

Post-exposure HIV prophylaxis adherence to full 28-day course versus weekly therapy in Tehran

Ladan Abbasian¹, Sahar Rezaee¹, Golbarg Alavian², SeyedAhmad SeyedAlinaghi¹, Abbas Alipour³, Seyed Ali Dehghan Manshadi¹, Hossein Hosseinpoor¹, Minoo Mohraz¹

¹Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High-Risk Behaviors, Department of Infectious Diseases, Imam Khomeini Hospital Complex, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

²Department of Clinical Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

³Community Medicine Department, Medical Faculty, Mazandaran University of Medical Sciences, Sari, Iran

Abstract

Introduction: This randomized clinical study was conducted to compare the adherence of post-exposure human immunodeficiency virus (HIV) prophylaxis (PEP) in full 28-day course of antiretroviral (ARV) treatment versus weekly therapy, and to find reasons for insufficient compliance among people referred to HIV clinic of Imam Khomeini Hospital, a teaching, and referral university hospital in Tehran, from 2018 to 2019.

Material and methods: This study determined the most suitable PEP protocol between full 28-day and weekly courses. After obtaining informed consent from 293 participants with exposure to HIV (both sexual and non-sexual), 106 and 111 individuals were randomly divided into two groups of a 28-day course and weekly PEP protocol, respectively, by simple randomization method, and the remaining 76 persons were lost to follow-up during the study. Adherence to PEP was defined as taking 95% of the prescribed antiretroviral therapy (ART) in each group. Chi-square test (Fisher exact test) and t-test were performed using SPSS software considering other variables, including age, gender, marital status, educational level, occupation, and distance from work or residence to a hospital.

Results: After analyzing data and possible factors affecting treatment adherence, it was found that 28-day PEP protocol increased ARV compliance (OR = 4.14; 95% CI: 1.79-9.58%; $p = 0.001$) compared with weekly protocol. Furthermore, no associations between adherence and demographic characteristics, such as gender, age, education level, occupation, income, marital status, and factors, including distance from people's place of residence or work, were found.

Conclusions: Adherence to PEP was much higher in the 28-day protocol than the weekly course of treatment.

HIV AIDS Rev 2024; 23, 2: 173-177
DOI: <https://doi.org/10.5114/hivar/148176>

Key words: post-exposure prophylaxis (PEP), treatment adherence, human immunodeficiency virus.

Address for correspondence: Prof. SeyedAhmad SeyedAlinaghi, Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran, e-mail: s.a.alinaghi@gmail.com

Article history:
Received: 18.01.2022
Received in revised form: 06.04.2022
Accepted: 08.04.2022
Available online: 18.05.2024



Introduction

Reducing the incidence of human immunodeficiency virus (HIV) infection is one of significant concerns of health professionals worldwide. Since the HIV can be detected in lymph nodes within 72 hours after contact and subsequently spread in the blood, preventive intervention after exposure plays a crucial and influential role [1].

Various factors, such as deep injury, high blood volume, progressive disease, and high viral load can increase the risk of HIV transmission after occupational exposure, and this risk is higher with the presence of sexually transmitted infections or hepatitis C (HCV), or in the case of non-occupational exposures, i.e., victims of sexual assault [2].

According to the World Health Organization's (WHO) recommendations to prevent new cases of HIV infection after a high-risk exposure, individuals should be treated with an antiretroviral regimen within 72 hours of exposure [2].

Antiretroviral drugs (ARVs) are recommended in high-risk exposure groups for 28 days to prevent HIV infection and therefore, strengthening adherence to post-exposure prophylaxis (PEP) remains an important consideration [3].

PEP is usually prescribed in two ways. In a weekly protocol, PEP is provided gradually during treatment, while in a 28-day treatment, all medicines are supplied during the first visit. In a systematic review and meta-analysis, it was found that adherence to PEP completion is usually poor, and efforts should be made to simplify PEP administration guidelines and support the increase of commitment, especially in adolescents and victims of sexual assault [4]. Furthermore, enhanced adherence support for completing PEP is also recommended by WHO recommendations [2].

Although psychological counseling is an effective way, combined modalities to increase adherence should be identified [3, 5].

Despite the different methods for prescribing PEP, it seems that the weekly plan with a weekly follow-up visit and the entire 28-day course prescription in an initial visit are noteworthy options in terms of outcomes and adherence to treatment. In addition, in some HIV post-exposure prophylaxis guidelines, the entire 28-day course of antiretroviral regimen is recommended rather than a partial prescription [2, 6].

