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Factors associated with progression from HIV to death in patients receiving antiretroviral therapy in Southern Iran: a 21-year survival analysis and follow-up study

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Abstract

Introduction: The expansion of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) epidemic has been considered a serious issue globally, and the disease is currently a major contributing factor to morbidity and mortality rates in many developing countries. This study aimed to investigate survival rate of HIV-positive patients, and its' contributing factors among individuals receiving antiretroviral therapy in Southern Iran.

Material and methods: A prospective cohort study was conducted among 1,327 HIV patients, who started antiretroviral therapy (ART) between June 2000 and March 2021. Kaplan-Meier analysis and Cox proportional hazard regression analyses were applied to define the survival rate of patients.

Results: In this study, of 1,327 registered HIV/AIDS patients who were under ART, 30.6% died during the study period. The 1-, 2-, 5-, and 10-year survival rates of the patients were 90%, 87%, 78%, and 67%, respectively. Based on the results of multivariate Cox regression analysis, older age ($HR_{\geq 40/<40}$ = 1.48), occupation ($HR_{unemployment/employment}$ = 1.29), history of addiction ($OR_{yes/no}$ = 1.64), route of transmission ($HR_{IDU/sexual}$ = 0.48), baseline CD4+ < 200 ($HR_{< 200/> 500}$ = 2.91), clinical stage IV ($HR_{IV/I}$ = 1.70), ART adherence ($HR_{adherence/non-adherence}$ = 0.37), time on ART > 5 ($HR_{> 5/< 1}$ = 0.06), and anemia ($HR_{yes/no}$ = 1.58) were directly associated with the survival in patients.

Conclusions: Mortality in adults HIV-positive patients on antiretroviral therapy is relatively high in Iran. Age, history addiction, WHO clinical stage, low CD4+ count, and anemia are associated with poor survival in HIV patients. Concerned stakeholders should focus on early detection, timely ART onset, and adherence to treatment.

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Introduction

Acquired immune deficiency syndrome (AIDS) is currently one of the serious public health challenges worldwide [1]. AIDS is defined as the last stage of the disease that deteriorates immune system and makes the patient susceptible to opportunistic infections [2]. The disease is responsible for socio-economic crises, reduction in life expectancy, and devastating costs to health services [1]. The United Nations program on HIV/AIDS (UNAIDS) reported that in 2021, 37.7 million people were living with human immunodeficiency virus (HIV) worldwide [3]. Estimates from Iran show that the number of adults living with HIV/AIDS was as big as 53,000, of which 3,100 died by the end of 2020 [4]. Although all countries, including Iran, are committed to ending the AIDS epidemic by 2030, evidence indicates that the virus continues to spread widely [5].

To date, despite international scientific efforts, no cure is available for HIV/AIDS. However, with the introduction of antiretroviral therapy (ART), HIV infection has evolved from an acute and fatal disease to a chronic illness [1]. ART reduces transmission (by preventing viral replication and increasing immune function), complications, drug resistance, and mortality [6]. According to the UNAIDS statistics, 68% of patients are under ART, while only 28% of Iranian patients use this treatment [3]. This rate is very important, because ART can improve quality of life and life expectancy of Iranian HIV patients [7, 8]. New data from countries in the Middle East, including Iran, indicate an increase in the incidence of burden of the disease in this region in recent years [9, 10]. To decrease this trend, these countries should strengthen HIV surveillance and improve the use of ART therapy [9].

Despite providing ART to HIV patients, investigating survival rate of AIDS patients and factors affecting survival is critical for better understanding of the actual prognosis of AIDS, better clinical decisions, and planning healthcare interventions [11]. Demographic, behavioral, clinical, and socio-economic factors are associated with survival of HIV patients [12]. Results of previous studies show that factors, such as age, education, sex, co-infection, clinical stage of the disease, and CD4+ count predict survival in HIV patients [13, 14]. In a study by Zolopa *et al.* it was reported that in addition to ART use, early detection of the infection can reduce mortality of HIV-infected individuals [15].

