Research Article

Factors Associated with Early and Late Initiation of Antiretroviral Therapy among People Living with Human Immunodeficiency Virus in Lahore, Pakistan

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Abstract

Background: Despite the availability of antiretroviral therapy (ART), HIV is still responsible for substantial illness and death, especially in developing countries. Early start of treatment (ART) is associated with better therapeutic outcome, reduced transmissibility of HIV, reduction in loss to follow-up, and remarkably reduced death rate.

Objectives: To find out the factors associated with early and late Initiation of ART among patients affected by HIV in Lahore, Pakistan

Methods: From November 2017 to April 2018, researchers conducted an analytical cross-sectional study on 156 HIV patients aged 18 and older that began antiretroviral therapy (ART) at Jinnah & Mayo Hospital, Lahore's HIV clinics. Samples were selected by non-probability convenience sampling and Univariate and multivariate analyses were performed to assess factors related to early and late Initiation of ART. The p-value of less than <0.05 was taken as statistically significant.

Results: Among 156 HIV patients, 62.4% were more than 25 years, while 74.6% were male. The proportion of patients who started HIV therapy at an early stage of disease was 68.8%, while the delayed start of HIV therapy was seen in 31.2% study population. Two factors, type of household income and initial CD4 count (cells/ mm3), were reported to relate to early and late ART initiation.

Conclusion: The study results highlighted the need to stress upon early treatment of HIV, giving special attention to how programs, research, policies, strict supervision, and required interventions can provide support in the continuum of HIV care.

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Keywords: HIV; AIDS; Early and Late Initiation of ART; HIV patients; Pakistan

Introduction:

The human immunodeficiency virus (HIV) is still responsible for a global disease burden even after antiretroviral therapy (ART). Data from the USA shows that in 2017 there were 1,018,346 diagnosed cases of Human immunodeficiency virus (HIV) and several deaths due to Acquired immunodeficiency syndrome (AIDS) was 16,350[1,2]. Life expectancy has no marked difference in HIV seropositive and seronegative individuals but data from some populations' shows that a difference exists[3,4]. For example, HIV seropositive patients on antiretroviral therapy (ART) having a history of Intravenous (IV) drug abuse, smoking, viral hepatitis and who are black with low CD4 count have a lower life expectancy than other groups[4,5].

All HIV-seropositive individuals should receive ART according to the Department of Health and Human Services (DHHS) guidelines to decrease progression to advance stages of the disease and control its spread to others[6]. Characteristics responsible for delayed Initia-

tion of ART include being non-Hispanic, the existence of many psychosocial barriers, female gender, absence of a comorbid, and higher CD4 count[7,8]. The achievement of our goal to control the HIV epidemic by 2030 depends upon early detection and Initiation of ART, compliance to medical therapy, and a very low viral load persistently for very long periods[9]. As it is a public health issue, The Joint United Nations Program on HIV/AIDS set the 90-90-90 targets to be achieved by 2020 to finish this disease across the whole world. According to these targets, 90% of patients with HIV should be aware of their diagnosis, 90% should receive ART, and 90% of those receiving antiretroviral therapy (ART) should show a marked reduction in viral load[9,10].

Although the whole world is struggling to control HIV, its prevalence is high due to either delay in starting treatment of antiretroviral therapy (ART)[10,11]. WHO suggests decreasing this time interval between diagnosis and Initiation of therapy depending upon the willingness of the patient to start therapy. The time for initiating therapy has the crucial rule in patient outcome and compliance. Despite several efforts, various studies have been conducted in different countries that have reported the factors related to the early and late time of Initiation of ART and show the decision of the patient to start therapy as the most important factor in this regard[12,13]. However, no available published data was available on the early and late time of Initiation of ART among HIV patients in Lahore, Pakistan. Therefore, the current study was designed and conducted to determine the prevalence and factors related to early and late commencement of antiretroviral therapy (ART) among patients affected by HIV in Lahore, Pakistan. An imp-roved understanding of these factors affecting early and late commencement of ART among HIV/AIDS patients will help guide programs, research, policies, and required interventions in the continuum of HIV care.

