Case Study

Assoiciated factors with adherence to treatment in people who live with HIV in Fars, Iran: a nested case-control study

Fatemeh Rezaei[1], Mehdi Nejat[2], Maryam Taghipour[2], Maryam Nasirian[3*]

[1] Student Research Committee, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran. [2]Vice Chancellor for Health Affairs , Shiraz University of Medical Sciences , Shiraz, Iran. [3]Infectious Diseases and Tropical Medicine Research Center; and Epidemiology and Biostatistics Department, Health School, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence: Maryam Nasirian, Master Student, Infectious Diseases and Tropical Medicine Research Center; and Epidemiology and Biostatistics Department, Health School, Isfahan University of Medical Sciences, Isfahan, Iran. maryamnasirian17@gmail.com

ABSTRACT

Adherence to antiretroviral treatment (ART) is vital for successful human immunodeficiency virus (HIV) treatment and can be enhanced through intervention. Identifying factors leading to non-adherence can guide efforts to improve adherence. We aimed to investigate adherence to treatment and related factors in people who live with HIV (PLHIV). This nested case-control study was performed in Fars province in Iran in 2023. Data was collected from the clinical paper records of patients. We used risk set sampling to select controls from the PLHIV. Adherence status was calculated as a percentage by dividing the total doses taken by the total doses prescribed. The result was then categorized into two groups: good (>=95%) and poor (<95%). We used conditional logistic regression to identify factors associated with adherence to treatment using the STATA software (version 16). we included 1437 eligible PLHIV in our study. The rate of treatment adherence was about 30.68%. HIV infection through unsafe sex (OR = 3.40, 95% CI = 1.67-4.06), prison history (OR = 2.45, 95% CI = 1.56-5.30), addiction (OR = 3.86, 95% CI = 2.80-5.35), and infections such as tuberculosis (OR = 3.22, 95% CI = 2.29-4.20) and hepatitis C (OR = 2.43, 95% CI = 2.09-3.89) increase the odds of non-adherence to treatment. The rate of non-adherence to treatment is considerable. To treatment of PLHIV more effective, reducing HIV transmission and the number of AIDS-related deaths, improving the treatment adherence rate seems necessary. It is recommended to plan for tailored treatment and counseling based on patient records, such as incarceration history, transmission route, and co-morbidities.

Keywords: Adherence, Treatment, HIV, PLHIV

Introduction

The acquired immunodeficiency syndrome (AIDS)is spreading quickly around the world, without any consideration for gender, borders, or sexual orientation (1). The World Health Organization's (WHO) latest data indicate that at the end of 2022, there were 39 million people living with HIV. Out of this total, 20 million are female and 19.4 million are male. Africa has 25.6 million patients, the most of any region, while the Eastern Mediterranean region has the fewest with 490 thousand (2). In Iran, at the end of the year 2023, 43,360 people are living with HIV. 9,141 of them are women, 38,126 are men, and there are fewer than 1,000 children under 15 years old (3). The number of people living with HIV in Fars province is 3852. There are still 2198 of them alive. 1436 patients are receiving medical care, while 1485 patients have died (4).

Since 2004, more than 30 low-income and middle-income countries (LMICs) worldwide have established HIV prevention, care, and treatment programs. These programs have enabled around 19.5 million people living with HIV (PLHIV) to receive antiretroviral treatment (ART) as of 2022. The development of powerful antiretroviral therapy (ART) has revolutionized the treatment of individuals who are living with the human immunodeficiency virus (HIV). By fully adhering to a potent combination of ART, HIV can be transformed from being a life-threatening condition into a manageable chronic illness (5).

WHO recommended in 2016 that all adults living with HIV should start ART, regardless of clinical stage or CD4 cell count. This "treat-all" recommendation has led to increased treatment in over 130 countries, with improved monitoring (6). The 2017 recommendation for rapid ART initiation promotes starting ART within seven days of HIV diagnosis and offering same-day ART

start. People with advanced HIV disease should be prioritized for assessment and treatment initiation (7).

