

## Reviews in Clinical Medicine

# Adherence to Antiretroviral Therapy and Its Determinants in HIV Patients in Mashhad, IRAN, 2018: a Prospective Study

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### ABSTRACT

**Introduction:** Proper adherence to antiretroviral therapy (ART) provides good viral load suppression, while poor adherence can give rise to resistant strains and failure of the treatment.

**Methods:** We performed a prospective cohort study from December 2017 to March 2018. Of 245 patients, 103 of them were compliant with ART. Patient adherence is determined through the self-report method and pill-count method. Pill-count failed, and only self-reports of adherence were used for analysis. In each visit, we gave each patient medication needed for one month's treatment and asked them to bring back drug-pockets in the next visit. We also ask the number of tablets they did consume in this period. Mean adherence in three months is considered final adherence. Pearson chi-square model was used for analysis.

**Results:** Mean age  $\pm$  SD was  $40 \pm 1.36$  years. 44.7% were female. 84.5% of patients are considered adherent ( $\geq 95\%$  of doses were consumed). Married patients had better adherence ( $p = 0.04$ ). Age, sex, addiction, imprisonment history, intravenous drug usage were not associated with adherence ( $p > 0.05$ ). We also extracted previous history of treatment cessation and regimen changes. Efavirenz containing regimens had a higher rate of failure ( $p = 0.001$ ).

**Conclusion:** Although the adherence level was acceptable, the lack of a self-report control method might overestimate adherence.

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## Introduction

Human immunodeficiency virus (HIV) is considered a significant obstacle for all health systems globally. At the end of 2017, 36.9 million people were recognized HIV-positive, and 940,000 HIV-related deaths were reported in 2017 (1).

0.5 to 1.25% of the health budget of several European countries is dedicated to the economic burden of HIV (2).

Antiretroviral therapy (ART) is a crucial weapon to control the virus and provides a significant decrease in patient complications and virus trans-

mission through the community. It enhances the quality of life and increases the life span. Meanwhile, ART is a double-edged sword, and its inappropriate use can give rise to a resistant virus. When resistance occurs, firstly, the current regimen is useless, and consequently, we have to switch to a second-line regimen, which costs at least three times more. Secondly, the resistant strains have reduced sensitivity to second- and third-line drugs compared to those who began these regimens for reasons other

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than drug resistance. Finally, viral load suppression is not achieved appropriately, and transmission facilities (3,4).

These are only a few reasons why in 2016, World Health Organization (WHO) programmed a global action plan on HIV drug resistance (GAP on HIVDR) to react more efficiently to HIVDR and extend monitoring and responding against it (4).

Different factors drive HIVDR; one of them is adherence to ART. 95% of adherence is necessary to accomplish the desired viral load suppression (4,5).

Several methods were proposed to evaluate adherence. The self-report method is one of the easiest and cheapest subjective methods, which provides reliable results (6).

Another technique is pill-count, which is an objective way of adherence assessment. Some others include blood concentration of drugs, electronic medication monitors (MEMS), pharmacy claims, and cathepsin zymography (7-10).

Naturally, each method has its pros and cons. Yet, self-report is considered an inexpensive, available method in developing countries which its results correlate with viral load suppression targets (6,9,10). On the other hand, it overestimates adherence and strongly depends on interviewer-patient interaction.

About 60,000 patients were diagnosed with HIV at the end of 2017, and 3500 HIV-related deaths occurred in Iran. 9.3% of intravenous drug users (IVDU), 2.1% of sex workers, and 0.9% of prisoners are estimated to be infected with HIV in Iran (1,11).

ART coverage for adults, children, and pregnant women is 53%, 18%, and 55%, respectively (11). ART adherence reported 60 to 70% in big cities like Tehran and Shiraz, assessed by self-report and pill-count methods (9,10).

However, we found no studies regarding the measurement of ART adherence in Mashhad. We designed this study to determine the compliance and adherence level amongst HIV patients in Mashhad.

## Methods

This prospective cohort study started on December 15, 2017, to March 16, 2018, at the "center of control and counseling of infectious and behavioral diseases" in Mashhad, the second-most populous city of Iran. HIV-positive patients who were compliant with ART and intended to participate included in our survey. No limits are considered regarding the age of participants or their treatment duration. Exclusion criteria are considered as unwillingness to cooperate in the study. Still, we were aware of the

bias, which may occur because patients with an unwillingness to cooperate may have lower adherence.

