for HIV-infected patients. The possibility of developing TB, the major cause of HIV-related death, can be positively affected by ART as well [3].

Although the HIV-related mortality has declined in recent years, better understanding of the prognostic factors affecting the survival of the HIV-positive patients to improve their life expectancy is of great importance, especially in developing countries where limited studies regarding survival of these patients have been conducted [3-5]. To this end, utilizing appropriate and powerful statistical methods for data analyzing that take their structure into account plays an important role.

There are several clinical and epidemiological follow-up studies that survival is the ultimate outcome while individuals may experience intermediate events during the study period [6]. In such cases, modeling the passage of subjects through states is often useful. However, this is usually conducted by utilizing multiple separate analyses for every single endpoint [6]. Nevertheless, this does not allow for uncovering relationships between different endpoints [7]. Multistate models provide a relevant modeling framework for this type of data [8] and constructing these models provides a comprehensive view of a disease process. Multistate models allow for estimation of proportions of individuals who will be in the various states at some time in the future and make more efficient use of incomplete information when only fairly short portions of individual's disease histories are available [9]. In HIV disease, where survival of the patients is the outcome of interest, there is an intermediate event (AIDS) for the patients suggesting that the time from HIV to death process should be modeled by a progressive multi-state statistical model (Figure 1). This is an important issue that is not taken into account in most studies about HIV/AIDS. For example, there were

FIGURE 1. A schematic view of multi-state models for HIV data; a) Progressive multi-state model, b) Illness-death multistate model.



found two recently conducted study about HIV/AIDS that analyzed survival of the patients without considering the intermediate event [3, 4]. However, as mentioned it can affect dramatically the coefficients of the covariates and their standard errors as well as achieved results. This is because of the fact that they fail to show the relations between different types of events [10].

Modeling censored follow-up data and investigating prognostic factors affecting survival time focus on employing Cox proportional hazards (PH) model most of the time. However, the Cox model is not the only existed model to analyze censored time to event data. Alternative models for survival analysis are (semi) parametric and non-parametric models [11-13]. Parametric models are acceleration failure time models, since survival time is modeled directly as a function of predictors or risk factors [14]. Using parametric survival models leads to some benefits. For example, whenever the parametric models provide a good fit to data, they result in more precise estimates of the quantities of interest. In parametric models all parts of the model (the baseline hazard functional form and the effect of covariates) are specified and their estimates are based on fewer parameters [15]. A parametric model provides more flexibility because the associated hazard rates are not constant with respect to time [16]. Efron [17] and Oakes [18] showed that parametric models lead to more efficient estimates compared with the Cox model in some special situations. Moreover, several studies compared parametric survival models performance with Cox regression and confirmed that parametric models fit the data better than the Cox model [19-21]. Furthermore, the estimated coefficients are directly interpreted in terms of accelerating survival times [14]. The aim of the present study was to estimate the effect of potential risk factors on progression from HIV to AIDS and from AIDS to death based on a multi-state model to take into account the effect of the intermediate event within a parametric perspective. We also compared the performance of the parametric model with the Cox model.

METHODS

Data set

The present study was a registry-based retrospective cohort study conducted in Tehran, Iran, from April 2004 to March 2014, approved by the Research Council of Hamadan University of Medical Sciences. The study population consisted of HIV-positive people with a medical record in one of the two electronic registry based Behavioral Diseases Counseling Centers in Tehran (Imam Khomeini and Zamzam Centers). The data collected using a checklist of items, which was developed according to the information documented in the medical records. The collected information involved demographic information (age, sex, marital status, and educational level), behavioral information (drug/alcohol abuse, smoking, and being in prison), CD4 cell count, ART, coinfection with TB, and causes of death [3].

An individual who was infected with HIV, irrespective of clinical stage confirmed by laboratory criteria according to the country definitions and requirements, was an HIV-positive case [3]. In the Islamic Republic of Iran, an individual whose two sequential enzyme-linked immunosorbent assay (ELISA) tests for HIV antibody followed and confirmed by a western blot test are positive is defined as an HIV case [22]. Also, a case of AIDS was defined as a presumptive or definitive diagnosis of stage 4 condition and/or CD4 count less than 200 per mm3 of blood in an HIV-infected subject [3, 23]. The outcomes of interest included the duration of time (1) from the HIV diagnosis date to AIDS progression and (2) from AIDS to AIDS-related death. During data collection, a registry expert called patients (or their family members) to ask about their status (alive/dead) and the reason of death. The censoring included those patients who were lost to follow up or died due to reasons other than AIDS and those who were alive at the end of the study period [3].

