Patient Retention in Antiretroviral Therapy Programs; A Retrospective Cohort Study in a Triangular HIV Clinic

Azadeh Khalatbari Limaki[1], Behnam Farhoudi[1⊠], Mehrnaz Rasoolinejad[2], Saeed Safari[3]

[1] Clinical Research Development Center, Amir-Almomenin Hospital, Islamic Azad University, Tehran Medical Sci-ences Branch, Tehran, Iran
[2] Iranian Research Center for HIV/AIDS (IRCHA), Tehran University of Medical Sciences, Tehran, Iran
[3] Emergency Department, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: High rate of adherence to antiretroviral therapy (ART) is critical for the optimized outcome. The present study aimed to determine the rate of retention in ART programs and its' associated factors in a triangular clinic. **Materials and Methods:** The present retrospective co-hort study was conducted on people living with HIV receiving care in a triangular clinic affiliated with Iranian research center for HIV/AIDS, Tehran, Iran, from 2003 to 2008. Baseline variables, duration of ART, and cause of treatment discontinuation were gathered using patients' profile and analyzed by SPSS 21 and STATA 11. **Results:** Three hundred and seventeen cases with the mean age of 37.69 ± 10.63 (2–76) years were included (83.9% male). Treatment discontinuation had happened in 142 (45.2%) cases. Cause of treatment discontinuation was death in 20 (13.7%) cases and personal preference in 126 (86.3%) individuals. 6, 12, 18, 24, 36, and 60 months retention rates were 81.1%, 58.4%, 48.3%, 35.6%, 22.9%, and 6.3%, respectively. The results of multivari-ate logistic regression analysis showed a significant association between treatment retention and female sex (OR: 4.10; 95% CI: 1.59–10.56, P=0.003), addiction/drug use (OR: 0.39; 95% CI: 0.21– 0.77, P=0.007), and lamivudine+ zidovudine+ indinavir treatment regimen (OR: 0.63; 95% CI: 0.46 -0.87, P= 0.005). **Conclusion:** Based on the findings, male sex, addiction/drug use, and type of treatment regimen were among the most important risk factors for ART attrition in HIV-in-fected patients. **[GMJ.2017;6(2):110-117] DOI: 10.22086/GMJ.V6I2.819**

Keywords: Antiretroviral Therapy; Highly Active; Human Immunodeficiency Virus; Withholding Treatment; Survival Rate

Introduction

The high rate of adherence to antiretrovi-ral therapy (ART) is critical for optimized outcome [1, 2]. A variety of factors may pre-dict medication retention among human im-mune deficiency virus (HIV)-infected adults [3].

Studies have documented relations between personality traits and quality of life among individuals living with HIV [4]. Persons liv-ing with HIV have a higher likelihood of sub-stance abuse, depression, and anxiety [5], and personal characteristics of HIV-infected pa-tients may influence their adherence to ART programs.

⊠ **Correspondence to:**
Behnam Farhoudi, Clinical Research Development Cen-ter, Amir-Almomenin Hospital, Islamic Azad Universi-ty, Tehran Medical Sciences Branch, Tehran, Iran
Telephone Number: +989123833398
Email Address : behnam.farhoudi@gmail.com

In a study in this regard, Lessells *et al*. revealed the poor retention of younger and patients at an earlier stage of infection [6].

Rosen and Fox, in a systematic review on Sub-Saharan Africa population, showed a considerable retention to HIV care at three stages: testing to receipt of the CD4 count, staging to ART eligibility, and eligibility to ART initiation [7].

 Missed visits to the clinic was accounted as an important obstacle to ART initiation in a study of patients at 1917 HIV/AIDS Clinic, University of Alabama, Birmingham [8].

The triangular clinic is an innovative and programmatic concept that deals with three frequently overlapping issues; drug abuse, sexually transmitted infections, and HIV/AIDS [9]. The triangular clinic utilizes the services of medical doctors as well as paramedical staff and counselors. By 2015 there were more than 160 such clinics across the country in Iran [10, 11], but there is little information regarding ART retention among Iranian people living with HIV.