The consolidated ARV guidelines for WHO recommend a standard dose of 600 mg (EFV 600) of TDF with either 3TC or FTC and EFV. This is considered to be the preferred first-line ART regimen for adults and adolescents due to its known safety and efficacy profile. This recommendation aims to improve harmonization across the majority of subpopulations. Furthermore, the WHO recommends a second-line regimen for individuals for whom previous treatments have failed. The preferred regimen is two nucleoside reverse transcriptase inhibitors (NRTIs) plus lopinavir/ritonavir (LPV/r) or atazanavir/ritonavir (ATV/r). If these are not available, alternatives are two NRTIs plus darunavir/ritonavir (DRV/r) or raltegravir (RAL). The choice of NRTI backbone for second-line antiretroviral therapy (ART) depends on which NRTI was used in first-line ART. If the first-line therapy was abacavir/lamivudine (ABC + 3TC) or tenofovir/lamivudine (TDF + 3TC or FTC), then zidovudine/lamivudine (AZT + 3TC) should be used in second-line ART and vice versa. This is to optimize sequencing in the context of lack of access to genotyping (8).

In Iran, the ARV drugs used to treat HIV/AIDS patients include Abacavir, Emtricitabine, Lamivudine, Tenofovir Disoproxil Fumarate, Tenofovir Alafenamide, Zidovudine, Efavirenz, Nevirapine, Atazanavir/Ritonavir, Darunavir, and Lopinavir/Ritonavir, Dolutegravir, and Raltegravir (9). Monthly ARV drugs are provided to patients with HIV in Iran. After the treatment stability (when the viral load is under 1000 copies/ml and there are no adverse complications from the medicine for a year), the patients can get three months of ARV drugs at a time (10).

ART can provide numerous benefits for PLHIV and society as a whole by achieving viral suppression. This reduces the morbidity and mortality associated with HIV, improves the overall Health-Related Quality of Life (HRQoL), and prevents HIV transmission. However, different ART regimens can have varying levels of dosing complexity, toxicity, and tolerability which can influence adherence to treatment and overall outcomes (11-13).

Adherence refers to how well a person follows the recommended behaviors given by a healthcare worker, such as taking medication, adhering to a diet, or making lifestyle changes. For antiretroviral treatment (ART) to be effective, complete adherence is necessary. Failure to take the medicine doses as recommended can lead to the development of medical resistance, making the HIV virus resistant to the prescribed medication, or even to similar medication that the patient has not yet taken. This, in turn, can lead to treatment failure (14). Poor adherence to treatment reduces the chances of achieving viral suppression, which in turn increases the risk of transmission and the development of drug resistance, limiting future treatment options. Moreover, suboptimal adherence can have both clinical and economic consequences, including accelerated disease progression and mortality, lowered HRQoL, and increased healthcare costs (15).

In a recent study conducted in America, it was found that 45% of people with HIV have poor adherence to ART (16). Hewer, it is difficult to determine the actual amount of drug use and patient adherence to antiretroviral drugs due to lack of accurate information in Iran (17). In both developed and developing countries, there are several obstacles to adherence. Some studies conducted in Iran in 2012 estimated adherence to treatment at 60-69% (18). In a study conducted in Iran,, 24% of patients had poor adherence, while 75% had good adherence to medication. The research found that forgetfulness, high dosage of medication, lack of knowledge about the value and importance of ART, and transportation problems were the most common reasons for non-adherence to treatment (19).

It is imperative to investigate the factors that contribute to non-adherence to treatment due to its harmful effects on PLHIV. This study was designed to investigate the factors that affect adherence to ART at the Counselling Centre for Behavioural Disease in Fars province.

Materials and Methods

Study Setting

We conducted a nested case-control study in a cohort of PLHIV at the Counselling Centre for Behavioural Disease, in Fars province, Iran between January and December 2023.

Sampling

After evaluating the inclusion and exclusion criteria, the study included a total of 1437 patients. It included patients with a definite diagnosis of HIV living in Fars province, who had been on antiretroviral treatment for at least 6 months and had visited the clinic at least twice after starting treatment. Patients with incomplete medical records and those who had migrated from Fars province were excluded from the study.