Data Pre-processing and Dealing with Missing Values

Pre-processing of the data set was done in two steps: 1) fields with spelling errors, additional tokens, other irregularities and irrelevancies like outliers were corrected or removed; 2) Little MCAR test [24] was performed to assess the missing completely at random (MCAR) mechanism for missingness ($p = 0.433$), and since the MCAR assumption did not reject, persons with at least one missing variable were removed from analysis (the overall missing was about 24%). Table 1 shows the demographic and clinical characteristics of the patients.

Statistical methods

Multi-state model

Multi-state models are a generalization of survival analysis where time to death is the ultimate outcome of interest but there are intermediate states [25]. In this case, subjects are allowed to move between some finite states. The states can be defined by some clinical states, biological markers, etc. A transition or an event is occurred when a subject's state changes [26]. The progressive multi-state model is a model with three states. Here in the used data set, the first (initial) state is being infected with HIV, the second state is AIDS and the third state is death from AIDS. So, AIDS is the intermediate state. Another possible state for the used data set is the illness-death model where some of the patients may have a transition directly from the

TABLE 1. Characteristics of the study population infected with the HIV virus (n=2249).

VARIABLES	NUMBER	PERCENT
Gender		
Female	505	22.45
Male	1744	77.55
Age group (year)		
1-24	260	11.60
25-44	1639	73.10
45-74	343	15.29
Marital status		
Single	874	40.37
Married	852	39.35
Divorced	330	15.24
Widow	109	5.03
Education level		
High(academic)	147	7.34
Low (school)	1856	92.66
Being in prison		
No	899	39.97
Yes	1350	60.03
Smoker		
No	933	46.91
Yes	1056	53.09
Drug abuse		
No	1119	49.75
Yes	1130	50.24
Tuberculosis infection		
No	2012	89.46
Yes	237	10.54
Antiretroviral therapy		
No	1315	58.47
Yes	934	41.53
Baseline CD4 count (cells/mm3)		
500+	417	21.55
351-500	296	15.30
201–350	415	21.45
0–200	807	41.70

initial state of HIV to death state without experienceing the intermediate event of AIDS [10]. However, in the present study, there were no such transitions.

Let $S = \{1,\ldots,N\}$ be a finite state space. Then a multi-state process is a stochastic process $(X(t), t \in T)$, with S and $T = [0, \tau]$, where $\tau < \infty$. While the process evolves over time, H_t- (a history and σ- algebra) like the states previously visited and times of transitions are generated. Transition probabilities between two states of h and j states, are defined as

$$p_{hj}(s,t) = P(X(t) = j | X(s)=h, H_s) \quad (1)$$

for $h,j \in S, s,t \in T, s \leq t$ and transition intensities are defined as

$$\alpha_{hj}(t) = \lim_{\Delta t \to 0} \frac{p_{hj}(t, t+\Delta t)}{\Delta t} \quad (2)$$

In a multistate model, the insantaneous hazard of progression to state j conditionally on occupying state h, can describe and characterize the multi-state process [10]. "If $\alpha_{hj}(t)$ only depends on the history via the state $h=X(t)$ occupied at time t then the process is Markovian" [8].

Parametric survival model

In a parametric survival model, it is assumed that survival time or a function of it has a known statistical distribution. Some of the most widely used distributions are Exponential, Weibull, gamma, log normal, log logistic and normal. In a parametric regression model, an explicit relationship between survival time and the covariates is considered [27]. Survival time can be modeled by an accelerated failure time model like conventional regression model [27] where it is assumed that the logarithm of the survival time Y=ln(T) is related to the covariates (Z) linearly. This relationship is as follows:

$$Y = Ln(T) = \mu + y^t Z + \sigma W \quad (3)$$

where is the regression coefficients vector and W is the error distribution. Different distributions for W yield different regression models. A logistic distribution yields a log logistic regression model and estimation of covariates is performed via maximum likelihood methods [15]. In the present study, we used a parametric log logistic distribution to model the intermediate and final state in the progressive multi-state model. In this model the survival function is as follow:

$$S(t) = \frac{1}{1 + at^b}$$

where b>0 determines the shape of hazard function [15]. In order to evaluate the performance of the model, we devided the dataset to train and test sets. So the train dataset was used to model fit and the test set was used to evaluate the performance of the model and to calculate performance criteria. We repeat this 100 times. The criteria of Brier score [28] and c-index [29] were utilized to compare the performance of log logistic and Cox PH models.