Additionally, recognizing prognostic factors affecting survival of AIDS patients in developing countries, increasing their life expectancy is of great importance. However, limited studies have been conducted in these countries, especially in the Eastern Mediterranean region [2]. Investigating determinants of survival of HIV patients could help policy-makers, program planners, and clinicians' decision-making [16]. This study aimed to examine the survival rate and factors associated with progression from HIV to death in patients receiving antiretroviral therapy in Southern Iran.

Material and methods

Study design

A prospective cohort study was conducted in Fars Province, and enrolled HIV-positive patients who were on ART and diagnosed between June 2000 to March 2021. This province has the second highest HIV/AIDS prevalence rate in the country. The required information was obtained from behavioral diseases counseling center (BDCC). BDCC registers HIV-infected patients in South of Iran, and monitors their clinical progress, including treatment and death outcomes. At this center, after HIV confirmation, all patients complete a structured questionnaire with demographic characteristics, clinical status, drug use, high-risk behaviors, and presence of co-infections. Trained and experienced experts collect the data during a face-to-face interview. In this study, a total of 1,327 HIV/AIDS patients were included in the final analysis. Inclusion criteria were being over 15 years of age, diagnosed between June 2000 to March 2021, and on antiretroviral therapy.

Study variables

Clinical characteristics and demographics used in this study included date of HIV diagnosis (date of a positive test), age at diagnosis, gender, marital status, level of education, occupation, incarceration history, addiction history, baseline CD4+ count (cell/mm^3), disease stage (stage I, II, III, and IV according to the WHO's staging), transmission category, tuberculosis (TB), anemia (with hemoglobin level < 13 g/dl for male, and < 12 g/dl for women according to WHO's recommendation) [17], hepatitis C virus (HCV) co-infection, duration of ART, and death (date of death). Survival time (measured in months) in the present study was considered from the date of HIV/AIDS diagnosis to the date of death or the end of follow-up period for alive patients.

Informed consent was obtained from all patients at the first visit. The ethics committee of Shiraz University of Medical Sciences approved this study protocol (approval No.: IR.SUMS.SCHEANUT.REC.1400.047).

Statistical analysis

Mean, standard deviation, and number (%) were used to analyze numeric and quality variables. χ^2 and independent *t*-test were applied to measure the association between grouping and continuous variables. Kaplan-Meier curve was used to estimate the overall survival of patients. Survival time was defined based on CD4+ cells count. Cox proportional hazards model was applied to identify the predictors of mortality in patients. In order to do this, a univariate model was implemented, and variables with a p-value < 0. 25 in this model were included in multivariate analysis. Schoenfeld's residual test was utilized to investigate the model's proportional hazards (PH) assumption. All statistical analyses were

Table 1. Baseline socio-demographic characteristics of HIV/AIDS patients on ART treatment in Iran, 2006-2015