It seems that one of the factors in non-adherence to treatment is the prescription method, and data on comparing adherence in different methods of PEP prescribing, especially in developing countries, are limited. Therefore, this study was conducted to determine the best way of PEP prescription in order to increase the level of adherence to treatment and recommend changes in the national prophylaxis protocol.

Material and methods

Study design and participants

This randomized clinical trial study was conducted between January 2018 and January 2019. All patients referred to

HIV clinic of Imam Khomeini Hospital, a teaching and referral university hospital in Tehran, were evaluated for eligibility.

Eligibility criteria: Based on the national HIV guidelines, individuals who had non-protected sexual contact with a high-risk person or any high-risk non-sexual exposure, including needle stick and mucosal contact within 72 hours, were enrolled into this study after obtaining informed written consent. Patients were assigned into two groups, such as group A (full-course recipients) and group B (weekly recipients), according to the numbers obtained from a random digits table and simple random allocation method.

Exclusion criteria: Confirmation of HIV during the study, negative HIV test result of the source, cessation of treatment for more than 48 hours, refusing to respond to a call or return for follow-up visit, and person's desire to leave the study.

Study process

People in group A received all medications at their first visit, and those in group B received weekly PEP for four weeks.

Post-exposure prophylaxis prescription

ARV regimen included tenofovir disoproxil fumarate (TDF) 300 mg once daily and lamivudine 150 mg twice a day, or emtricitabine 200 mg daily in addition to atazanavir/ ritonavir (300 mg/100 mg) as a third drug prescribed to eligible patients.

Follow-up and adherence

Data collection was based on interviews with individuals and a questionnaire with socio-demographic information, including age, gender, occupation, education level, income, and distance between home or workplace to a hospital. Treatment adherence was determined based on self-declaration and pill count (95% of prescribed ART) in both prescription methods.

Ethical consideration

This study was approved by the ethical committee of Tehran University of Medical Sciences.

Statistical analysis

The obtained data were statistically analyzed using chi-square test (Fisher exact test) and t-test to evaluate differences in characteristics of participants. Confidence interval was 95%, and significance level was set at $p \leq 0.05$. All statistical analyses were performed using SPSS version 22.0.

Results

Out of 293 patients presented to the clinic, only 217 completed the study after randomization into two groups

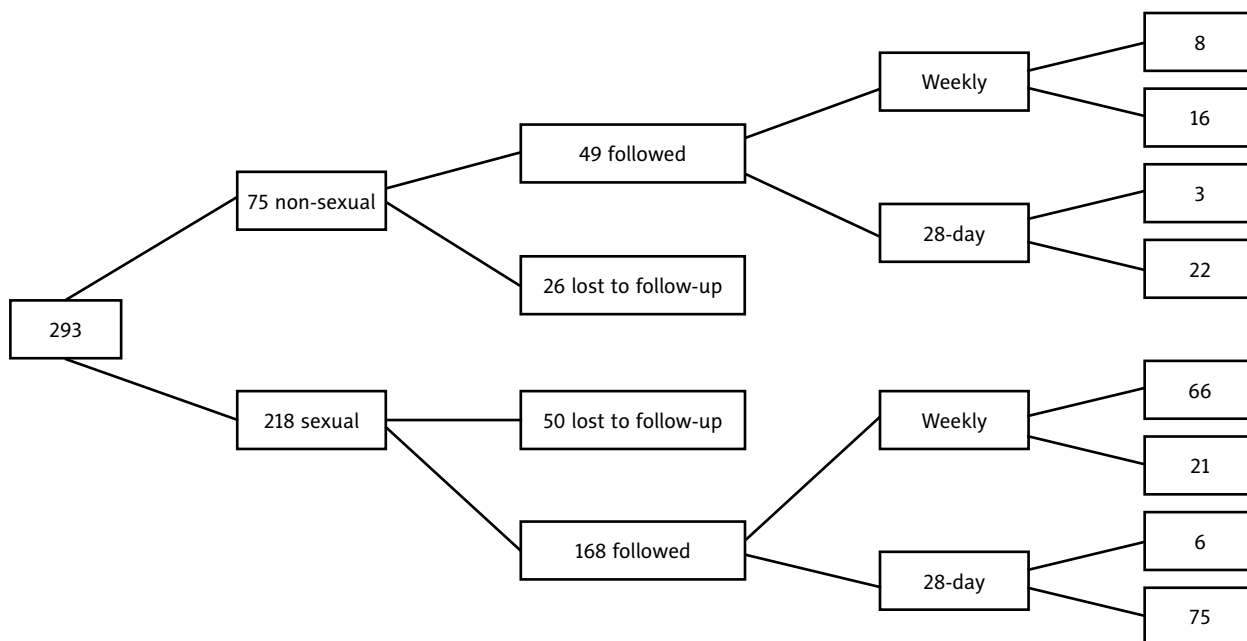


Figure 1. Individuals enrolled into the study’s each group and the number of people adherent to PEP treatment at the end of the course

of PEP administration, while the remaining 76 participants were lost to follow-up (Figure 1).