Therefore, we asked the caregiver to convince all available patients to enroll. Owing to the caregiver's friendly and professional relationship with the patients, no one dropped by exclusion criteria as the study went on. There were 245 HIV-positive patients recognized at the study initiation. One hundred three of them met the inclusion criteria and enrolled in our study.

Data collection took place through direct and indirect methods. We extracted demographic characteristics, the number of children, history of high-risk behaviors (unprotected intercourse, same-sex sexual contact, imprisonment history, intravenous drug use, same syringe usage, and other addiction types) from patients' medical records. Direct data collection was used to assess adherence. Informed consent was taken in the first visit, and adherence aimed to determine through two methods, self-report and pill-count. Both methods were considered useful for adherence assessment in similar studies but overestimate adherence compared to MEMS (12).

Lack of adequate financial support led to the exclusion of the MEMS method. The same treatment protocol of WHO's used to treat our study group (13).

Of note, the number of daily pills was different for each patient based on the regimen in which they were placed—patients with adherence of 95% or more, considered adherent.

As the study went on, we got several complaints of side effects of Efavirenz (EFV), especially in opium-addicted patients. Then we wondered that Efv-containing regimens might influence adherence. Thus, we extracted the history of treatment cessations and studied its association with Efv-containing regimens.

## Limitations

Despite frequent reminders by the healthcare provider, only six patients brought back their drug pockets. As a result, we only include the self-report method in our data analysis. When we questioned why not returning bags, the vast majority of them stated that HIV infection is the least they care about, considering their financial problems and low socioeconomic status.

At the beginning of the research, one goal was to measure patients' monthly income and their association with adherence. Still, most of them refused to reveal their salary, worrying that we may charge them for medication based on this information.

## Procedure

In each visit, we gave each patient drugs needed for a one-month treatment and asked them to bring back their drug pockets in the next visit.

We believed that fixating on the term "pill-count" can cause guards against a healthcare provider and lead to unreliable results, so we did not inform patients that our purpose is to count the leftover pills. We also asked the number of days they did consume their medications in the last three days, last week, and last month. The number of these days divided by the number of days we followed the patient, multiplied by 100, considered the percent of patient adherence every month.

The final adherence considered the mean of these three percentages. Due to the profound discrepancy between adherence of the last three and seven days compared to one month-adherence, only final adherence of one-month follow-up was used in our analysis. This discrepancy was explained by delayed returning for drug-refill, which inappropriately affected the last seven and three days' adherence.

### Statistics

We used chi-Squared analysis to ascertain the relation between adherence and suspected determinants (age, sex, number of pills, marital status, education degree, opium addiction, IVDU, imprisonment history, and CD4 level).

The same statistical model was used to reveal the EFV association with treatment cessation. The analysis was accomplished by SPSS version 16.

### Result

One hundred three patients were included in our study. The mean age was  $40 \pm 1.36$  years, with a minimum and maximum of 5 and 78 years old, respectively. 44.7% were female. Regardless of the patient's regimen, the mean number of daily pill usage was 2.67 pills (median=2) with a minimum and maximum of 1 and 8 tablets per day. Marital status, level of education, probable transmission route, encountered risk factors, and daily number of pills and reason for non-adherence are shown in Table 1.

About accompanying hepatitis infection, 5.8% were HBs antigen-positive, 9.7% were not assessed, and the rest were HBs-antigen negative. 24.3% were HBs-Antibody positive, 18.4% were not evaluated, and the rest were HBs-antibody negative. 31% of patients were HCV antibody positive, 7.8% had unknown serological status, and the rest were serologically negative. Amongst those with positive serological status for HCV, 81.2% reported a history of IVDU.

