

Non-adherence to antiretroviral treatment and associated factors among people living with HIV in Iran: a retrospective cohort study

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Abstract

Introduction: Although combination of antiretroviral therapy (cART) has been successful in improving health outcomes of people living with HIV (PLWH), optimal treatment adherence is required to maintain the benefits. This study aimed to determine factors associated with treatment non-adherence among PLWH in Iran.

Material and methods: In this cohort study, we included 988 PLWH (1997-2017) living in Southern Iran, Fars Province. Required demographic and clinical data was collected from patients' files. Non-adherence was defined by a physician of the center as skipping a visit or less than 90% intake of prescribed medicines (antiretroviral drugs) in the month preceding to the date of data collection.

Results: Of the 988 participants, 70.54% were males. Mean (SD) age of the participants was 35.80 (SD = 8.58) years and treatment non-adherence was found in 17.81% of patients ($n = 176$). Multiple regression model showed that injection drug use (IDU) (AOR = 2.53, 95% CI: 1.11-5.74%), and history of incarceration (AOR = 4.20, 95% CI: 1.65-10.66%) increased the likelihood of treatment non-adherence, while taking medications for pneumocystis pneumonia (AOR = 0.34, 95% CI: 0.22-0.52%), duration of being under ART (AOR = 0.13, 95% CI: 0.08-0.21%) for 1-5 years, and (AOR = 0.06, 95% CI: 0.02-0.16%) for more than 5 years, decreased the likelihood of treatment non-adherence.

Conclusions: These findings show that one in five PLWH did not adhere to cART. On the other hand, the likelihood of non-adherence was directly associated with IDU and incarceration history. Based on the results, tailored programs should be developed to improve adherence among individuals with a history of IDU or incarceration.

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Key words: non-adherence, antiretroviral, HIV, Iran.

Introduction

Human immunodeficiency virus (HIV) is a major public health concern worldwide [1]. According to the World Health Organization (WHO), 38 million people were living with HIV

at the end of 2019 [2]. Since the beginning of HIV/acquired immunodeficiency syndrome (AIDS) epidemic, about 32 million people have died of AIDS globally [3]. However, in recent years, effective viral therapies brought positive changes

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to the prognosis of the disease and improved life expectancy of HIV-positive patients [4].

There is evidence that antiretroviral therapy (ART) has significantly reduced global HIV-related mortality by shifting HIV/AIDS from a fatal to a more controllable chronic disease [5, 6]. Moreover, ART induces viral suppression of HIV virus and minimizes HIV transmission [7]. Although there has been great success in the control of this serious health condition, we need full patient's adherence to treatment to see the benefits [8]. Lack, or even poor adherence to ART has been indicated to be a major determinant of treatment failure, disease progression, drug-resistance, and higher risk of mortality [4, 6]. As a result, an adherence rate of at least 95% of all patients is recommended by the WHO to achieve acceptable results [9].

According to estimates provided by the United Nations Program on HIV/AIDS (UNAIDS) in 2019, about 59,000 of HIV-infected patients were living in Iran, of whom only 22,000 were aware of their disease status [10]. The majority of HIV/AIDS studies conducted in Iran have focused on social stigma, mental disorders, and suicide in PLWH [11]. Despite the critical role of adherence to ART in the success of HIV prevention and management programs, limited studies have focused on this important subject [12]. As such, Hooshyar *et al.* found that only 30% of HIV-infected patients were under ART regimen [13]. On the other hand, Morowatisharifabad *et al.* reported that 75.4% of HIV patients in Iran were adhering to their prescribed treatment [14]. An official estimate reported in 2019 suggested that only 8% of all HIV patients receive ART in Iran [15].

Due to the vital role of treatment in preventing HIV transmission and the lack of sufficient information about Iranian patients due to this disease's stigma, this study was carried out to determine the non-adherence to ART and its related factors in HIV-infected people in Iran.

Material and methods

Study design and population

A retrospective cohort study was conducted on HIV/AIDS patients who were registered with Shiraz Behavioral Diseases Counseling Centers in Southern Iran (Fars Province) from August, 1997 to May, 2017. Sampling method of this study was census.