The present study aimed to determine the rate of retention in ATR programs and its' associated factors in a triangular clinic. This information could be helpful in improving treatment programs as well as patients' outcome.

Materials and Methods

Study Design and Setting
The present retrospective cohort study, with 60 months follow-up, was conducted on people living with HIV receiving care in a triangular clinic affiliated with Iranian research center for HIV/AIDS, Imam Khomeini Hospital, Tehran, Iran, from 2003 to 2008.
The study protocol was approved by the ethics committee of Tehran University of Medical Sciences. Researchers adhered to Declaration of Helsinki protocol and confidentiality of patients' information.

Participants
Using census sampling, the clinic profiles of all HIV-infected patients referring to the mentioned triangular clinic during 2003 to 2008 were studied.
Patients known to be alive ≥ 18 months of re-

ceiving ART were defined as treatment retention group, and patients with discontinuation of ART for any reason other than death were defined as treatment attrition group. Change of treatment regimen was not considered as treatment attrition. The pregnant patients were excluded. There was not any sex or age limitation for patients' enrollment.

Data Gathering
A pre-designed checklist consisting of demographic variables (age, sex, level of education, marital status, employment status, and household tenure type), social history, HIV transmission route, history of hepatitis C virus (HCV) infection, history of psychiatric disease (based on self-report), indication of ART initiation (CD4 count, clinical, or both), treatment characteristics (regimen, change, discontinuation, restart, and side effect), and cause of treatment discontinuation was used for data gathering.
A trained medical student was responsible for data collection from patients' profiles (any conflict or problem was discussed and resolved with an infectious disease specialist).
Treatment regimen were standard triple combinations of lamivudine (3TC), zidovudine (ZDV), nelfinavir (NLF), nevirapine (NVP), efavirenz (EFV), indinavir (IDV).

Outcome
Treatment retention was considered as the outcome of the present study.

Statistical Analysis
Data were analyzed using SPSS 21 and STATA 11 statistical software. Qualitative variables were reported as frequency and percentage, and quantitative ones as mean ± standard deviation (SD).
Chi-square or Fisher exact tests were used for evaluation of significant associations between qualitative variables and treatment retention, and independent sample t-test was used to compare means. Independent risk factors of ART retention were assessed by multivariate regression analysis and calculation of odds ratio (OR) with 95% confidence interval (CI). A P-value < 0.05 was considered as statistically significant.

Results

Baseline Characteristics
Three hundred and seventeen cases with the mean age of 37.69 ± 10.63 (2–76) years were included (83.9% male). Table-1 and 2 show the baseline and treatment characteristics of studied patients. Treatment discontinuation had happened in 142 (45.2%) cases, 67 (47.2%) of which had restarted.

Table 1. Baseline Characteristics of Studied Patients

Variables	Treatment attrition Number (%)		P-value
	No	**Yes**	
Age (year)			
> 20	10 (5.8)	3 (2.1)	0.206
20 – 34.9	53 (30.5)	43 (30.3)	
35 – 49.9	86 (49.4)	82 (57.7)	
50 – 64.9	23 (13.2)	14 (9.9)	
< 65	2 (1.1)	0 (0.0)	
Sex			
Male	135 (77.6)	131 (91.6)	< 0.001
Female	39 (22.4)	12 (8.4)	
Marital status			
Single	98 (60.5)	95 (72.0)	0.012
Married	64 (39.5)	37 (28.0)	
HCV infection			
Positive	64 (36.8)	77 (53.8)	0.001
Negative	110 (63.2)	66 (46.2)	
Educational level			
Illiterate	11 (6.9)	5 (3.9)	0.030
Under diploma	73 (45.9)	78 (61.4)	
≥ Diploma	75 (47.2)	44 (34.6)	
Employment status			
Positive	89 (51.7)	64 (45.1)	0.045
Negative	83 (48.3)	78 (54.9)	
Householder			
Yes	119 (99.2)	100 (99.0)	0.706
No	1 (0.8)	1 (1.0)	
Addiction/drug abuse			
Yes	26 (15.6)	47 (35.6)	< 0.001
No	14 (84.4)	85 (64.4)	
HIV transmission			
Injection	58 (38.5)	62 (48.0)	0.003
Sexual activity	43 (28.5)	17 (13.2)	
Both	25 (16.5)	35 (27.2)	
etc.	25 (16.5)	15 (11.6)	
Psychiatric disease			
Yes	4 (2.3)	11 (7.7)	0.022
No	170 (97.7)	131 (92.3)	