**Table 1:** Demographic characteristics of patients

<b>Marital status</b>	
Temporarily married	2 (1.9%)
Permanently married	48 (46.6%)
Single	19 (18.4%)
Divorced	21 (20.3%)
Widowed	11 (10.6%)
Unknown	2 (1.9%)
<b>Educational status</b>	
No education	10 (9.7%)
Elementary school	36 (34.9%)
Guidance school	33 (32%)
High-school	16 (15.6%)
University degree	6 (5.8%)
Unknown	2 (1.9%)
<b>Probable transmission route<sup>1</sup></b>	
IVDU	34 (33%)
Heterosexual contact	34 (33%)
Men with men sexual contact	3 (2.9%)
Mother to child	7 (6.8%)
HIV positive partner	28 (27.1%)
Occupational/ transfusion	0 (0%)
Unknown	17 (16.5%)
<b>Reported risk factors</b>	
Opium	42 (40.7%)
imprisonment	36 (34.9%)
Condom-less sex	41 (39.8%)
addiction	20 (19.4%)
IVDU	47 (45.6%)
Needle/syringe sharing	26 (25.2%)
Extramarital sex	34 (33%)
<b>Daily number of pills</b>	
pill 1	48 (46.6%)
pill 2	5 (4.9%)
pill 3	12 (11.7%)
pill 4	18 (17.5%)
pill 5	16 (15.5%)
pill 6	1 (0.9%)
pill 7	0 (0%)
pill 8	3 (2.9%)
<b>Reason of non-adherence</b>	
Busyness	12 (11.5%)
(Unavailability (delay to pharmacy refill)	33 (32.7%)
Forgetfulness	24 (23.2%)
Traveling	10 (9.6%)
Addiction	6 (5.8%)
Multiple pills	4 (3.8%)
Drug adverse effects	10 (9.6%)
Unknown	4 (3.8%)

<sup>1</sup>Accumulative percentage is higher than 100% due to probability of multiple transmission route for each patient.

The mean initial CD4 level was 339 ( $\pm 289$ ),

and the mean last CD4 level was 385 ( $\pm 245$ ).

33% of patients had never evaluated for the viral load; among those who were assessed, the mean first and last viral load was 167253 and 138883, respectively.

50.5% (52 patients) of our study group had a history of regimen change. These 52 patients had 132 times of regimen change, an average of 2.3 times for each patient.

18.5% of these changes were due to drug resistance. 40.98% and 40.16% were due to "drug side-effects" and "patient poor-adherence," respectively, to "drug side-effects" and "patient poor-adherence," respectively.

15.5% of patients had adherence of less than 95%. This amount of adherence and its relationship with the following measures were statistically meaningless: age, sex, opium addiction, history of imprisonment, intravenous

drug usage, education status, number of daily pills, and CD4 level at the beginning of treatment. Only marital status had significant relevance to adherence of 95% (Table 2).

We also found no relationship between adherence of 95% and the presence of EFV in the regimen. However, by considering adherence at an acceptable level of 90%, this relationship would be meaningful (Table 3).

All patients with a history of EFV-containing regimens (41 patients) had a history of regimen change. For those with regimens lacking EFV (62 patients), only 11 people reported a regimen change history. ( $P=0.001$ ). In other words, the presence of EFV in previous regimens increases the chance of regimen change (Table 4).

**Table 2:** Pearson Chi-Square analysis of study variables and adherence of 95%

	Pearson Chi-Square		P-value
	Adherent patients (%)	Non-adherent patients (%)	
<b>Age</b>	50>	67 (82.7)	0.34
	50≤	20 (90.9)	
<b>Sex</b>	Male	49 (56.3)	0.64
	Female	38 (43.7)	
<b>Marital status</b>	Married	46 (52.9)	0.04
	Unmarried	41 (47.1)	
<b>Addiction</b>	Addict	34 (39.1)	0.41
	Non-addict	53 (60.9)	
<b>Imprisonment history</b>	Positive	29 (33.3)	0.46
	Negative	52 (59.8)	
	Unknown	6 (6.9)	
<b>IVDU history</b>	Positive	28 (32.2)	0.67
	Negative	59 (67.8)	
<b>High-school Education</b>	Present	69 (79.3)	0.69
	Absent	18 (20.7)	
<b>Number of daily pills</b>	1	38 (43.70)	0.16
	1<	49 (56.30)	
	4≥	70 (80.5)	
	4<	17 (19.5)	
<b>CD4 count</b>	350>	54 (62.1)	0.66
	350≤	33 (37.9)	
	500>	63 (72.4)	
	500≤	24 (27.6)	