In the current study, we included all PLHIV who were registered in Southern Iran. The center monitors clinical and health status of the patients. A sample of 988 PLHIV participated in our study. As a routine procedure, at the time of diagnosis, all patients completed a structured questionnaire via a face-to-face interview to collect data on demographic characteristics, risky behaviors, disease status, medication, and other health-related characteristics of the respondents. All diagnosed patients follow ART lines immediately and visit the center every six months for clinical follow-up. Data was collected by trained and experienced staff. This study was conducted according to the principles expressed in

Shiraz HIV center, and approved by local ethics committee of Shiraz University of Medical Sciences. Based on the approval of ethics committee, all information were collected only by patients' codes and their identity were not disclosed. Patient's information was kept private.

Written informed consent was obtained from all the participants at the initial visit to the center. Anonymous data, with no identifiable information on the patients were obtained from the data administrator. The study protocol was reviewed and approved by ethical committee of the Shiraz University of Medical Sciences (IR.SUMS.REC.1396.S369).

Instruments and measures

Data on demographic characteristics and risky behaviors was collected at the time of diagnosis. Data included age, gender, educational status, marital status, occupation, perceived route of HIV transmission (sexual or IDU), diagnosis delay (defined as < 1 year between HIV diagnosis and advanced AIDS clinical stages: stages 3 or 4 as defined by WHO), history of incarceration, addiction, baseline CD4+ count, clinical stage (stages 1 and 2 vs. stages 3 and 4 based on WHO), duration of ART, years since HIV diagnosis, pneumocystis pneumonia (PCP) prophylaxis, hepatitis C infection (HCI), and tuberculosis (TB) treatment. Data were extracted from patients' medical files. In this study, non-adherence was defined by the physician of the center as skipping a visit or less than 90% intake of the prescribed medicines (antiretroviral drugs) in the month preceding to the date of data collection. Baselines CD4+ count was measured at the first visit. Duration of ART was the duration of the patient's taking ART medication [1].

Data analysis

Data were analyzed using STATA software, version 14.0 (Stata, College Station, TX, USA). χ^2 test and multiple logistic regression (using backward selection strategy) was used to calculate odds ratios and 95% CI for an association of study variables with non-adherence to ART.

Results

In this study, the overall adherence rate was 82.18%, with 17.81% of participants not adhering to ART. Table 1 shows the prevalence of non-adherence and adherence in the study population and few other countries. Accordingly, the prevalence of non-adherence in Iran seems relatively high. In this study, we included 988 PLHIV, mostly men (54%), with a mean age of 35.80 years (SD = 8.58). Almost half of the participants were married (45.74%) and were employed (55.76%). Concerning educational status, 65.60% had a diploma or university degree. The transmission route was mainly through injecting drugs among males ($n = 585$; 83.93%), and sexual contact among females ($n = 251$; 58.91%). Moreover, 62.75% and 70.74% of patients reported having a history of incar-

Table 1. Prevalence of non-adherence and adherence in the study population and few other countries

	Country	Sample size	Non-adherence	Adherence
*	Iran	988	17.8 (15.4-20.1)	82.1 (79.7-84.4)
1	India	409	29.5 (25.0-33.9)	70.4 (65.5-74.4)
2	Pakistan	375	83.2 (79.0-86.8)	16.8 (13.1-20.9)
3	Korea	790	32.0 (28.7-35.2)	67.9 (63.7-70.2)
4	China	397	17.4 (13.6-21.2)	82.6 (78.8-86.3)
5	Myanmar	300	16.0 (11.8-20.3)	84.0 (79.8-88.1)
6	Kenya	416	18.0 (14.3-21.6)	82.0 (78.3-85.6)
7	Ethiopia	160	9.0 (4.6-13.4)	85.6 (86.5-95.4)
8	Brazil	253	28.4 (22.8-33.9)	71.5 (68.6-74.3)
9	United States	3,606	14.5 (13.2-15.6)	85.4 (84.2-86.5)

*Current study

ceration and addiction, respectively. Regarding the stage of HIV at the initial visit, 257 (26.01%) were in stage III and IV. The median CD4+ count was 211 cells/ μ l (IQR = 95-361 cells/ μ l). Almost half of the participants (48.10%) had CD4+ \leq 200 cells/ μ l at the initial visit. The median duration of ART treatment was 24.90 months (IQR = 5.60-52.32). However, the mean time of being diagnosed with HIV was 61.74 months (SD = 39.99). Of the patients, 8.19% and 53.23% were suffering from at least one co-infection, mostly pulmonary TB and hepatitis C, respectively. The distribution of relevant socio-demographic characteristics and ART adherence of the patients are provided in Table 2.