Two-hundred and seventeen participants completed their treatment course, and the cumulative incidence of adherent participants was 83.2% (179/217) in total, with 92.3% (97/105) in the 28-day group and 74.5% (82/110) in the weekly group, with OR = 4.14 (95% CI: 1.79-9.58%; $p = 0.001$). The association between demographic characteristics, type of exposure, PEP administration protocol, and patients’ adherence in each group is presented in Table 1. As shown, no statistically significant difference was found between age, sex ratio, marital status, education, occupation, income, and distance, and the type of the prescribed PEP ($p > 0.05$). While 97 (54.2%) patients in the 28-day course prescription were adherent to PEP treatment, there were 82 (45.8%) individuals in the weekly group ($p = 0.001$). Furthermore, in the analysis, no association between adherence and demographic characteristics, such as gender, age, education level, occupation, income, marital status, work and house distance, and type of exposure, was found. Of all the participants in the study, 36 (16.7%) individuals did not show adherence to PEP treatment, of which 8 (22.2%) were in the 28-day course group, and the remaining 28 (77.7%) were in the weekly group. Deliberate discontinuation (55.6%) and side effects (13.9%) of medicines were found as two main reasons for non-adherence to PEP treatment.

In the 28-day prescription protocol, two people (25%) did not adhere to treatment intentionally, and in the weekly prescription, this number reached 18 patients (64.3%), which showed a considerable difference, but was not statistically significant ($p > 0.05$). As shown in Table 1, there was no significant relationship between the type of exposure

and non-adherence to treatment ($p = 0.227$). However, there was a significant difference between the type of protocol and non-adherence to PEP treatment ($p = 0.001$).

Discussion

In the current study, two methods of PEP prescription were compared to find a more appropriate way to increase adherence to preventive treatment and reduce the risk of HIV infection. In a previous study by Hadadi *et al.*, the adherence to PEP was 59.6% among 89 people after occupational and non-occupational exposure to HIV. In this study, a significant relationship was observed between age and marriage and adherence to treatment [7]. Another retrospective study from 2013 to 2014 in Iran revealed that out of 453 eligible people to receive PEP, 274 (60.5%) completed the entire course [8].

The finding of the current research indicated a higher rate of adherence to PEP treatment (77.6%) than previous studies. The reasons might be increased awareness of the risk of HIV/AIDS, improved systems providing preventive medicine, and more appropriate PEP regimens with reduced adverse effects. In a systematic review and meta-analysis conducted by Chacko *et al.* to assess the adherence to PEP after sexual assault, the results showed a low level of compliance in this population. Also, they argued that the adherence to PEP is much lower in developing countries than in developed countries. Therefore, it may originate from a greater public awareness of the risk factors of HIV infection [9]. In a retrospective study by Malinverni *et al.* among 1,357 people to evaluate the accuracy of PEP prescription by emergency physicians and its compliance compared with literature

Table 1. Association between demographic characteristics, exposure, protocol type, and adherence