The cause of treatment discontinuation was death in 20 (13.7%) cases and personal preference in 126 (86.3%) individuals.

The mean time of treatment retention was 24.37 ± 24.88 months (1–156). Figure-1 shows ART retention among the studied patients. 6, 12, 18, 24, 36, and 60 months retention rate of studied patients on ART program were 81.1% (257 cases), 58.4% (184 cases), 48.3% (153 cases), 35.6% (112 cases), 22.9% (72 cases), and 6.3% (20 cases), respectively.

Association of Treatment Retention with Studied Variables

There was a significant association between sex (P<0.001), marital status (P=0.012), educational level (P=0.030), history of HCV infection (P=0.001), employment status (P=0.045), addiction/drug use (P=0.001), type of transmission route (P=0.003), history of psychiatric disease (P=0.02), treatment regimen (P=0.007), and change of regimen (P=0.01) with treatment retention. The mean age of patients with treatment retention was 38.33 ± 9.06 years compared to 37.12 ± 11.76 years in the other group (P= 0.75). The results of multivariate logistic regression analysis showed a significant association between treatment retention and female sex (OR: 4.10; 95% CI: 1.59 – 10.56, P= 0.003), addiction/drug use (OR: 0.39; 95% CI: 0.21–0.77, P= 0.007), and 3TC+ZDV+IDV treatment regimen (OR: 0.63; 95% CI: 0.46 – 0.87, P= 0.005).

Discussion

Based on the findings of the present study, 6, 12, 18, 24, 36, and 60 months retention rate of patients on ART therapy were 81.1%, 58.4%, 48.3%, 35.6%, 22.9%, and 6.3%, respectively. Male sex, addiction/drug use, and type of regimen are among the most important risk factors for ART attrition in HIV-infected patients. As far as the authors have examined, there is no study on the attrition rate among those on ART in Iran previously. However, in a systematic review, the averages of reported retention rate were 78%, 71% and 69% at 12, 24, and 36 months after treatment initiation [12]. In another systematic review, the median retention rate was 73.4%, 75.0% and 70.5% at 12, 24 and 36 months after ART, respectively.

Table 2. Treatment Characteristics of Studied Patients

Characteristics	Treatment Attrition number (%)		P-value
	No	Yes	
Indication			
Clinical	14 (8.1)	8 (5.6)	
CD4 count	141 (81.0)	115 (81.0)	0.592
Etc.	19 (10.9)	19 (13.4)	
Regimen			
3TC+ZDV+NLF	80 (46.0)	93 (65.5)	
3TC+ZDV+EFV	70 (40.2)	36 (25.4)	
3TC+ZDV+NVP	23 (13.2)	11 (7.7)	0.007
3TC+ZDV+IDV	0 (0)	1 (0.7)	
Etc.	1 (0.6)	1 (0.7)	
Change in regimen*			
Yes	116 (67.1)	77 (54.2)	
No	57 (32.9)	65 (45.8)	0.014
Adverse effect			
Positive	36 (20.7)	26 (18.3)	
Negative	138 (79.3)	116 (81.7	0.350