Characteristics	Number (%)	Deaths (%)	Survival time (months)	*p*-value
Overall	1,327	406 (30.6)	165.6 (159.1-172.2)	–
Age at diagnosis (year)				
< 40	358 (27.0)	59 (14.5)	173.1 (162.1-184.1)	< 0.001
≥ 40	969 (73.0)	347985.5)	160.4 (153.3-167.6)	
Sex				
Male	905 (68.2)	337 (83.0)	155.0 (147.6-162.3)	< 0.001
Female	422 (31.8)	69 (17.0)	198.0 (186.9-209.0)	
Education (at diagnosis)				
Illiterate and primary	455 (34.3)	146 (36.0)	161.1 (150.4-171.9)	0.007
Guidance	493 (37.2)	164 (40.4)	163.6 (153.6-173.5)	
High school and diploma	299 (22.5)	84 (20.7)	169.3 (154.9-183.7)	
Academic	80 (6.0)	12 (3.0)	169.6 (155.1-185.2)	
Marital status				
Married	665 (50.1)	169 (41.6)	178.9 (169.6-188.2)	< 0.001
Single	315 (23.7)	118 (29.1)	139.9 (129.8-150.0)	
Widowed/Divorced	347 (26.1)	119 (29.3)	160.2 (148.5-171.9)	
Occupation				
Employed	609 (45.9)	176 (43.3)	172.2 (162.8-181.7)	0.232
Unemployed	718 (54.1)	230 (56.7)	158.1 (149.5-166.7)	
Incarceration history				
Yes	728 (54.9)	307 (75.6)	148.9 (141.0-156.8)	< 0.001
No	599 (45.1)	99 (24.4)	192.9 (181.7-204.2)	
Addiction history				
Yes	811 (61.1)	331 (81.5)	149.3 (141.7-157.0)	< 0.001
No	516 (38.9)	75 (18.5)	201.0 (190.1-211.8)	
TB co-infection				
Yes	104 (7.8)	57 (14.0)	133.8 (116.8-150.7)	< 0.001
No	1,223 (92.2)	349 (86.0)	169.5 (162.5-176.5)	
HCV co-infection				
Yes	696 (52.4)	177 (56.4)	162.6 (151.5-173.8)	< 0.001
No	631 (47.6)	229 (56.4)	166.9 (158.7-175.0)	
WHO stage				
I	582 (43.9)	125 (30.8)	190.5 (181.2-199.8)	< 0.001
II	314 (23.7)	104 (25.6)	164.4 (152.3-176.5)	
III	311 (23.4)	114 (28.1)	137.8 (123.2-152.4)	
IV	120 (9.0)	63 (15.5)	100.4 (82.9-117.9)	
Baseline CD4+ count				
> 500	137 (10.3)	16 (3.9)	193.9 (180.2-207.6)	< 0.001
351-500	217 (16.4)	40 (9.9)	186.7 (173.8-199.6)	
200-350	327 (24.6)	101 (24.9)	175.3 (163.8-186.7)	
< 200	646 (48.7)	249 (61.3)	141.6 (132.3-150.8)	
Route of transmission				
Injection drug use	690 (52.0)	275 (67.7)	155.9 (148.1-163.7)	< 0.001
Sexual route	484 (36.5)	89 (21.9)	192.8 (181.2-204.4)	
Other	153 (11.5)	42 (10.3)	148.6 (130.4-166.8)	

Table 1. Cont.

Characteristics	Number (%)	Deaths (%)	Survival time (months)	*p*-value
Time on ART (years)				
< 1	266 (20.0)	200 (49.3)	47.6 (41.0-54.3)	< 0.001
1-5	589 (44.4)	167 (41.1)	139.3 (130.4-148.1)	
> 5	472 (35.6)	39 (9.6)	228.3 (221.2-235.4)	
Adherence to treatment				
Yes	977 (73.6)	121 (29.8)	213.7 (207.6-219.8)	< 0.001
No	350 (26.4)	285 (70.2)	74.1 (66.7-81.4)	
Anemia				
Yes	932 (77.6)	178 (57.4)	105.6 (95.4-115.7)	< 0.001
No	269 (22.4)	132 (42.6)	207.4 (200.0-214.8)	

performed using statistical software Stata version 14 (Stata, College Station, TX, USA).

Results

Demographic, clinical, and laboratory characteristics

A total of 1,327 patients were included in this study, of which 406 (30.6%) died, and 921 (69.4) were alive at the end of the study period (censored). Moreover, more than half of the patients (50.1%) were married, and a majority (71.5%) did not complete compulsory education. The patients were predominantly males (68.2%), and the mean age of the patients was 45.12 ± 9.42 years. The most common potential route of transmission (52%) was injecting drug use (IDU). Moreover, 61.1% and 54.9% of the participants reported a history of addiction or imprisonment, respectively. According to the WHO's definition, 67.6% of the patients were in stage I or II, and 32.4% were in stage III or IV at the time of diagnosis. In terms of CD4+ cell count, 48.7% of the patients had CD4+ < 200 and 10.3% had CD4+ > 500, and the mean hemoglobin level was 13.86 ± 2.69 g/dl. In this study, 472 (35.6%) patients used ART for more than five years at the end of the study period. Age (being older) and gender (being male) were predictors of death among the patients ($p < 0.05$). Also, the mortality rate was significantly higher in those who used ART for less than one year, and in those with a baseline CD4+ count of less than 200 ($p < 0.05$). Mortality was significantly higher in IDU individuals ($p < 0.001$). More details of the patients are presented in Table 1.