Case defined as a patient on ART at the Counselling Centre for Behavioural Disease in Fars province who was non-adherent to the prescribed HIV medicine whereas patients on ART who were adherent to their HIV medications were considered as control.

we marked the date of non-adherence as the "index date". Also, we employed risk set sampling to select controls from the study population of HIV patients who had not experienced poor adherence during the time between their treatment initiation and the index date that matched their case. In risk set sampling, a control is selected from the population at risk when a case is diagnosed. We performed 2:1 matching of cases to controls using age (±1 year), gender, index date (control available in the database at the case index date), and duration of HIV infection (±6 months) (Figure 1). The process of data analysis and matching ("ccmatch" command in STATA) was conducted using Stata software (version 6).

Data Collection

The data was collected from the medical records of patients and the HIV/AIDS registery and surveillance system. The dependent variable was the non-adherence to treatment. Adherence status was calculated as a percentage by dividing the total doses taken by the total doses prescribed. A patient with a dose adherence percentage of ≥95%, as per the scale used by the Ethiopian Federal Ministry of Health, is considered adherent, while others are considered non-adherent (20). Independent variables were age, gender, marital status, education level, history of behaviors high risk (prison, addiction, injection, unsafe injections, and unsafe sexual behaviors), ways of transmission, time gap between the diagnosis of HIV and the ART onset, and comorbidities (tuberculosis, hepatitis B, and hepatitis C).

Statistical Analysis

Mean, Standard Deviation (SD), median, and interquartile range (IQR) were used to describe quantitative variables, while frequency and percentage were used for qualitative variables. To compare the groups of cases and controls, chi-square and independent sample t-tests were used. To investigate the factors associated with non-adherence to HIV treatment, Conditional Logistic Regression ("clogit" command in STATA) was utilized to compute the odds ratio (OR) with 95% confidence intervals (CI). The adjusted OR was estimated regarding age, educational level, comorbidities, and duration of HIV infection. The significance level of 5% was considered for all analyses.