As presented in Table 2, age, education, employment, CD4+ count, and taking medicine for TB were not significantly associated with the patients' non-adherence.

The results of multiple logistic regression indicated that having an incarceration history (AOR_{yes/no} = 4.20; 95% CI: 1.65-10.66%) and drug injection as reported transmission route (AOR_{yes/no} = 2.53; 95% CI: 1.11-5.74%) were significant risk factors for non-adherence. On the other hand, receiving prophylaxis for PCP (AOR_{yes/no} = 0.34; 95% CI: 0.22-0.52%), 1-5 years of receiving ART (AOR_{yes/no} = 0.13; 95% CI: 0.08-0.21%), and > 5 years of receiving ART (AOR_{yes/no} = 0.06; 95% CI: 0.02-0.16%) were significantly associated with ART adherence (Table 3).

Discussion

The results of the present study showed that the percentage of treatment adherence rate in Southern Iranian patients was 82%. History of imprisonment and drug injection were significantly associated with non-adherence to treatment, whereas, receiving prophylactic drugs and duration of ART treatment reduced the odds of treatment non-adherence in the Iranian patients.

The results of our study revealed that the rate of non-adherence to treatment (17.8%) in Southern Iranian patients was less than rates reported from Asian countries, such as Pakistan (83.2%) and India (29.5%) [16, 17]. The higher ART

adherence in Iran can probably be attributed to free of charge accessibility of treatment and medical care services. Ali *et al.* stated that improper use of health services and lack of access to healthcare contribute to lower treatment adherence in Pakistan [16]. Another study in Iran showed that only half of the diagnosed patients had started antiretroviral drugs, and only 30% of PLWH were on ART. It is expected that due to the new strategy (i.e., start ART at the time of diagnosis regardless of CD4+ count or WHO clinical stage) for HIV patients in 2017, the start of antiretroviral drugs and its' continuation in these patients will improve [13]. The rate of non-adherence to ART treatment in our study was similar to results of studies in Kenya and Indonesia [18, 19], but was higher when compared to non-adherence rates in Vietnam and Ethiopia [20, 21]. The variation in treatment adherence among countries may also be due to differences in research methodology, HIV stigma, structure of countries' health systems, access to healthcare facilities, and economic status of patients. For example, people living in European, Asian, African, and American countries highly differ in terms of quality and accessibility of health services as well as socio-economic status [22, 23].

We discovered that a history of imprisonment increases the risk of non-adherence in HIV patients. According to the literature, many HIV-infected prisoners discontinue their viral therapy after they are released [24, 25]. Moreover, Bailargeon *et al.* reported that more than 90% of HIV-infected prisoners did not receive ART or stopped their treatment sometime after their release. This may indicate that most prisoners encounter socio-economic or personal difficulties in accessing ART after their release when returned to the society. As a result, after their release from prison, individuals may require further support from healthcare system and authorities to eliminate social barriers to access treatment [26]. Adherence to ART can be achieved through government and family supports. Many people with a history of imprisonment feel that there is a huge gap between them and their family due to the stigma of HIV infection and addiction. On the other hand, relationship with friends and peers en-

Table 2. Socio-demographic characteristics and ART non-adherence among PLHIV at HIV clinic (2006-2017)

Variables	Population, n (%)	Non-adherence, n (%)	p-value
Age at the time of diagnosis			
< 30 years	237 (23.98)	39 (16.64)	0.221
30-40 years	499 (50.50)	83 (16.63)	
> 40 years	252 (25.50)	54 (21.43)	
Gender			
Male	697 (70.54)	161 (23.10)	< 0.001
Female	291 (29.45)	15 (5.15)	
Education levels			
< Diploma	340 (34.41)	67 (19.71)	0.294
≥ Diploma	648 (65.58)	109 (16.82)	
Marital status			
Married	452 (45.74)	57 (12.61)	< 0.001
Single	251 (25.40)	59 (23.51)	
Widowed/divorced	285 (28.84)	60 (21.05)	
Employment			
Employed	551 (55.76)	93 (16.88)	0.388
Unemployed	437 (44.23)	83 (18.99)	
Diagnosis delay			
Yes	532 (53.84)	76 (14.29)	0.002
No	456 (46.15)	100 (21.93)	
History of addiction			
Yes	699 (70.74)	162 (23.20)	< 0.001
No	289 (29.25)	14 (4.80)	
Baseline CD4+ count			
≤ 200	475 (48.07)	90 (18.95)	0.519
200-500	415 (42.00)	72 (17.35)	
≥ 500	98 (9.91)	14 (14.29)	