Variables	Groups		OR (95% CI) Referent	p-value Referent
	Full adherence, n (%) [*]	Non-adherence, n (%) [*]		
Gender				
Female	30 (16.8)	9 (25.0)	1.66 (0.71-3.87)	0.245
Male	149 (83.2)	27 (75.0)	–	
Age (years), mean ± SD	30.56 ± 8.41	28.69 ± 7.85	0.97 (0.92-1.02)	0.222
Education				
Non-academic	39 (21.8)	11 (30.6)	0.63 (0.29-1.40)	0.259
Academic	140 (78.2)	25 (69.4)	–	
Occupation				
Healthcare workers (HCWs)	23 (12.8)	5 (13.9)	0.94 (0.39-2.27)	
Others	114 (63.7)	23 (63.9)	–	0.898
Income in Tomans, mean ± SD	2,632.94 ± 3,510.25	2,782.86 ± 4,471.58	1.00 (0.50-1.50)	0.826
Marital status				
Married	58 (32.4)	9 (25.0)	0.70 (0.31-1.57)	0.383
Single	121 (67.6)	27 (75.0)	–	
Work distance				
< 1 hour	98 (71.5)	24 (82.8)	–	
1 hour	24 (17.5)	3 (10.3)	0.51 (0.14-1.84)	0.303
1-2 hours	8 (5.8)	2 (6.9)	1.02 (0.20-5.12)	0.980
> 2 hours	7 (5.1)	0 (0.0)	0.05 (0.0-2.92)	0.999
House distance				
< 1 hour	119 (66.5)	26 (72.2)	–	
1 hour	37 (20.7)	5 (13.9)	0.66 (0.13-3.43)	0.617
1-2 hours	7 (9.5)	3 (8.3)	0.41 (0.06-2.59)	0.340
> 2 hours	6 (3.4)	2 (5.6)	0.53 (0.07-3.98)	0.537
Exposure type				
Non-sexual	38 (21.2)	11 (30.6)	0.61 (0.28-1.36)	0.227
Sexual	141 (78.8)	25 (69.4)	–	
Protocol				
28 days	97 (54.2)	8 (22.2)	4.14 (1.79-9.58)	0.001 ^{**}
Weekly	82 (45.8)	28 (77.8)	–	

^{*}Sub-groups did not always added up to the total due to missing data.

^{**}Statistically significant

reports, the results indicated that the adherence was 60%, while sexual assault victims showed the lowest compliance to treatment (40%). They noted that pill burden and adverse effects might be the reasons [10]. In another recent prospective cohort study by the same author and colleagues, factors, such as being MSM, having health insurance, previous PEP treatment, day-time consultations, and older age increased the adherence to non-occupational PEP treatment. Conversely, reduced treatment adherence is associated with sexual assault survivors and foreign individuals [11].

Intolerance to the adverse effect was the reason for truncating PEP in another cohort study from Ghana that included 228 exposed healthcare workers (HCWs). This study

highlighted the role of education and counseling in increasing treatment adherence [12]. Recent studies have also emphasized the importance of on-line education and capabilities of web- and mobile-based programs in preventing HIV infection [13]. In a prospective observational study on 2,731 prescribed cases of PEP in Canada, it was concluded that PEP regimen, mainly tenofovir/ emtricitabine-based ones, was associated with better adherence to treatment following sexual exposure. Furthermore, first-time PEP receivers, older and male patients were more adherent to treatment [14].

Deliberate discontinuation (55.6%) and side effects (13.9%) of medicines were two main reasons for non-adherence to PEP treatment in our study. From another per-

spective, this study showed that none of the defined possible factors are necessarily related to the adherence to PEP completion. The 28-day PEP protocol remained related to patient compliance in our study (OR, 4.14; 95% CI: 1.79-9.58; $p = 0.001$).

Evidence from a systematic review conducted to assess the outcome of starter packs method for PEP (providing two divided doses of PEP) compared with full prescription suggested overall better outcome, higher completion rate, and fewer refusals for an entire 28-day course PEP. However, over a quarter of individuals receiving a PEP starter pack failed to return for a follow-up appointment and receive the rest of medications. Finally, the study concluded that starter packs did not improve the adherence to PEP [15].

As mentioned earlier, in a critique review, Rudy Zimmer states that PEP starter packs are not designed to improve or impair treatment adherence. Instead, he believes that compliance depends on the active participation of individuals in receiving PEP related to factors, such as perception of risk or drug tolerance that are not associated with the starter pack method [16].

In the current study, considering the significant difference between the prescribed protocol types, it can be concluded that only the 28-day prescription method is among the influencing factors in increasing the adherence to treatment completion.

During the course of the study, there were some limitations, including the fact that we could not bring the number of people in both sexually and non-sexually exposure groups closer together. Also, the authors did not have the access to data of a significant number of patients until the end of the study process.

Conclusions

The present study showed that the adherence to PEP treatment is better if the full-course prescription is provided. It should be considered that although the 28-day PEP protocol is preferable to the weekly protocol, both can be used at the physician's discretion.

Disclosures

1. Institutional review board statement: The study was approved by the Ethical Committee of Tehran University of Medical Sciences, with the approval number of IR.TUMS.IKHC.REC.1397.032.
2. Assistance with the article: The authors would like to thank the staff for their help.
3. Financial support and sponsorship: Grant number of 9011215055.
4. Conflicts of interest: None.