Methods:

An analytical cross-sectional study was conducted from November 2017 to April 2018 in the HIV clinics of Jinnah & Mayo Hospital Lahore from November 2017 to April 2018. Non-probability convenience sampling was done. 156 HIV patients having age 18 years or more, who initiated ART treatment, cases of HIV/AIDS initially screened by Enzyme link immunosorbent assay (ELISA) and confirmed by polymerase chain reaction (PCR) test study were included in the study. The patients who were already on antiretroviral therapy (ART) before reporting to HIV clinics of Jinnah Hospital & Mayo Hospital, Lahore, were not made part of the study based on the history and clinical records.

Early Initiation was defined as if patients started antiretroviral therapy (ART) within three months of diagnosis after positive PCR test result, while late Initiation was defined as if patients did not start antiretroviral therapy (ART) within three months and beyond after the period of HIV diagnosis after positive PCR test result. Variables included in the current study were reasons for early and delayed start of Anti-HIV therapy. Clinical and laboratory data include initial CD4+cell count, physical disability, and presence of chronic diseases. The socio-demographic factors such as age (above 25 years, below 25 years), gender (Male, Female), marital status, level of education, residence and type of household income (permanent, occasional), employment status (employed, unemployed) were included. Marital status was defined as married, unmarried or divorced, or widowed. The clinical and laboratory data include initial CD4+cell count (< 300, >300), physical disability (No, pre-HIV and post-HIV), and presence of chronic diseases (Tuberculosis, Diabetes, Hypertension, Hepatitis B and C as determined on history and examination).

Statistical Package for the Social Sciences®, version 24 (SPSS) was used for entering and analyzing required information. Descriptive exploratory data analysis was initially performed. For continuous variables, Mean and Stan-dard deviation were computed, whereas, for categorical variables, frequency and proportion were calculated. For comparison of categorical variables like frequency of early and late start of antiretroviral treatment, chi-square test or the Fisher's exact test was applied. The Odds ratios, confidence intervals, and p-values were computed, and to determine factors related to the early or late start of ART in HIV affected population, statistically significant variables (p-value less than 0.05) in Univariate analysis were chosen and were used for multivariate binary logistic regression calculation. A p-value of less than 0.05 was taken as significant. Data collection was started after taking approval from the Project Director, Punjab AIDS Control Program

(PACP), Primary and Secondary Health Department, Government of the Punjab, Lahore. The data was collected using a standard questionnaire and in the language that the respondent was most comfortable with (English). Additionally, if a patient did not feel comfortable continuing with the study at any point throughout the interview, they were offered the choice to withdraw from it. Confidentiality was further protected by maintaining the anonymity of respondents.

Results:

Table 1 shows the socio-demographic characteristics of the study participants; out of the 156 HIV patients, 59 (37%) were less than 25 years, and 98 (62.4%) were more than 25 years. The majority of study participants were male, 117 (74.6%), and most of them, 126 (80.3%), resided in urban areas. Regarding marital status, the majority of all the study participants, 84(53.5%), were unmarried, while 67 (42.7%) of them were married (Table 1).

Table 1: *Socio-demographic characteristics of HIV-infected patients visited HIV Clinics of Jinnah Hospital and Mayo Hospital, Lahore, Pakistan (N = 156)*

Variables	Frequency	Percentage
Age		
Less than 25 years	59	37
More than 25 years	98	62.4
Gender		
Male	117	74.6
Female	30	19.2
Transgender	9	5.7
Marital status		
Unmarried	84	53.5
Married	67	42.7
Separated	1	0.6
Divorced	3	1.92
Widowed	2	1.28
Educational level		
No schooling	59	37.6
Up to primary school	39	24
Up to secondary school	49	31.2
Up to college	9	5.7
Up to university	1	0.6
Employment status		
Employed	92	58.6
Unemployed	64	41.02
Type of household income		
Permanent income	105	66.9
Occasional income	51	32.6

By the results of our study, 108 (68.8%) participants started ART within less than three months of diagnosis, while 49 (31.2%) patients started ART after three months of disease confirmation.