*Treatment restarted in 142 cases on discontinuation.
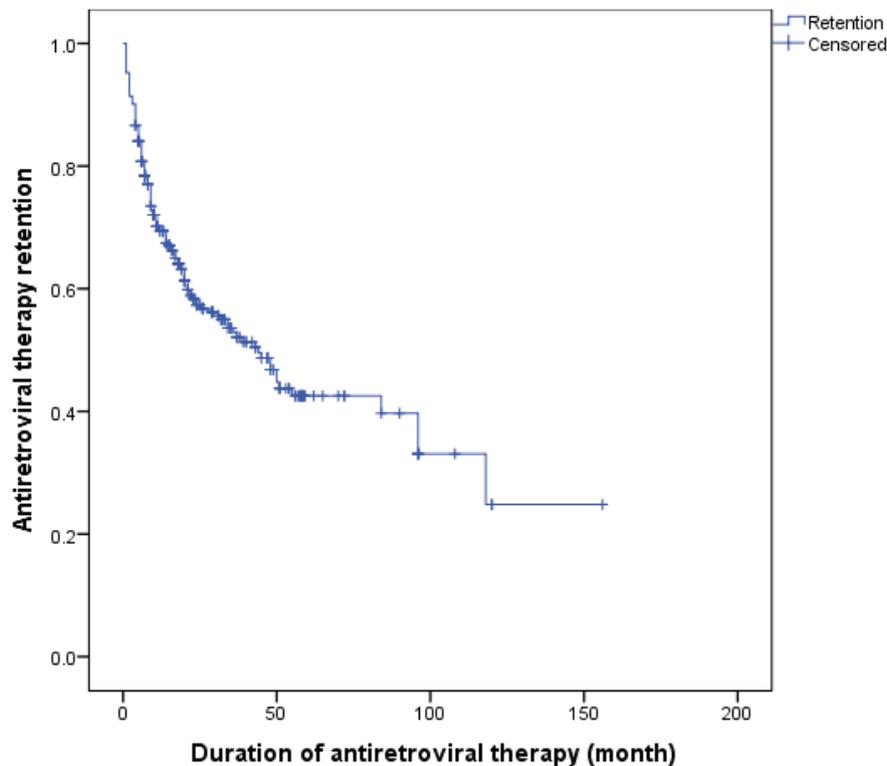
Figure 1. Retention on ART among studied patients.

The attrition rate was higher in our study compared to these systematic reviews [13].
Male sex, addiction/drug use, and type of regimen are among the most important risk factors for ART attrition in HIV-infected patients. It seems that attrition rate was relatively stabilized beyond 12 months in other studies comparing to our study [12, 13]. Further studies are needed to address this topic because usually early loss to follow-up after ART initiation are higher but after stabilization of patients the attrition rate decreases [14].
Considering the impact of ART on patients' morbidity and mortality, scrutinizing this issue cannot be underestimated [15].
Multiple factors may affect adherence to ART and be retained in treatment. In one study, male sex has been associated with lower rate of using health services probably due to employment. It shows the need for developing plans and programs to engage and retain employed men in HIV care at work [16].
In our study, a lower rate of ART retention among male patients may be due to a higher

proportion of being from IV drug user group among male patients. It seems that substance abuse has a negative impact (OR: 0.39) on retention and recent studies also bear this out [17]. It has been shown that HCV/HIV co-infected injection drug users are less likely to adhere to ART program compared to those under methadone therapy [18].
In contrast to other studies [19, 20], different types of regimen significantly affected ART program retention. Indinavir containing regimen has significant adverse drug reaction that may impede to adherence. In general, older age has been associated with better adherence to ART in previous studies [21-23].
We did not find such an association in our study, which may be due to our young sample size. In line with Siddall *et al*. study [24], the current study also showed that those who were unemployed had a higher rate of treatment discontinuation but only in univariate analysis. It may be caused by higher care commitment in the employed population, which may be a result of less financial constraints [25].

Moreover, unemployment may be considered as a factor negatively affecting the quality of life [26]. It has been shown that lower quality of life is associated with lower retention [4].