**Table 3:** Effect of EFV on medication-adherence

			EFV-containing regimen	Regimens lacking EFV	p
Pearson Chi-Square	95% of adherence	Present	54(62.1%)	33(37.9%)	0.63
		Absent	8(50%)	8(50%)	
	90% of adherence	Present	61(63.5%)	35(36.5%)	0.01
			1(14.3%)	6(85.7%)	

**Table 4:** Effect of EFV on the frequency of regimen-change

		EFV containing regimen		P-value
		Yes	No	
Regimen change	Yes	41(78.8%)	11(21.2%)	0.001
	No	0(0%)	51(100%)	

## Discussion

Proper adherence to ART is necessary to achieve clinical improvement and adequate viral load suppression. There were no previous data on adherence to ART in Mashhad. We decided to evaluate adherence through two methods: self-report and pill-count. Data of pill-count method did not use in our analysis because only six patients brought back their pill pockets.

Although the caregiver had established a friendly relationship, when she asked them to bring back the pockets, patients manifested defensive reactions; they assumed that the center is questioning their trustworthiness. This method did not provide the expected data. Another reason could be due to patients' low socioeconomic status like being homeless, addicted, IVDU, and outcaste from their family. Some patients declare that "HIV is the least we worry about in life."

The target level of adherence is considered 95% and 84.5% of our patients achieved this goal. The reported adherence level in similar studies was 86% in Brazil (14), 88.2% in Ethiopia (15), 81.3% in India (16), and 70% in Latin America (17).

In Iran, reported adherence was 60-70%, but our results were obtained only through the self-report method that can overestimate the level of adherence compared to the pill-count method (10,15,18).

Age, sex, opium addiction, history of imprisonment, intravenous drug usage, education status, number of daily pills, and CD4 level at the beginning of treatment; none of them were found to be statistically relevant to adherence level of 95%.

Age could be considered a factor affecting adherence based on some experiments, though some other studies like ours did not find any relation (9,10,19).

Aging can cause either tedium of the treatment or increase commitment to it. It seems that a more

approach, rather than quantitative studies, is needed to determine the effect of age on adherence. The vast majority of studies declared that adherence is irrelevant to the sex of the patient (9,10).

Enhancement of adherence by marriage is shown in this study, while there were several articles for and against this factor (19-21).

Speaking of Iran, marital status alone is not a good indicator of family support, considering our cultural features. For instance, some patients are rejected by their partner without judicial separation. On the other hand, celibacy does not equal loneliness. We suggest assessing emotional support in terms beyond marital status for Iran in future experiments.

The recent status of IVDU was asked during the study. Still, because the answers showed discrepancies with patients' files, results considered unreliable, and only the history of previous IVDU was considered in our analysis. Patients assume that if they declare their real status, they may lose health care supports (methadone maintenance therapy, free medications, etc.). We found no relation between the history of IVDU and adherence, similar to previous studies in Iran (10).

Meantime, several similar studies found that IVDU decreases adherence while methadone maintenance therapy improves it (5,22).

Imprisonment reduces the adherence in most articles (23); however, we found no other similar study proceeding to the relation between the history of imprisonment and adherence.

Efavirenz (EFV) is an inexpensive, first-line drug for ART and available in low-income countries, yet it has short- and long-term adverse effects on patients' adherence. For instance, neuropsychiatric effects occur in 60-90% of patients, decreasing adherence in 2-24%. Several complaints (insom-

nia, depression, anxiety, etc.) urged us to evaluate its probable relevance to low adherence (24,25).

Those with a previous history of EFV-containing more frequently abandoned the treatment. Patients on current EFV-containing regimens were less likely to achieve an adherence level of 90% than those on regimens not containing EFV.

### Conclusion

The most common reason for non-adherence was a delay in pharmacy refills. This factor can easily eliminate via active patient follow-ups and revision of medication-refill strategies. Moreover, out of 245 recognized HIV positive patients, only 103 (42.04%) were compliant with ART. More interventions are needed to include non-compliant patients into treatment programs and determine reasons for non-compliance among them. Additionally, 33% of patients never assessed for viral load level, which can delay the recognition of HIV-VDR (5). Using EFV in the first-line regimen needs stricter follow-up and psychological support, especially during the first months of its initiation.

### Conflict of interest

None to declare.

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