111 (70.7%) patients had Initial CD4 count <300 cells/mm3 before starting ART while 46 (29.3%) patients reported initial CD4 count >300 cells/mm3 before starting ART. About 135 (86.0%) patients reported to have no physical disability, 18 (11.5%) patients reported developing some physical debilitation after getting infected by HIV, and 4 (2.5%) patients already had a physical disability before getting infected by HIV.

The results of the present study showed that the symptoms of HIV (41.4%) were the most common reasons for HIV testing because of symptoms, while only (6.4%) HIV patients had testing because of pregnancy (Figure 1). The study result showed that heterosexual HIV transmission (57%) was the most common factor (Figure 2)

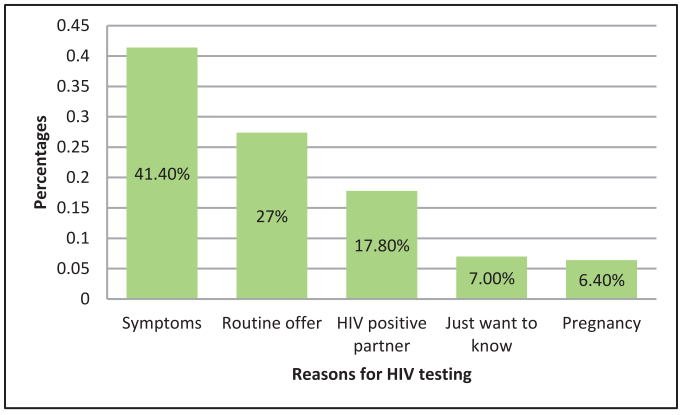

Figure 1: *Reasons for HIV Testing*

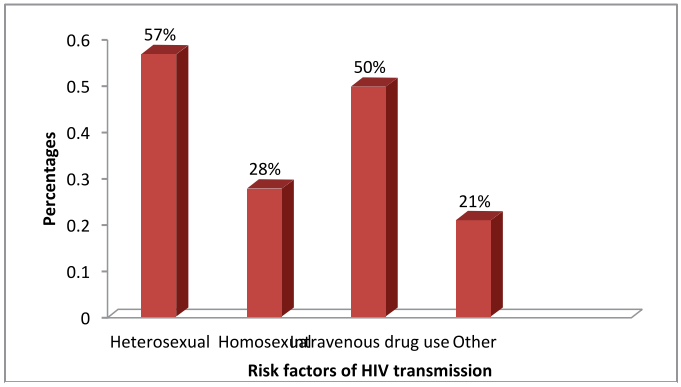

Figure 2: *Factors of HIV transmission*

Table 2: *Socio-demographic factors associated with Early and Late Initiation (Chi-square)*

Characteristics	Early Initiation <3months N (%)	Late Initiation >3months N (%)	OR	95 %CI	p-value
Age(years)					
< 25	43 (27.6)	16(10.3)	1.32	0.64-2.70	0.441
25 and above	65(41.7)	32(20.5)			
Education					
Primary and less	92(59.0)	41(26.3)	0.982	0.37-2.56	0.970
Secondary and above	16(10.3)	7(4.5)			
Place of residence					
Urban	82(52.6)	43(27.6)	0.36	0.13-1.02	0.04
Rural	26(16.7)	5(3.2)			
Marital status					
Married	39(25.0)	27(17.3)	0.44	0.220-0.87	0.01
Unmarried/divorced/widowed	69(44.2)	21(13.5)			
Employment status					
Employed	48(30.8)	17(10.9)	1.45	0.72-2.94	0.291
Unemployed	60(38.5)	31(19.9)			
Type of Household Income					
Permanent income	78(50.0)	27(17.3)	2.02	0.99-4.10	0.05
Occasional income	30(19.2)	21(13.5)			
Initial CD4 count (cells/ mm^3)					
< 300	71(45.5)	39(25.0)	0.44	0.194-1.01	0.05
>300	37(23.7)	9(5.8)			

Table 3 *Multivariate analysis of factors associated with early Initiation and late Initiation*