Software

All statistical analyses were performed at a significance level of 0.05 using the mstate library [30, 31] from the R software, version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

Brier score and c-index were calculated using "pec" package [32].

RESULTS

The number of 2519 patients was identified, of which 25 patients were ineligible and 21 patients had a medical record in both centers. In order to fit progressive multi-state model, we prepared the data and use a subset of the original data. So, the analysis was based on data from the remaining 2249 patients (1744 men and 505 women). There were 130 patients whose HIV/AIDS had been diagnosed before April 2004, the establishment of the centers and their information was registered and included in the study. This led to the survival times to be longer than 10 years (from 2004 to 2014). The mean (SD) age of the patients was 34.01 (10.43) years, with a range from infancy to 74 years.

The characteristics of the study population are given in Table 1. Some of information of the patients was not registered (seen from Table 1). Of 2473 patients infected with the HIV virus (initial state), 1249 patients developed AIDS (transition from initial state to AIDS state; i.e. HIV→AIDS), 292 patients out of 1249 patients with AIDS died from AIDS-related causes (transition from AIDS state to death state; i.e. AIDS →Death) and the rest of them were censored (alive or lost to follow up) at the end of the study period. The majority of the HIV-infected patients aged 25–44 years, was male (77.55%), single (40.37%), low-educated (92.66%), smoker (53.09%), drug abuser (50.24%) and had a history of being in prison (60.30%).

Figure 2, illustrates the cumulative hazards of transition from HIV to AIDS and AIDS to death for the patients, obtained from progressive multistate model. In addition, stacked transition probabilities (a convenient way to interpret transition probabilities) were plotted (Figure 3). The distance between two adjacent curves represents the probability of being in the corresponding state. As can be seen, the probability of transition from HIV to AIDS and the probability of transition from AIDS to death increase over time.

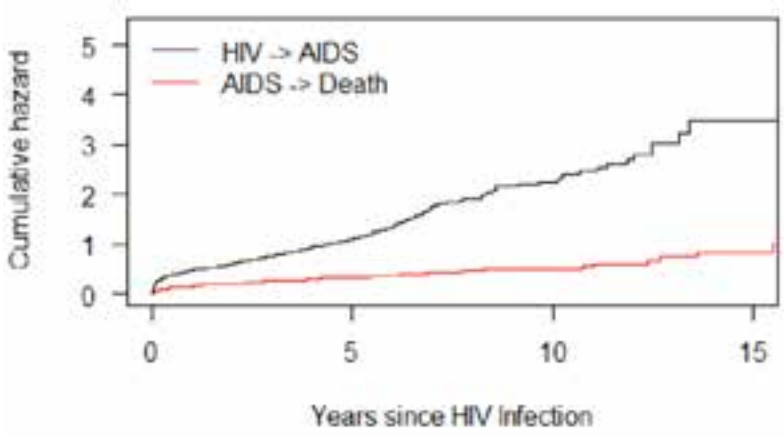
Several parametric distributions were fitted to time of transition from HIV to AIDS and time of transition from AIDS to AIDS-related death. The Akaike information criterion (AIC) for the models was shown in Table 2. As can be seen, the log logistic distribution had a better fit than the others (AIC = 9347.95 for HIV→AIDS and AIC = 3244.039 for AIDS →Death). The performance of the models was assessed using Brier score and c-index. The results over 100 replications showed smaller Brier score for log logistic model (0.22±0.08) compared with the Cox model (0.24±0.11). Moreover, the log logistic model had larger c-index (0.798±0.06) compared with the Cox model (0.773±0.09).

The effect of several predictors on progression to AIDS and AIDS-related death is given in Tables 3. Based on the coefficient estimations, there was a significant association between an increase in age (P = 0.017), low educational levels (P = 0.026), using Antiretroviral therapy (P = 0.014) and a decreased level CD4 cell count (P = 0.003 and 0.001) and time to progression to AIDS (transition HIV→AIDS). In addition, there was a significant

TABLE 2. Akaike information criterion value of different distributions for each transition.