In our study, being single was a risk factor for the patients only in univariate analysis. It has also been shown to be independently associated with early loss to follow-up [27]. In contrast to Lessells *et al.* study [6], lower education (less than high school diploma) in our patients was also associated with attrition only in univariate analyses. Since years of education can be a measure of health literacy, lower education levels may lead to lower retention of ART [28]. Furthermore, a patient with lower education level may have difficulties in comprehending the instructions. Mathematical models have shown that pre-ART monitoring using CD4 counts maximizes the benefit of HIV treatment programs and is cost-benefit in South Africa [29, 30].

In a study, the lower CD4 count was associated with a higher probability of loss to follow-up [31]. However, the CD4 count was not found to be a risk factor for attrition in this report, and it needs more consideration in future studies.

The findings of this study, reveal the need to develop strategies and programs to engage patients to retain in HIV care. The effect of regimen type should be further evaluated and in case it is confirmed, professionals may want to consider the most followed regimen when choosing a treatment for the patients.

Factors that affected retention in other studies such as loss of follow-up and distance to treatment [32, 33] were not evaluated in our study. These categories were not applicable since patients are closely followed by the triangular clinic health professionals, all patients had a contact route like telephone and could be called if absent.

As the study was done in a retrospective manner, some limitations such as missing data were among another most important limitations.

Conclusion

Based on the findings of the present study, 6, 12, 18, 24, 36, and 60 months retention rate of patients on ART therapy were 81.1%, 58.4%, 48.3%, 35.6%, 22.9%, and 6.3%, respectively. Male sex, addiction/drug use, and type of regimen were among the most important risk factors for ART attrition in HIV-infected patients.

Acknowledgments

Conflict of Interest

None

References

1. Mannheimer S, Friedland G, Matts J, Child C, Chesney M, Beirn T. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for Human Immunodeficiency Virus—infected persons in clinical trials. Clin Infect Dis. 2002;34(8):1115-21.
2. Giordano TP, Gifford AL, White AC, Almazor MES, Rabeneck L, Hartman C, et al. Retention in care: a challenge to survival with HIV infection. Clin Infect Dis. 2007;44(11):1493-9.
3. Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, et al. Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. AIDS. 2004;18(Suppl 1):S19.