courages drug use and other risky behaviors in these people, which further jeopardizes adherence to ART [27].

Adherence to treatment in HIV-infected individuals who inject drugs is influenced by unstable lifestyle, and psychological and social problems [28]. Findings of previous studies showed that illicit drug use was associated with depression and low social support, which can negatively affect a person's success in following the targets. As a result, health services regarding the process of HIV diagnosis and treatment for these people is delivered with a delay, leading to late onset of medication and ultimately, lower adherence to treatment [29, 30]. Results of a Canadian study showed that 63% of HIV-infected injecting drug users quit ART at least once during their life [31]. In that regard, the present study results were in accordance with that reported by previous studies.

Table 2. Cont.

Variables	Population, n (%)	Non-adherence, n (%)	p-value
Clinical stage			
I-II	731 (73.98)	73 (10.00)	< 0.001
III-IV	257 (26.01)	103 (40.10)	
Prophylaxis for PCP			
Yes	569 (57.59)	58 (10.19)	< 0.001
No	419 (42.40)	118 (28.16)	
HCV co-infection			
Yes	526 (53.23)	118 (22.43)	< 0.001
No	462 (46.76)	58 (12.55)	
TB treatment			
Yes	81 (8.19)	20 (24.69)	0.096
No	907 (91.80)	156 (17.20)	
Duration of ART			
< 1 year	350 (35.42)	143 (40.86)	< 0.001
1-5 years	444 (44.93)	28 (6.31)	
> 5 years	194 (19.63)	5 (2.58)	
Years since HIV diagnosis			
< 5 years	512 (51.82)	121 (23.36)	< 0.001
≥ 5 years	476 (48.17)	55 (11.55)	
Route of transmission			
Injection	598 (60.52)	150 (25.08)	< 0.001
Sexual	321 (32.48)	19 (5.92)	
Other*	69 (6.98)	7 (10.14)	
Incarceration history			
Yes	620 (62.75)	158 (25.48)	< 0.001
No	368 (37.24)	18 (4.89)	

*Other modes of transmission included unknown cause, blood transition, and dentistry

PCP is a fatal infection that occurs in immunocompromised individuals and can be extremely dangerous in HIV-infected patients, especially when they experience lower CD4+ counts [32]. Results of previous studies showed that preventive treatment and ART should be initiated as soon as possible to prevent adverse outcomes of moderate to severe PCP in people with low CD4+ counts [33, 34]. Qin *et al.* demonstrated that in HIV-infected patients with concomitant PCP, ART and prophylaxis should be initiated immediately to increase the patients chance of survival [35]. The findings of our study also revealed that PCP treatment was preventive for ART non-adherence. It seems that the use of antiretroviral drugs and PCP prophylaxis in HIV-infected people with low CD4+ count can significantly reduce the risk of death and improve overall health status of HIV-infected patients.

Table 3. Univariate and multivariable analysis of socio-demographic characteristics and ART non-adherence of PLHIV at HIV clinic (2006-2017)