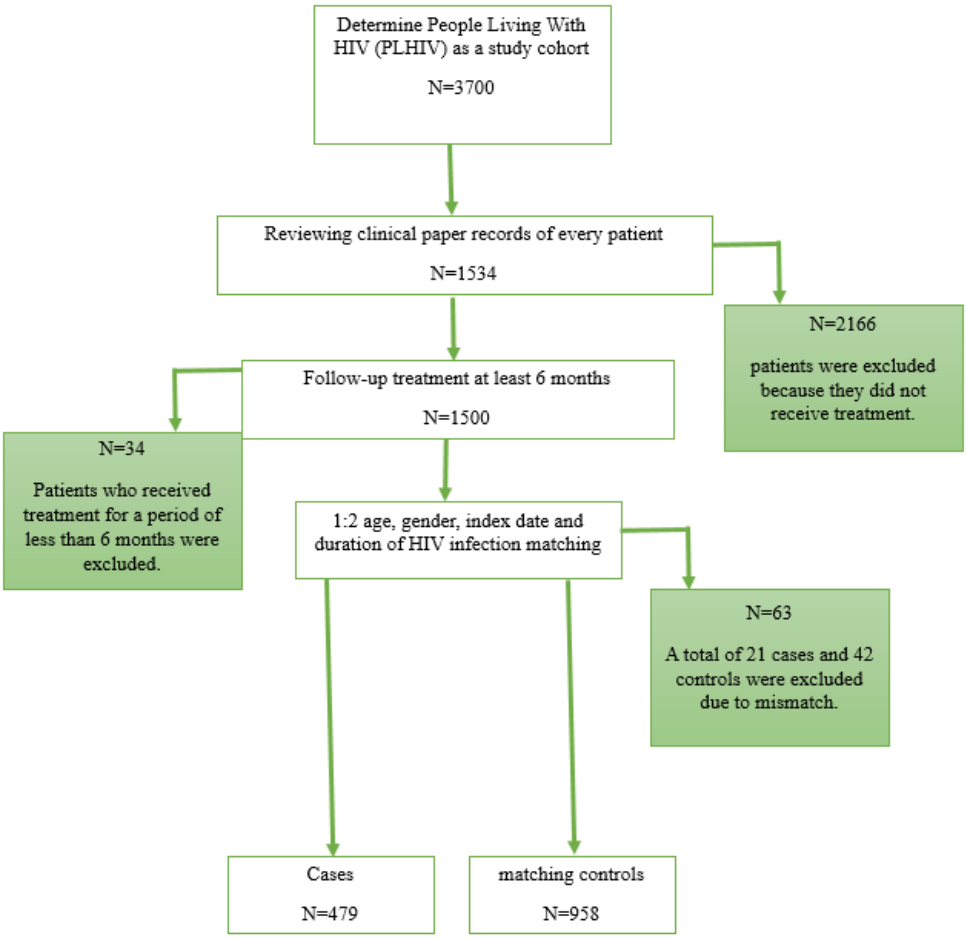

Figure 1. Flow chart of subjects in the nested case–control study

Results and Discussion

A total of 1437 subjects were included in the study. Among them, 479 (33.3%) were cases (non-adherence group) and 958 (66.7%) were controls (adherence group) who had been on ART for at least six months before the survey. The mean age (±SD) was 43.71 ± 3.76 years for cases group and 44.04 ± 3.29 years for controls group (p=0.212). Approximately, 70 % of non-adherence and adherence group were male (p=0.425). Within the participants, 35 (7.31%) in the cases group and 446 (46.56%) in the controls group were married, while 284 (59.29%) in the cases group and 369 (38.52%) in the controls group had never been married (p=0.061). The evaluation of educational status revealed that 479 (100%) in the cases group and 133 (13.88%)

in the controls group were Undergarduated (p=0.011) (**Table 1**)

The results showed that about 4.38% of the cases group was infected with HIV through condomless anal or vaginal sex, which was more than the controls group (p<0.0001). The frequently of individuals who have a history of high-risk behaviors, such as prison (99.58%) and addiction (99.21%), was higher in the cases group compared to the controls group (p<0.0001), whereas the frequently of individuals who have had injecting drugs (85.15%), sharing injections (70.03%) and unsafe sexual behaviors (53.98%) was higher in the controls group compared to the cases group (p=0.789, p<0.0001, p=0.654). In the cases group, the history of hepatitis B (3%) was reported more frequently than in the controls group (p=0.379). Conversely, the controls group reported a higher frequently of previous hepatitis C (63.14%) and tuberculosis (55.70%) cases group (p=0.001) (**Table 1**).

Table 1. Demographic and behavioral characteristics of participants in the Counseling Center for Behavioral Diseases, Fars Province

Characteristics		Non-adherence (479)	Adherence (958)	P-value
		n (%)		
Age – mean (SD)		43.71 (3.76)	44.04 (3.29)	0.212
Gender	Female	143 (29.85)	286 (29.97)	0.425
	Male	334 (70.15)	668 (70.03)	
Marital status	Single	284 (59.29)	369 (38.52)	0.061
	Divorced	160 (33.40)	143 (14.93)	
	Married	35 (7.31)	446 (46.56)	
Education level	Undergarduated	479 (100)	133(13.88)	0.011*
	Garduated	0(0)	825 (86.12)	
Transmission ways	Injecting drugs	458 (95.62)	496 (51.99)	<0.0001**
	Unsafe sex	21 (4.38)	13 (1.36)	
History of high-risk behaviors	Prison	477 (99.58)	542 (56.58)	<0.0001**
	Addiction	476 (99.21)	798 (83.39)	<0.021**
	Injecting drugs	405 (84.55)	787 (85.15)	0.789
	Sharing injections	334 (52.93)	505 (70.03)	<0.0001**
	Unsafe sex	242 (50.52)	515 (53.98)	0.654
Comorbidities	Tuberculosis	176 (20.40)	151 (55.70)	0.001**
	Hepatitis B	14 (3)	28 (2.9)	0.379
	Hepatitis C	204 (36.86)	603 (63.14)	0.001**

** P-value considered significant if <0.05 for chi-squre test or independent sample t-test .

Crude analysis results indicated that a transmission way (OR=3.39, p=0.021), history of prison (OR=2.43, p=0.016), addiction (OR=2.35, p=0.001), and comorbidities (like tuberculosis (OR=2.90, p=0.046), hepatitis B (OR=1.89, p=0.042) and hepatitis C (OR=2.41, p=0.034) raise the odds of treatment non-adherence.