Characteristics	Adjusted OR	95% CI	p-value
Type of Household Income			
Permanent income	0.474	0.292-0.768	**0.002**
Occasional income	1	1	1
Initial CD4 count (cells/ mm^3)			
< 300	0.535	0.294-0.973	**0.04**
>300	1	1	1
Marital status			
Married	0.618	0.04-7.82	0.710
Unmarried/divorced/widowed	1	1	1
Place of residence			
Urban	0.505	0.284-0.898	**0.02**
Rural	1	1	1

The present study showed that place of residence (p=0.04), marital status (p=0.01), type of household income (p=0.05), and initial CD4 count (cells/mm^3) (p=0.05) determinants had a statistically significant association with initial and late commencement of antiretroviral therapy (ART) in HIV/AIDS diagnosed participants. There was no statistically significant difference found between the initiations of HIV treatment with age (p=0.441), education (p=0.970), and employment status (p=0.291) (Table 2).

Three factors such as type of household income (p=0.002), initial CD4 count (cells/mm3) (p=0.04), and place of residence (p=0.02) were resulted to be associated with initial and late Commencement of antiretroviral therapy (ART) treatment following the multivariate logistic regression analysis (Table 3).

The major reasons for initiating early ART are given in

Table 4: *Reasons why respondents accepted early Initiation to ART*

Characteristics	Number	Percentages
The desire to live a healthy life		
Yes	96	61.5
No	60	38.5
Scared of death		
Yes	99	63.5
No	57	36.5
To avoid transportation costs of subsequent hospital visits		
Yes	70	44.8
No	86	55.1
Healthcare workers recommendations		
Yes	98	62.8
No	58	37.1

(Table 4).

The most important causes of delaying HIV treatment by affected patients, according to results of the present study, are having no time to visit HIV clinic 91 (58.3%), the danger of stigma and discernment at HIV clinic 88(56.4%), fear of medication side effects 82 (52.6%), far-flung location of HIV clinic 77 (49.4%), fear of detention or imprisonment 72 (46.2%) and don't want to think about being affected by HIV 45 (28.8%).

Discussion:

A total of 156 HIV-diagnosed participants were made part of the study, of which (62.4%) were more than 25 years old, and the majority of the participants, 84 (53.5%), were unmarried. Most of them were male; 117 (74.6%) and 126 (80.3%) resided in the urban areas. This finding is comparable to that revealed in a research study conducted in Brazil in 2016 in addition to Kenya in 2016[15,16]. It has been found that being unmarried, male gender and residing in the urban area was associated with delay in seeking medical care compared to being married. The female gender showed that unmarried men preferred to hide their HIV status rather than getting ART.

In our study, 59 (37.6%) participants were illiterate, more than half of study participants, 92 (58.6%) were unemployed, while 105(66.9%) had permanent household income. The other studies also found that majority of study participants were unemployed and had no formal education[16,17]. Lower level of education in participants of the study was related to delay in starting medical treatment after HIV diagnosis due to the lack of knowledge about HIV/AIDS. One possible explanation of these inconsistencies may be studied population variation; different studies have different sample sizes, study settings, and study design.

In this study, 108(68.8%) of the study participants were those who had initiated early treatment of HIV infection[4]. In this study, the initial CD4 count, was < 300 cells/mm^3 in 111 (70.7%) participants before starting ART[17,18]. Our study concluded that the symptoms of HIV(41.4%) were the most common reasons for HIV testing because of symptoms. In contrast, only (6.4%) HIV patients had testing because of pregnancy Cape Verda[22,23]. The study result showed that heterosexual HIV transmission (57%) was the most common associated factor, and only (21%) of patients had HIV transmission due to other reasons[15,24,22].

The present study showed that the major reason for initiating early ART was the fear of death 99 (63.5%)[20,21]. However, the major reason for the delay of treatment in HIV participants was lack of time to attend HIV clinic in 91 (58.3%)[17].