Survival rate

Figure 1 shows the survival and hazard functions of the applied model. The overall 1-, 2-, 5-, and 10-year survival rates of the patients were 90%, 87%, 78%, and 67%, respectively. The mean survival time (months) was 165.6 (95% CI: 159.1-172.2%). According to results of log-rank test, the cumulative survival was significantly lower in men than in women (1-, 5-, and 10-year survival rates were 89%, 75%, and 60% in men compared to 93%, 86%, and 78% in women, respectively(. The results showed that the survival rate of HIV patients was significantly higher in those with high CD4+ counts than in those with low CD4+ counts ($p < 0.001$ by log-rank test).

Survival rate prognostic factors

Crude and adjusted Cox proportional hazard model of the progression from HIV to death is presented in Table 2. Accordingly, age, unemployment, addiction history, IDU, clinical stage (based on WHO's staging), level of CD4+ cells, and duration and adherence to ART were significantly associated with survival of the patients ($p < 0.05$). Based on the results, risk of mortality increased with age ($HR_{\geq 40/< 40} = 1.48$; 95% CI: 1.04-2.11%, $p = 0.027$), and unemployment ($HR_{unemployment/employment} = 1.29$; 95% CI: 1.00-1.67%, $p = 0.042$). Mortality was lower in IDU patients than in sexually-infected individuals ($HR_{IDU/sexual} = 0.47$; 95% CI: 0.31-0.69%, $p < 0.001$). HIV patients, with a positive addiction history, presented a higher risk of death than those with a negative addiction history ($HR_{yes/no} = 2.42$; 95% CI: 1.46-4.01%, $p = 0.001$), and patients on ART with higher stage were at a higher risk of mortality compared to patients at stage I of the infection ($HR_{III/I} = 2.06$; 95% CI: 1.49-2.83%, $p < 0.001$). Moreover, patients with a lower CD4+ count ($HR_{< 200/> 500} = 2.91$; 95% CI: 1.65-5.10%, $p < 0.001$) had a higher risk of death. Compared to those who adhered to ART, non-adhering to ART patients had a 63% higher risk for progression from HIV to death ($HR_{adherence/non-adherence} = 0.37$; 95% CI: 0.27-0.50%, $p < 0.001$). In addition, the risk of progression from HIV to death in patients with a longer ART duration was significantly lower ($HR_{> 5/< 1} = 0.06$; 95% CI: 0.03-0.09%, $p < 0.001$), and the mortality risk in patients with anemia was higher than in non-anemia patients ($HR_{yes/no} = 1.58$; 95% CI: 1.19-2.10%, $p = 0.001$).