Upon adjusting for confounding variables (e.g., age, education level, duration of HIV infection and comorbidities), it was determined that a transmission way (OR=3.40, p=0.03), history of prison (OR=2.45, p=0.005), addiction (OR=3.86, p<0.0001), and comorbidities (like tuberculosis (OR=3.22, p=0.049), hepatitis B (OR=1.89, p=0.042) and hepatitis C (OR=2.43, p=0.009)) elevate the odds of non-adherence (**Table 2**).

Table 2. Factors associated with non-adherence to ART among study participants in the Counselling Centre for Behavioural Disease, Fars province

Characteristics	Crude Odds Ratio (95%CI)	Adjusted Odds Ratio (95%CI) #
Age	1.11 (0.14-5.78)	1.12(0.19-5.91)
Education level		
Graduated	1	1
Undergarduated	2.40* (1.39-4.14)	2.39* (1.38-4.13)
duration of HIV infection	0.72 (0.68-1.07)	0.90 (0.84-1.29)
Transmission ways		
Injecting drugs	1	1
Unsafe sex	3.39*(1.66-4.05)	3.40*(1.67-4.06)
History of high-risk behaviors		
Prison	2.43*(1.53-5.26)	2.45*(1.56-5.30)
Addiction	2.35*(1.46-4.36)	3.86*(2.80-5.35)
Injecting drugs	1.17(0.13-3.57)	1.15(0.12-3.56)
Sharing injections	1.89* (1.09-2.95)	2.13* (1.11-3.22)
Unsafe sex	1.15(0.57-2.31)	1.17(0.59-2.36)
Comorbidities		
Tuberculosis	2.90*(2.19-4.08)	3.22*(2.29-4.20)
Hepatitis B	1.89* (1.07-2.60)	1.89* (1.07-2.60)
Hepatitis C	2.41*(2.06-3.86)	2.43*(2.09-3.89)

*Conditional logistic regression was used to estimate the odds ratio considering p-value<0.05

#adjusted for age, educational level, duration of HIV infection, comorbidities (tuberculosis, hepatitis B, and hepatitis C)

This study aimed to assess various factors' impact on ART adherence in PLHIV receiving antiretroviral therapy. The findings revealed that engaging in condomless anal or vaginal sex, education level, a history of prison, sharing injections, substance addiction, tuberculosis, hepatitis B and hepatitis C were significantly linked to non-adherence to ART.

Our research indicates that individuals with lower levels of education are more prone to being non-adherent to antiretroviral therapy (ART). This highlights the importance of education and access to information in ensuring the successful management of HIV/AIDS. Individuals with a university education demonstrate improved adherence to treatment. Their understanding of HIV treatment leads to the recognition that proper adherence results in better health outcomes. Therefore, educating those with lower levels of education is essential to enhance treatment adherence. Efforts should be made to provide targeted support and resources to individuals with lower education levels to improve adherence to ART and overall health outcomes. Individuals with lower education levels may face barriers such as limited understanding of the importance of ART, difficulty in following complex treatment regimens, and challenges in accessing healthcare services. By addressing these barriers through education and targeted support, we can help improve

adherence rates and ultimately enhance the health and well-being of individuals living with HIV/AIDS (21).

In this study, it was discovered that engaging in unprotected anal or vaginal sex was strongly associated with non-adherence to ART. Engaging in unprotected anal or vaginal sex was about three times more frequent among non-adherent individuals than adherent individuals. These results align with studies from Atlanta and United States, suggesting that participating in unprotected sexual activities could lower adherence to ART (22, 23). Most people who have unprotected sex are sex workers. These people feel more isolated than other people. This is because they may receive only temporary emotional connections through their work and are frequently subjected to harassment by their clients. As a result, these peoples are at a higher risk of experiencing psychological issues and emotional difficulties. Unfortunately, the fear of being judged by healthcare workers can make it challenging for them to seek help and receive the care and treatment they need(24). Patients who engage in unprotected sex may have lower adherence to treatment due to a lack of concern for their health (25).