According to the univariate analysis, participants with HIV/AIDS had a statistically significant relationship with initial or late commencement of anti-HIV therapy based on their marital status, type of household income, and baseline CD4 count. However, after performing a multivariate regression analysis, the current study recognized two determinants; type of household income (p=0.002), initial CD4 count (cells/mm^3). These outcomes are in coherence with previous researches done in Cameron, Ukraine, and Brazil[16,17]. These findings may highlight that interventions addressing delayed engagement in seeking HIV medical care might require being conducive towards HIV patients who have low household income and low CD4 count <300. This result also demonstrates the necessity to expand the relationship between HIV analysis and early healthcare-seeking behavior for HIV patients in Pakistan.

Our study has few limitations/restrictions. First, the cross-sectional type of data cannot assess the cause and effect relationship between dependent and independent variables, and only associations are reported. Second, due to the small sample size, non-probability sampling technique, and limited study area, we cannot

generalize its results at the national level. Moreover, the possibility of accessing time to seek medical advice following diagnosis of HIV found on substitute indicators like period of initial CD4 cell count and a viral load of HIV patients following after diagnosis has been hardly found.

A major strength of the present study was that it was conducted in two large public sectors HIV clinics that have a standardized clinical data storehouse depending on the forthcoming collection of comprehensive patient data. Hence, a significant quantity of missing data was not found for any of the study's variables.

Second, according to our knowledge, it is the first research conducted in Pakistan that focuses on the frequency and causes for timely and delayed anti-retroviral therapy (ART) initiation in HIV/AIDS patients.

Conclusion:

The present study identified that the low household income and low CD4 count <300 were associated with initial and delayed commencement of antiretroviral treatment (ART) in HIV/ AIDS positive patients in Lahore, Pakistan. It enlightens that all these identified factors will be critical in policies and initiating treatment in HIV patients as soon as possible support in controlling the advancement in HIV afterward.

Ethical Approval: Given

Conflict of Interest: The authors declare no conflict of interest.

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References:

1. Gupta RK, Gregson J, Parkin N, Haile-Selassie H, Tanuri A, Forero LA, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. The Lancet Infect Dis. 2018;18 (3):346-55.
2. Günthard HF, Calvez V, Paredes R, Pillay D, Shafer RW, Wensing AM, et al. Human immunodeficiency virus drug resistance: 2018 recommendations of the International Antiviral Society–USA panel. Clin Infect Dis. 2019;68(2):177-87.
3. Althoff KN, Chandran A, Zhang J, Arevalo WM, Gange SJ, Sterling TR, et al. Life-expectancy disparities among adults with HIV in the United States and Canada: The impact of a reduction in drug-and alcohol-related deaths using the lives saved simulation model. Am J Epidemiol. 2019;188 (12):2097-109.
4. Marcus J L, Chao CR, Leyden W A, Xu L, Quesenberry CP, Klein D B, et al. Narrowing the Gap in Life Expectancy between HIV-Infected and HIV-Uninfected Individuals With Access to Care. J Acquir Immune Defic. Syndr.2016;73(1): 39–46.
5. Modo R, Frazier E, Dube S, Mattson C, Sutton M, Brooks J, et al. Cigarette Smoking Prevalence Among Adults With HIV Compared With the General Adult Population in the United States. Ann Intern Med. 2015;162(5):335-344.
6. Winston A, Post FA, DeJesus E, Podzamczer D, Di Perri G, Estrada V, et al. Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomized, double-blind, active-controlled, non-inferiority phase 3 trial. Lancet HIV. 2018;5(4):162-71.
7. Ngom NF, Faye MA, Ndiaye K, Thiam A, Ndour CT, Etard JF, et al. ART initiation in an outpatient treatment center in Dakar, Senegal: A retrospective cohort analysis (1998-2015). PloS one. 2018;13(9): e0202984.
8. Novak RM, Hart RL, Chmiel JS, Brooks JT, Buchacz K. Disparities in Initiation of Combination Antiretroviral Treatment and Virologic Suppression Among Patients in the HIV Outpatient Study, 2000–2013. J Acquir Immune Defic Syndr. 2015;70(1):23–32.
9. Bain LE, Nkoke C, Noubiap JJN. UNAIDS 90-90-90 targets to end the AIDS epidemic by 2020 are not realistic: comment on "Can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades. BMJ Glob Health. 2017; 2(2):e000227.
10. Auld A, Shiraishi R, Oboho I, Ross C, Bateganya M, Pelletier V, et al. Trends in Prevalence of Advanced HIV Disease at Antiretroviral Therapy Enrollment — 10 Countries, 2004–2015. Morb Mortal Wkly

Rep. 2017;66(21):558-563.