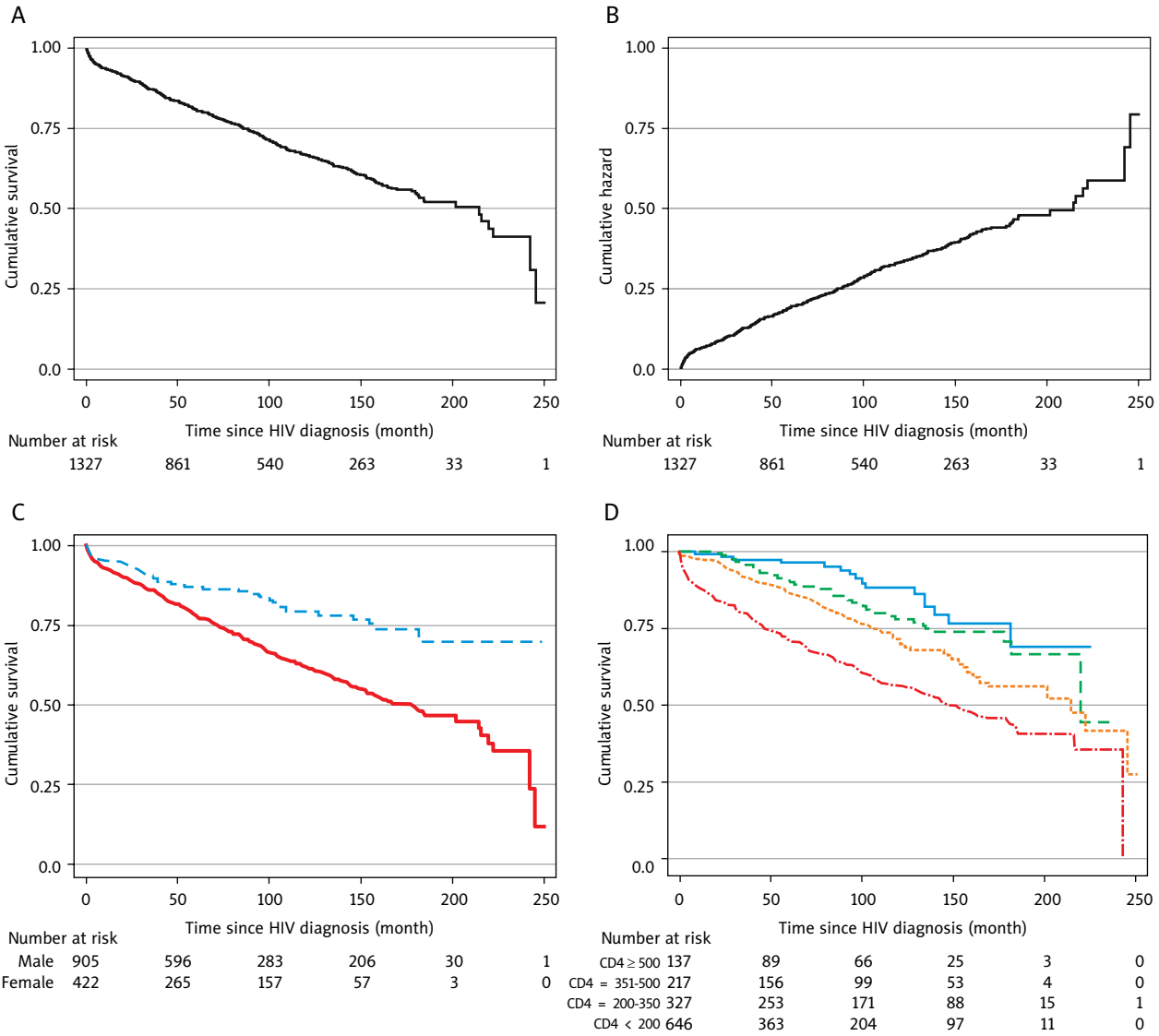

Figure 1. Kaplan-Meier survival and hazard estimates for all patients by sex and CD4+ count. Corresponding numbers at risk at different time points are indicated below the graph

Discussion

The present study aimed to define factors associated with the survival rate of HIV/AIDS who were on ART. By the end of the study period, more than 30.6% of patients died. The results revealed that patient's age, employment, history of addiction, IDU, clinical stage, baseline CD4+ count, duration of ART use, adherence to treatment, and anemia were important predictors of the survival rate of the patients.

Compared to other studies in developed and developing countries, such as China (19%), Ethiopia (12.2%), France (10.8%), and Japan (5.9%), the mortality rate in Iranian patients in a follow-up of 21 years was very high [13, 18-20]. Also, our results showed that the mean survival time of patients was about 14 years, again lower than in several other developing countries [21, 22]. Yaghoobi *et al.* showed that life expectancy in HIV-positive patients in Iran was very low compared to the general population [23]. In another study, life expectancy in HIV-positive patients in Iran was reported low [24]. The low quality of medical care services for HIV patients in Iran, especially inadequate coverage of ART program, can explain the observed differences between our findings and those reported from other countries [14].

We found that patient's age is an important predictor of the patients' survival, with older patients at higher mortality risk than younger patients. Our findings are supported by other studies [14, 25]. It is to be noted that older age is associated with delayed diagnosis of HIV/AIDS, lower CD4+ counts, advanced stages of the disease, and bedridden functional status [26]. In a study among HIV-infected individuals, Manosuthi *et al.* showed that older age in people with HIV/AIDS is associated with lower status of disclosure,

Table 2. Multivariate Cox proportional hazard regression analyses with all-cause mortality after starting ART