In this study, the non-adherent group had a history of prison that was 2.1 times higher, showing a significant association with non-adherence to ART. These findings underscore the importance of addressing the specific needs of individuals with a history of incarceration to improve ART adherence rates and overall health outcomes in this population (26). Efforts to provide self-care and education interventions for this subgroup are crucial in promoting successful HIV treatment outcomes. Healthcare providers need to recognize the unique challenges faced by individuals with a history of incarceration and tailor interventions accordingly. By implementing targeted support programs and fostering a supportive environment, we can empower this subgroup to effectively manage their HIV treatment and enhance their overall well-being. Collaboration between healthcare professionals, social services, and community organizations is key to creating a comprehensive care approach that addresses the multifaceted needs of this vulnerable population (27).

Substance addiction was significantly associated with non-adherence to ART. Individuals struggling with substance addiction were found to have lower rates of adherence to their antiretroviral therapy (ART) regimen compared to those without addiction issues. Drug and alcohol addiction is a significant challenge for people living with HIV. Addiction can lead to the rapid progression of HIV disease, a decreased willingness to receive regular HIV care, and lower chances of receiving antiretroviral therapy (28). Drug users are individuals who neglect their well-being and health, leading to a disregard for medication and recovery, highlighting the importance of education. They may lack awareness of HIV prevention and treatment strategies and may resist following doctors' and health workers' treatment and preventive recommendations. Research indicates that many health workers view drug users as individuals who are indifferent to their health (29).

Our findings indicate that individuals with a history of tuberculosis and hepatitis C virus are more likely to exhibit non-adherence to antiretroviral therapy (ART). Mortality rates are higher among those with co-infection (HIV/TB) than for HIV only. HIV infection affects the immune system, making it more susceptible to reactivation of latent TB infection. It is important to note that individuals who are receiving treatment for both tuberculosis (TB) and human immunodeficiency virus (HIV) at the same time may face challenges in adhering to both treatments. Failure to comply with the prescribed TB and HIV treatment regimen can result in an increased risk of drug resistance, relapse, death, and also the spread of infection (30).

It is important to note that the side effect of ART drugs can significantly reduce treatment adherence in tuberculosis and hepatitis patients. Research has shown that common side effects of antiretroviral drugs in HIV patients with co-infections include headache, nausea, fatigue, diarrhea, cough, and pancreatitis.Patients experiencing these side effects may be less likely to continue taking their medication as prescribed, which can lead to treatment failure and the development of drug-resistant strains of the infections (31, 32).

Suffering from co-infections such as tuberculosis, hepatitis B, and HIV at the same time can make it harder for patients to stick to their HIV treatment. This can lead to worse health outcomes and a higher chance of passing the virus to others. It is crucial for healthcare providers to offer comprehensive care and support to individuals facing such complex health challenges. By addressing the multiple infections simultaneously and providing tailored treatment plans, the chances of successful management and improved outcomes can be significantly enhanced. Early detection, effective monitoring, and a holistic approach to care are essential in ensuring the well-being of patients dealing with these intersecting health issues (33, 34). The cross-sectional study from Toronto, Canada also found that history of hepatitis C in individuals with HIV decreases adherence to ART (35).

This study had a few limitations. First, this nested case-control study utilized data from existing registries. Some factors such as personal habits, smoking, and lifestyle that may be associated with treatment adherence were not recorded. Nevertheless, we attempted to evaluate as much information as possible. Second, high-risk behaviors were obtained through person-to-person interviews conducted retrospectively. Information bias might lead to underreporting of high-risk behaviors. However, this bias should be similar in both "case couples" with high-risk behaviors and "control couples". Thired, we only included patients who were registered in the HIV/AIDS registery and surveillance system, which may have caused selection bias as some patients may not have been identified.

Conclusion

The study found that non-adherence to ART was significantly linked to engaging in condomless anal or vaginal sex, education level, history of prison, substance addiction, tuberculosis, and hepatitis C. By addressing factors contributing to non-adherence, healthcare providers can better support patients in achieving optimal health outcomes and reducing HIV transmission.

Providers must create a supportive environment for open discussions about sexual health and medication adherence, fostering trust and communication. Behavioral interventions and counseling sessions empower patients to make informed decisions. A comprehensive approach is essential for enhancing adherence to ART for those affected by HIV.

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Conflict of interest: None

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Ethics statement: This study was approved by the ethical committee of Isfahan University of Medical Sciences with code IR.MUI.RESEARCH.REC.1401.295. In order to protect patient privacy, anonymous patient information was extracted from the HIV/AIDS registery and surveillance system.

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