4. Penedo FJ, Gonzalez JS, Dahn JR, Antoni M, Malow R, Costa P, et al. Personality, quality of life and HAART adherence among men and women living with HIV/AIDS. J Psychosom Res. 2003;54(3):271-8.
5. Johnson MO, Dilworth SE, Neilands TB. Partner reports of patients' HIV treatment adherence. J Acquir Immune Defic Syndr. 2011;56(4):e117.
6. Lessells RJ, Mutevedzi PC, Cooke GS, Newell M-L. Retention in HIV care for individuals not yet eligible for antiretroviral therapy: rural KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr. 2011;56(3):e79.
7. Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. PLoS Med. 2011;8(7):e1001056.
8. Ulett KB, Willig JH, Lin H-Y, Routman JS, Abroms S, Allison J, et al. The therapeutic implications of timely linkage and early retention in HIV care. AIDS Patient Care STDS. 2009;23(1):41-9.
9. Eshrati B, Asl RT, Dell CA, Afshar P, Millson PM, Kamali M, et al. Preventing HIV transmission among Iranian prisoners: initial support for providing education on the benefits of harm reduction practices. Harm Reduct J. 2008;5(1):1.
10. Nissaramanesh B, Trace M, Roberts M. The rise of harm reduction in the Islamic Republic of Iran. Beck Found Drug. 2005;8:1-7.
11. Islamic Republic of Iran AIDS Progress Report. March 2015(http://www.unaids.org/sites/default/files/country/documents/IRN_narrative_report_2015.pdf).
12. Fox MP, Rosen S. Retention of Adult Patients on Antiretroviral Therapy in Low- and Middle-Income Countries: Systematic Review and Meta-analysis 2008-2013. J Acquir Immune Defic Syndr. 2015;69(1):98-108.
13. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. Trop Med Int Health. 2010;15(s1):1-15.
14. Stringer JS, Zulu I, Levy J, Stringer EM, Mwango A, Chi BH, et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. JAMA. 2006;296(7):782-93.
15. Group ISS. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;2015(373):795-807.
16. Mills EJ, Ford N, Mugyenyi P. Expanding HIV care in Africa: making men matter. The Lancet. 2009;374(9686):275-6.
17. Lucas GM, Gebo KA, Chaisson RE, Moore RD. Longitudinal assessment of the effects of drug and alcohol abuse on HIV-1 treatment outcomes in an urban clinic. AIDS. 2002;16(5):767-74.
18. Palepu A, Tyndall MW, Joy R, Kerr T, Wood E, Press N, et al. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: the role of methadone maintenance therapy. Drug Alcohol Depend. 2006;84(2):188-94.
19. Squires K, Lazzarin A, Gatell JM, Powderly WG, Pokrovskiy V, Delfraissy J-F, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. J Acquir Immune Defic Syndr. 2004;36(5):1011-9.
20. Van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. The Lancet. 2004;363(9417):1253-63.
21. Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, et al. Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. AIDS (London, England). 2004;18(Suppl 1):S19.
22. Becker S, Dezii C, Burtcel B, Kawabata H, Hodder S. Young HIV-infected adults are at greater risk for medication nonadherence. Med Gen Med. 2002;4(3):21-2.
23. Wutoh AK, Brown CM, Kumoji EK, Daftary MS, Jones T, Barnes NA, et al. Antiretroviral adherence and use of alternative therapies among older HIV-infected adults. J Natl Med Assoc. 2001;93(7-8):243.
24. Siddall JW, Conway GL. Interactional variables associated with retention and success in residential drug treatment. Int J Addict. 1988;23(12):1241-54.
25. Goudge J, Gilson L, Russell S, Gumede T, Mills A. The household costs of health care in rural South Africa with free public primary care and hospital exemptions for the poor. Trop Med Int Health. 2009;14(4):458-67.
26. Bernklev T, Jahnsen J, Henriksen M, Lygren

I, Aadland E, Sauar J, et al. Relationship between sick leave, unemployment, disability, and health-related quality of life in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2006;12(5):402-12.

27. Hassan AS, Fielding KL, Thuo NM, Nabwera HM, Sanders EJ, Berkley JA. Early loss to follow-up of recently diagnosed HIV-infected adults from routine pre-ART care in a rural district hospital in Kenya: a cohort study. Trop Med Int Health. 2012;17(1):82-93.

28. Kalichman SC, Ramachandran B, Catz S. Adherence to combination antiretroviral therapies in HIV patients of low health literacy. J Gen Intern Med. 1999;14(5):267-73.

29. Hallett TB, Gregson S, Dube S, Garnett GP. The impact of monitoring HIV patients prior to treatment in resource-poor settings: insights from mathematical modelling. PLoS Med. 2008;5(3):e53.

30. Bendavid E, Young SD, Katzenstein DA, Bayoumi AM, Sanders GD, Owens DK. Cost-effectiveness of HIV monitoring strategies in resource-limited settings: a southern African analysis. Arch Intern Med. 2008;168(17):1910-8.

31. Wang B, Losina E, Stark R, Munro A, Walensky RP, Wilke M, et al. Loss to follow-up in a community clinic in South Africa: roles of gender, pregnancy and CD4 count. S Afr Med J. 2011;101(4):253-7.

32. Cornell M, Myer L, Kaplan R, Bekker LG, Wood R. The impact of gender and income on survival and retention in a South African antiretroviral therapy programme. Trop Med Int Health. 2009;14(7):722-31.

33. Massaquoi M, Zachariah R, Manzi M, Pasulani O, Misindi D, Mwagomba B, et al. Patient retention and attrition on antiretroviral treatment at district level in rural Malawi. Trans R Soc Trop Med Hyg. 2009;103(6):594-600.