Variables	Unadjusted hazard ratio (95% CI)	*p*-value	Adjusted hazard ratio (95% CI)	*p*-value
Age at diagnosis (years)				
< 40	1.00	–	1.00	–
≥ 40	1.63 (1.23-2.15)	0.001	1.48 (1.04-2.11)	0.027
Sex				
Male	1.00	–	1.00	–
Female	0.48 (0.37-0.63)	< 0.001	1.45 (0.92-2.28)	0.101
Education (at diagnosis)				
Illiterate and primary	1.00	–	1.00	–
Guidance	1.01 (0.814-.27)	0.875	–	–
High school and diploma	0.95 (0.73-0.1.25)	0.765	–	–
Academic	0.61 (0.34-1.11)	0.108	–	–
Marital status				
Married	1.00	–	1.00	–
Single	1.54 (1.21-1.95)	< 0.001	–	–
Widowed/Divorced	1.30 (1.03-1.65)	0.026	–	–
Occupation				
Employed	1.00	–	1.00	–
Unemployed	1.22 (1.00-1.49)	0.041	1.29 (1.00-1.67)	0.042
Incarceration history				
No	1.00	–	1.00	–
Yes	2.26 (1.80-2.83)	< 0.001	–	–
History of addiction				
No	1.00	–	1.00	–
Yes	2.58 (2.01-3.31)	< 0.001	2.42 (1.46-4.01)	0.001
Route of transmission				
Sexual route	1.00	–	1.00	–
Injection drug use	1.77 (1.39-2.25)	< 0.001	0.47 (0.31-0.69)	< 0.001
Other	1.91 (1.32-2.76)	0.001	0.82 (0.44-1.23)	0.468
TB co-infection				
No	1.00	–	1.00	–
Yes	1.64 (1.24-2.17)	< 0.001	1.26 (0.90-1.76)	0.169
HCV co-infection				
No	1.00	–	1.00	–
Yes	1.01 (0.82-1.23)	0.911	–	–
WHO stage of the disease				
I	1.00	–	1.00	–
II	1.65 (1.27-2.14)	< 0.001	1.39 (1.03-1.87)	0.027
III	2.56 (1.98-3.30)	< 0.001	2.06 (1.49-2.83)	< 0.001
IV	4.21 (3.10-5.72)	< 0.001	1.70 (1.11-2.59)	0.014
Baseline CD4+ count				
> 500	1.00	–	–	1.00
351-500	1.50 (0.84-2.68)	0.169	2.06 (1.10-3.88)	0.023
200-350	2.29 (1.35-3.88)	0.002	2.70 (1.52-4.79)	0.001
< 200	4.04 (2.43-6.70)	< 0.001	2.91 (1.65-5.10)	< 0.001

Table 2. Cont.

Variables	Unadjusted hazard ratio (95% CI)	*p*-value	Adjusted hazard ratio (95% CI)	*p*-value
Time on ART (years)				
< 1	1.00	–	1.00	–
1-5	0.17 (0.14-0.22)	< 0.001	0.44 (0.33-0.59)	< 0.001
> 5	0.02 (0.01-0.02)	< 0.001	0.06 (0.03-0.09)	< 0.001
Adhere to treatment				
No	1.00	–	1.00	–
Yes	0.09 (0.07-0.12)	< 0.001	0.37 (0.27-0.50)	< 0.001
Anemia				
No	1.00	–	1.00	–
Yes	5.67 (4.52-7.11)	< 0.001	1.58 (1.19-2.10)	0.001

social isolation, depression, and adverse clinical outcomes. Therefore, strict management instructions and clinical recommendations are needed for optimal care in the elderlies infected with HIV/AIDS [27].

The results of the present study suggested that unemployment is a risk factor for patient survival. Job is a valid representative of an individual's socio-economic status in society, and low socio-economic status can affect quality of life and increase the risk of death in HIV-positive patients [28]. A study in Vietnam showed that employment was also associated with a reduction in general mortality [29].

We reported a higher risk of death among patients with a history of drug use. Deren *et al*. showed that by interfering with treatment and decreased adherence, substance use could reduce the effectiveness of ART. They added that substance users suffer from stress, social stigma, and disparities during their treatment period, which increase their detrimental health consequences [30]. Results of another study showed that despite complete treatment, drug use has a significant role in increasing the risk of mortality and reducing life expectancy in HIV-positive individuals [31]. As a result, an assessment of drug use status for proper management of HIV patients is crucial.