Variables/Categories	Univariate odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Age at the time of diagnosis				
< 30 years	1.00	–	1.00	–
30-40 years	1.01 (0.66-1.53)	0.952	0.87 (0.52-1.46)	0.621
> 40 years	1.38 (0.87-2.18)	0.162	1.22 (0.68-2.18)	0.497
Gender				
Female	1.00	–	1.00	–
Male	5.52 (3.19-9.56)	< 0.001	1.01 (0.32-3.16)	0.986
Education				
< Diploma	1.00	–	1.00	–
≥ Diploma	0.82 (0.58-1.15)	0.261	–	–
Marital status				
Married	1.00	–	1.00	–
Single	2.12 (1.42-3.18)	< 0.001	1.09 (0.66-1.80)	0.725
Widowed/divorced	1.84 (1.24-2.75)	0.002	1.55 (0.95-2.54)	0.076
Employment				
Employed	1.00	–	1.00	–
Unemployed	1.15 (0.83-1.60)	0.388	–	–
Incarceration history				
No	1.00	–	1.00	–
Yes	6.64 (4.00-11.04)	< 0.001	4.20 (1.65-10.66)	0.002
Route of transmission				
Sexual	1.00	–	1.00	–
Injection	5.32 (3.23-8.76)	< 0.001	2.53 (1.11-5.74)	0.026
Other*	1.79 (0.72-4.45)	0.207	1.47 (0.50-4.26)	0.476
History of addiction				
No	1.00	–	1.00	–
Yes	5.92 (3.36-10.42)	< 0.001	0.70 (0.19-2.49)	0.588
Diagnosis delay				
No	1.00	–	1.00	–
Yes	0.59 (0.42–0.82)	0.002	0.84 (0.55–1.28)	0.427
Baseline CD4+ count				
≤ 200	1.25 (0.67-2.34)	0.466	–	–
200-500	1.40 (0.76-2.58)	0.277	–	–
≥ 500	1.00	–	1.00	–
Prophylaxis for PCP				
No	1.00	–	1.00	–
Yes	0.28 (0.20-0.40)	< 0.001	0.34 (0.22-0.52)	< 0.001
HCV infection				
No	1.00	–	1.00	–
Yes	2.01 (1.42-2.83)	< 0.001	1.02 (0.62-1.69)	0.920
TB treatment				
No	1.00	–	1.00	–
Yes	1.57 (0.92-2.69)	0.094	1.49 (0.77-2.90)	0.229
Duration of ART				
< 1 year	1.00	–	1.00	–
1-5 years	0.09 (0.06-0.15)	< 0.001	0.13 (0.08-0.21)	< 0.001
> 5 years	0.03 (0.01-0.09)	< 0.001	0.06 (0.02-0.16)	< 0.001

*Other modes of transmission included unknown cause, blood transition, and dentistry.

The present study results revealed that the duration of ART was positively associated with treatment adherence. Belayihun *et al.* also reported a negative relationship between the duration of ART and adherence to the treatment, i.e. the longer the duration of treatment, the lower the adherence to ART [8]. On the other hand, Mitiku *et al.* suggested that adherence to treatment among HIV-infected patients is inversely associated with duration of ART. That is, the longer being under ART, the higher the adherence to treatment [36]. A study in Africa showed that patients might adhere to their treatment due to a sense of well-being at early stage of medication, which may decline due to tiredness of the treatment [37]. Similar to our results, another study showed that patients who were on ART for less than 2 years were two times more likely to be non-adherent when compared to those on medication for more than 2 years [38]. In another study, people who were treated for a longer time reported a higher adherence, and were more likely to continue treatment [39]. This pattern may be explained by the fact that a long-term use of ART treatment improves quality of life of HIV patients, improves physical function and general health, and even enhances social performance and mental health in HIV patients [40].

This study used a population-based sampling method with a relatively large sample size. However, routine data sources with incomplete records were applied. In addition, the infectious diseases surveillance system (including HIV registry) in Iran confronts serious under-reporting [41]. Low-rate of HIV diagnosis due to social stigma of HIV/AIDS may cause some degree of bias in findings [41, 42].

Conclusions

The ART adherence rate is not optimum (82%) in Iranian patients. In this study, acquiring HIV infection through injection and history of imprisonment increased the risk of treatment non-adherence. On the other hand, the use of PCP prophylactic drugs and longer duration of antiretroviral drug use were shown to be the factors protecting from non-adherence. Given the importance of the role of treatment in the survival of HIV patients, and also the importance of reducing viral load in preventing new infections, regular follow-up of patients and promotion of their awareness towards the benefits of adherence to treatment should be focused by health authorities and health planners. Further research should be conducted to examine the main barriers in achieving treatment adherence, so that better adherence of patients towards treatment can be achieved by effective intervention programs and health services.

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Conflict of interest

The authors declare no conflict of interest.

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