	Transition	
	HIV → AIDS	**AIDS → Death**
Exponential	14201.4	3322.428
Weibull	10045.62	3245.898
Log-normal	10334.4	3272.165
Log-logistic	9347.95	3244.039
Gaussian	15992.41	3565.093
Logistic	15936.94	3602.228

FIGURE 2. Cumulative hazards from HIV to AIDS and AIDS to Death.



association between male sex (P = 0.010), TB coinfection (P = 0.001), antiretroviral therapy (P = 0.001) and a decreased level CD4 cell count (P = 0.035) and time to AIDS-related deaths (transition AIDS →Death).

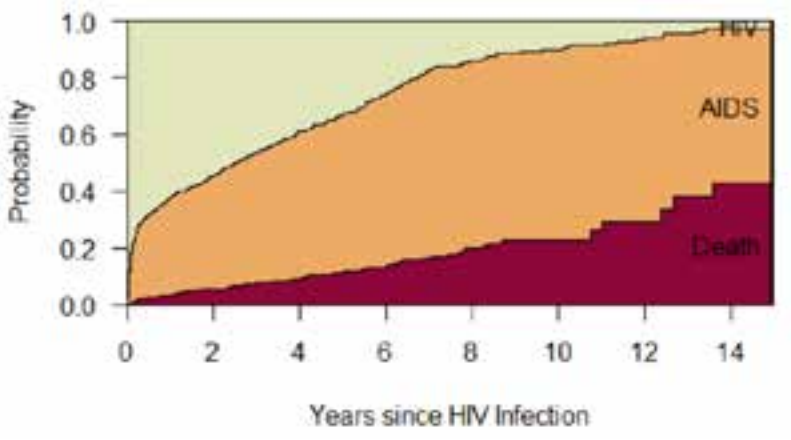
DISCUSSION

There are many studies in medical fields with intermediate events playing an important role in the disease courses. The use of the multi-state models improves

TABLE 3. Adjusted Regression coefficients (and standard errors) for the full model.

	TRANSITION			
	HIV → AIDS		AIDS → DEATH	
Covariates	**β (SE)**	**p-value**	**β (SE)**	**p-value**
Gender				
Female	Ref.		Ref.	
Male	0.36 (0.19)	0.051	-1.19 (0.46)	0.010
Age group (year)				
1-24	Ref.		Ref.	
25-44	-0.48 (0.20)	0.017	0.44 (0.46)	0.339
45-74	-0.60 (0.25)	0.017	0.23 (0.53)	0.664
Marital status				
Single	Ref.		Ref.	
Married	0.04 (0.14)	0.797	0.09 (0.28)	0.758
Divorced	-0.08 (0.17)	0.644	-0.10 (0.33)	0.762
Widow	-0.16 (0.27)	0.567	0.96 (0.80)	0.230
Education level				
High(academic)	Ref.		Ref.	
Low (school)	-0.52 (0.23)	0.026	-1.19 (0.68)	0.083
Being in prison				
No	Ref.		Ref.	
Yes	-0.32 (0.20)	0.118	-0.29 (0.40)	0.471
Smoker				
No	Ref.		Ref.	
Yes	-0.18 (0.19)	0.364	0.35 (0.37)	0.354
Drug abuse				
No	Ref.		Ref.	
Yes	-0.03 (0.21)	0.882	-0.08 (0.43)	0.854
Tuberculosis infection				
No	Ref.		Ref.	
Yes	0.021 (0.18)	0.241	-1.03(0.28)	0.001
Antiretroviral therapy				
No	Ref.		Ref.	
Yes	-0.29 (0.12)	0.014	2.39 (0.25)	0.001
Baseline CD4 count (cells/mm^3)				
500+	Ref.		Ref.	
351-500	-0.56 (0.19)	0.003	-0.81 (0.64)	0.207
201–350	-1.71 (0.19)	0.001	-0.43 (0.57)	0.447
0–200	-4.43 (0.16)	0.001	-1.10 (0.52)	0.035

FIGURE 3. Stacked transition probabilities.



the understanding of variation in risk factors related to the evolution of diseases substantially [33]. By using these models, the probabilities and hazards of occurrence of different events could be obtained. Our study presented the effect of several predictors on the duration of time to two different states in HIV-infected patients (the duration of time from HIV diagnosis to AIDS progression and from AIDS initiation to AIDS-related death) using parametric multi-state model. The acceleration factor in the utilized Log-logistic models in both transitions allows us to readily interpret obtained coefficients in terms of either survival probabilities or times. We identified several risk factors strongly associated with survival times of transitions to both states (HIV→AIDS and AIDS →Death).