The results of the present study showed that IDU patients present a lower risk of mortality than those infected through sexual routes. This finding contradicts with results of other studies showing that HIV-positive IDU experience more complications [14, 32]. The authors believe that faster progression of HIV among IDU is mainly related to social factors and injection-related infections, such as HCV and HBV as well as limited access to medical services [32, 33]. However, supporting our results, Jiang et al. showed that IDU presented less mortality, which can be related to their younger age [34]. Slower progression of HIV infection in IDU compared to sexually transmitted routes may be because intravenously transmitted HIV immediately encounters target cells for infection, while sexually transmitted virus first encounter antigen-presenting Langerhans cells and then spread. Therefore, the mode of transmission can affect the nature of initial immune response and its' severity as well as the loading of the virus. It is also possible that some factors unrelated to HIV, but related to the mode of transmission of the virus, such as use of drugs or concomitant infection, may affect the progression of the infection [35].

According to the results of the present study, adherence and longer duration of ART use increase the survival of patients. In support of our findings, many studies have shown that ART is an important intervention in reducing mortality in HIV/AIDS patients [26, 36]. Low adherence to ART affects the successful long-term virological suppression of ART, and leads to treatment failure, drug resistance to ART, and viral multiplication. As a result, it increases patients' vulnerability to opportunistic infections and mortality [12, 36]. Numerous studies have shown that ART strengthens the immune system, improves quality of life, increases life expectancy, and plays a very effective and protective role in reducing complications of HIV and mortality in these patients [37, 38]. This is why ART treatment is recommended to be provided free of charge to all HIV-positive patients as soon as possible after diagnosis.

According to our findings, patients in advanced clinical stages (WHO stage II, III, and IV) present a higher risk of death. This could indicate an advanced immunodeficiency status that increases the risk of death in HIV patients. Various studies are in line with our findings [13, 26]. Nigussie *et al*. showed that patients lose their lives mainly due to late onset of ART (being in advanced stages of the disease). Therefore, early ART initiation is recommended to reduce complications and mortality before disease progression as soon as HIV infection is confirmed. In addition, in people with advanced HIV disease after receiving ART, monitoring response to ART and possible immune reconstitution of inflammatory syndrome is essential [13].

We found that patients with less than 500 CD4+ cells count had a higher risk of death. Thus, CD4+ cell count is an important predictor of progression from HIV to death in these patients. CD4+ counts reflects patients' immune status; therefore, when reduced, it exposes patients to opportunistic

infections and serious conditions. Moreover, a reduced CD4+ count predisposes patients to some micro-nutrient deficiencies (i.e., iron) that in turn causes anemia and low blood hemoglobin level, which is yet another important predictor of HIV mortality found in our study and several others [13].

In HIV patients, hemoglobin levels can predict the prognosis of the disease, and thus indicate the rate of disease progression [39]. Our study showed that anemia is an important predictor of mortality in HIV/AIDS patients, as increased hemoglobin levels are associated with lower mortality risk. This finding is consistent with various studies conducted in other countries [11, 13, 40]. Teshale *et al*. reported that anemia starts mainly in the progression of HIV, which can indicate a higher immune suppression in patients with anemia. Also, HIV patients with anemia may develop complications while taking medications, including a suppressing immune system, all of which lead to higher mortality [12].

Strengths and limitations

The present study used a relatively large sample size. However, a part of our data was based on routine data sources with incomplete records. Also, due to the long follow-up period of the patients and problems, such as social stigma in Iranian society, reporting error and bias (especially in addiction, sexual relationships, and incarceration) in our data can not be ruled out. However, the interviewers were well-trained to reduce such problems in the time of data collection.

Conclusions

In the current study, the survival rate and its' related factors were evaluated. The mortality of adults on antiretroviral therapy was high. Factors, such as age, history of addiction, injecting drug use, clinical stage, low CD4+ count, anemia, and unemployment were associated with survival of HIV-positive patients in Iran. These findings suggest that adherence to treatment and increasing duration of ART use are very important protective factors in Iranian HIV/AIDS patients. The above-mentioned factors should be used to identify patients with higher risk of early mortality. This finding emphasizes that reduction in HIV/AIDS mortality could easily be achieved through early diagnosis of patients, with immediate ART treatment and treatment adherence.

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Conflict of interest

The authors declare no conflict of interest.

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