11. Nash O, Tymejczyk T, Gadisa T, Kulkarni SG, Hoffman S, Yigzaw M, et al. Factors associated with antiretroviral therapy in the advanced stages of HIV infection in six Ethiopian HIV clinics, 2012 to 2013. J Inter AIDS Soc. 2016;19(1): 1–19.
12. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach [Internet]. 2016. [Cited 25 January 2020]. Available from: https://www.who.int/hiv/pub/arv/arv-2016/en/.
13. Pacheco P, Zara A, Silva e Souza L, Turchi M. Late Onset of Antiretroviral Therapy in Adults Living with HIV in an Urban Area in Brazil: Prevalence and Risk Factors. J Trop. Med. 2019;1(1):1-8.
14. SP Z. Sample size and power analysis in medical research. Indian J Dermatol Venereol Leprol. 2004;70(1):123.
15. MacCarthy S, Hoffmann M, Nunn A, Silva LAV, Dourado I. Barriers to HIV testing, linkage to care, and treatment adherence: a cross-sectional study from a large urban center of Brazil. Rev Panam Salud Publica. 2016;40(6):418–26.
16. Johnson M, Lemi BL, Tonny HL, David AD, Boru W, Ransom J. Late entry to HIV and AIDS care and treatment, Juba Teaching Hospital, Juba, South Sudan, 2013–2016. Afr J AIDS Res. 2018;17(2): 213-6.
17. Neduzhko O, Postnov O, Perehinets I, DeHovitz J, Joseph M, Odegaard D, et al. Factors Associated with Delayed Enrollment in HIV Medical Care among HIV-Positive Individuals in Odesa Region, Ukraine. JAPAN. 2016;16(2):168-173.
18. Jeong SJ, Italiano C, Chaiwarith R, Ng OT, Vanar S, Jiamsakul A, et al. Late presentation into the care of HIV disease and its associated factors in Asia: results of TAHOD. AIDS Res Hum Retrovir. 2016; 32(3):255-61.
19. Chelsea L, Fekadu G, Tesfaye G, Belayneh F, Melaku T, Mekonnen Z. Effects of time of Initiation of antiretroviral therapy in treating patients with HIV/TB co-infection: A systemic review and meta-analysis. Ann Med Surg. 2020;55(1):148-158.
20. Coffey S, Bacchetti P, Sachdev D, Bacon O, Jones D, Ospina-Norvell C, et al. Rapid antiretroviral therapy: high virologic suppression rates with immediate antiretroviral therapy initiation in a vulnerable urban clinic population. AIDS. 2019;33(5):825.
21. Sam D, Halle-Ekane G, Njamen T, Atanga P, Mbah E, Mbu R, et al. Associated Factors of Early and Late Initiation of ART in HIV Infected Pregnant Women in the South West Region, Cameroon. Int J STD AIDS. 2018;7(3):1-9.
22. Moreira A, Fronteira I, Augusto G, Martins M. Unmatched Case-Control Study on Late Presentation of HIV Infection in Santiago, Cape Verde (2004–2011). Int. J. Environ. Res. 2016;13(3): 320.
23. Alvarez-Uria G. Factors associated with delayed entry into HIV medical care after HIV diagnosis in a resource-limited setting: Data from a cohort study in India. Peer J. 2013;1(1):e90.
24. Geese HA, Ward P, Woldemichael K, Mwangi L. Late presentation for HIV care in Southwest Ethiopia in 2003–2015: prevalence, trend, outcomes and risk factors. BMC Infect Dis. 2018;18(1):59.
25. Egbe T, Tazinya R, Halle-Ekane G, Egbe E, Achidi E. Estimating HIV Incidence during Pregnancy and Knowledge of Prevention of Mother-to-Child Transmission with an Ad Hoc Analysis of Potential Cofactors. J Pregnancy. 2016;2016(1):1-9.