Age was shown to have a strong association with progression to AIDS (transition HIV→AIDS). These results suggest that the time for transition from HIV to AIDS is accelerated for patients aged 45–74 years compared to those aged 1–24 years by an estimated factor of 0.55 (exp(-0.60)). In terms of the survival functions estimated from this model, $\hat{S}_1(t) = \hat{S}_2(0.55t)$ where $\hat{S}_1(t)$ and $\hat{S}_2(t)$ are the respective survival functions for patients with 1-24 and 45-74 years old, which means it needs about two fold more time for an HIV positive patient aged 1-24 year to progress AIDS compared to a patient aged 1-24 year. It has been indicated by the epidemiological studies that patients aged 50 years or more are at a higher risk of progression to AIDS compared to younger patients [3, 34-36].

According to our findings, a significant association between educational level and time to progression to AIDS (transition HIV→AIDS) was observed. These results suggest that the time for transition from HIV to AIDS is accelerated for patients with lower education compared to those with higher education by an estimated factor of 0.59 (exp(-0.52)). Recent studies confirmed that lower educational level was related to late HIV diagnosis and late initiation of ART [3, 37].

A leading preventable cause of death among people living with HIV is TB [38]. The results indicated that time to transition to death for an HIV-infected patient who had developed AIDS and were co-infected with TB is accelerated by an estimated factor of 0.36 (exp(-1.03)) compared to those who infected with HIV alone. This finding is in concordance with the results of other epidemiological studies [3, 4, 39]. Therefore, the importance of treatment of TB in HIV infected people is revealed by this evidence.

According to the results, both time to progression to AIDS and time from AIDS initiation to AIDS related deaths were significantly associated with decreased levels of CD4 cell counts. These results suggest that the time for transitions HIV→AIDS and AIDS →Death are accelerated dramatically for patients that have a CD4 cell count less than 200 cells/mm3 compared to those with a CD4 cell count over 500 cells/mm3 by an estimated factor of 0.01 and 0.33, respectively (exp(-4.43) and exp(-1.10)). Moreover, it has been shown by several epidemiological studies that there is an increase in the risk of HIV/TB coinfection with decreasing the CD4 cell count [3, 40, 41]. A CD4 cell count over 500 cells/mm3 reduced TB-related mortality among HIV-positive people akin to those are not co-infected with TB and therefore it plays an important role in the incidence of HIV/TB coinfection [42].

In the present study, we utilized a multistate model from a parametric modeling perspective to analyze different states of HIV disease. This data set was previously analyzed by [3] using Cox PH model. Although Cox PH model has several advantages like consistency of the regression coefficients, it suffers from a restrictive assumption of proportionality of hazards. When the PH assumption does not hold, the Cox model can give unreliable results. In contrast, parametric models provide the interpretation based on a specific distribution directly for times to events with no need to the PH assumptions. According to previous studies parametric models lead to more efficient estimates compared to the Cox model if the underlying distributional assumption holds [17, 18]. The

results over 100 replications of utilizing log logistic and Cox model showed that in this dataset the parametric model outperformed the Cox model. In the used parametric multistate model for the current data set, ART (known as a very important factor) was significant for HIV→AIDS transition while the Cox model could not reveal this relationship. Similar to this, in the parametric model CD4 had a significant effect on the second transition (AIDS →Death) and again in the Cox model it was not significant statistically. Several studies were in concordance with our findings [43-45].

It should be noticed that reliable sources of data obtained from prospective designs were required for survival analysis and associated prognostic factors. However, in the present study a data set of a retrospective study recorded by registry centers was used and we were not able to verify the accuracy of the data. Information bias may be caused by this issue. Despite this limitation, the present study was conducted on a large data-set and the results can be generalized to the Iranian HIV-infected population. Furthermore, it was apparent the effect of several predictors on AIDS progression and AIDS-related deaths in a high–middle-income country. They may be useful information for institution of intervention measures to suppress the progression of HIV to AIDS and to reduce the risk of death among HIV-positive patients [3].

CONCLUSION

The focus of the present study was to identify more efficiently the important prognostic factors that affect the duration of time from HIV infection to AIDS and the duration of time from AIDS to death using parametric multi-state models. The results showed that several modifiable and non-modifiable predictors including co-infection with TB and decreased level of CD4 cell count affect the progression of AIDS and HIV-related death and accelerate time to AIDS and death. In addition, using antiretroviral therapy decelerates time to death dramatically and improves the survival of patients living with AIDS.

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Conflict of interest

The authors declare no conflict of interest.

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