References

1. Spira AI, Marx PA, Patterson BK, Mahoney J, Koup RA, Wolinsky SM, Ho DD. Cellular targets of infection and route of viral dissemination after an intravaginal inoculation of simian immunodeficiency virus into rhesus macaques. *J Exp Med* 1996; 183: 215-225.
2. World Health Organization. Guidelines on post-exposure prophylaxis for HIV. Recommendations for a public health approach. Geneva: WHO; 2014.
3. Blashill AJ, Ehlinger PP, Mayer KH, Safren SA. Optimizing adherence to pre-exposure and postexposure prophylaxis: the need for an integrated biobehavioral approach. *Clin Infect Dis* 2015; 60 Suppl 3: S187-190.
4. Ford N, Irvine C, Shubber Z, Baggaley R, Beanlanda R, Vitoria M, et al. Adherence to HIV post-exposure prophylaxis: a systematic review and meta-analysis. *AIDS* 2014, 28: 2721-2727.
5. SeyedAlinaghi S, Taj L, Mazaheri-Tehrani E, Ahsani-Nasab S, Abedinzadeh N, McFarland W, et al. HIV in Iran: onset, responses, and future directions. *AIDS* 2021; 35: 529-542.
6. Dominguez KL, Smith DK, Vasavi T, Crepaz N, Lang K, Heneine W, et al. Updated guidelines for antiretroviral post-exposure prophylaxis after sexual, injection drug use, or other non-occupational exposure to HIV – the United States. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2016.
7. Hadadi A, Rasoulinezhad M, Jamali S, Seyed Ali Naghi SA, Paydari K, Boyer MA, et al. Adherence to antiretroviral prophylaxis after occupational and non-occupational exposure to human immunodeficiency virus in patients consulting the voluntary counseling and testing center of Imam Khomeini Hospital, Tehran, 2008-2009. *Journal of School of Public Health and Institute of Public Health Research* 2012; 9: 37-44.
8. Rasoolinejad M, Naghib Sadat B, Najafi Z, Baesi K, Heidari H, Seyedalinaghi S. Epidemiological and clinical information of people at risk for HIV referred to the voluntary counseling and testing center, Tehran, Iran, 2013-2014. *J Int Transl Med* 2018; 6: 176-180.
9. Chacko L, Ford N, Sbaiti M, Siddiqui R. Adherence to HIV post-exposure prophylaxis in victims of sexual assault: a systematic review and meta-analysis. *Sex Transm Infect* 2012; 88: 335-341.
10. Malinverni S, Libois A, Gennotte AF, La Morté C, Mols P. Prescription of non-occupational post-exposure HIV prophylaxis by emergency physicians: an analysis on accuracy of prescription and compliance. *PLoS One* 2016; 11: e0153021. DOI: <https://doi.org/10.1371/journal.pone.0153021>
11. Malinverni S, Gennotte AF, Schuster M, De Wit S, Mols P, Libois A. Adherence to HIV post-exposure prophylaxis: a multivariate regression analysis of a 5 years prospective cohort. *J Infect* 2018; 76: 78-85.
12. Tetteh RA, Nartey ET, Lartey M, Mantel-Teeuwisse AK, Leufkens HGM, Nortey PA, Dodoo ANO. Adverse events and adherence to HIV post-exposure prophylaxis: a cohort study at the Korle-Bu Teaching Hospital in Accra, Ghana. *BMC Public Health* 2015; 15: 573. DOI: <https://doi.org/10.1186/s12889-015-1928-6>.
13. Niakan S, Mehraeen E, Noori T, Gozali E. Web and mobile based HIV prevention and intervention programs pros and cons – a review. *Stud Health Technol Inform* 2017; 236: 319-327.
14. Thomas R, Galanakis C, Vézina S, Longpré D, Boissonnault M, Huchet E, et al. Adherence to post-exposure prophylaxis (PEP) and incidence of HIV seroconversion in a major North American cohort. *PLoS One* 2015; 10: e0142534. DOI: [10.1371/journal.pone.0142534](https://doi.org/10.1371/journal.pone.0142534).
15. Ford N, Venter F, Irvine C, Beanland RL, Shubber Z. Starter packs versus full prescription of antiretroviral drugs for post exposure prophylaxis a systematic review. *Clin Infect Dis* 2015; 60 (Suppl 3): S182-S186.
16. Zimmer R. HIV post-exposure prophylaxis starter packs were not designed to help or hinder adherence. *Clin Infect Dis* 2016; 62: 667-668.