

What influences adherence among HIV patients presenting with first-line antiretroviral therapy failure (ART failure)? A retrospective, cross-sectional study from a private clinic in Nagpur, India

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ABSTRACT

Background: Multiple reports show increasing occurrences of ART failure in India. Despite the fact that a significant volume of outpatient and on-going healthcare occurs in private clinics, there are very few studies on adherence from private clinics in India. **Objective:** To evaluate the factors influencing adherence to ART in patients with first-line ART failure. **Materials and Methods:** Data were collected from a convenience sample of 139 individuals diagnosed with clinical, immunological or virologic failure from a private HIV clinic in Nagpur, India. A retrospective cross-sectional study was undertaken and data were statistically analysed. **Results:** Of the 139 patients, 118 (84.9%) were male and 21 (15.1%) were female. 64 (46%) had received pre-treatment and adherence counselling. 81 (58.3%) were not told about the side effects of ART medications and 65 (46.8%) avoided friends and family. Most common reasons for suboptimal adherence by stopping treatment were high cost, alcoholism, choosing non-allopathic medications and depression. Reasons cited for suboptimal adherence due to missed doses included feeling healthy, depression, forgetfulness and busy schedule. A significant association was found between pre-treatment counselling, adherence counselling and being told the importance of lifelong treatment and decreased occurrence of complete stoppage of treatment. **Conclusion:** This study brings to light some of the predictors of ART failure. Counselling, having a strong support system as well as early identification and tackling of reasons for suboptimal adherence plays an important role in preventing ART failure.

Keywords: Adherence, antiretroviral therapy, compliance, first-line, HIV, India

Introduction

India is a signatory to the 90-90-90 UNAIDS treatment target, which aims to have 90% of all people living with HIV (PLHIV) to be detected, 90% of them to be started on treatment and 90% of those on treatment to be virally suppressed by the year

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How to cite this article: Shanmukhappa SC, Abraham RR, Huilgol P, Godbole R, Anand AK, Prasad R, *et al.* What influences adherence among HIV patients presenting with first-line antiretroviral therapy failure (ART failure)? A retrospective, cross-sectional study from a private clinic in Nagpur, India. *J Family Med Prim Care* 2020;9:6217-23.

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Received: 11-06-2020

Revised: 08-09-2020

Accepted: 25-09-2020

Published: 31-12-2020

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_1155_20

2020.^[1] Currently, with over a million HIV infected individuals on antiretroviral therapy (ART), about 50% of PLHIV in India are on the government’s free ART program, which is continuing to scale up rapidly and massively to reach its target of 90%.^[2] However, with expansion of HIV ART programs there is an increasing threat of HIV drug resistance, which can not only undermine the beneficial effects of ART but also fuel a costlier, more deadly epidemic of drug resistant HIV.^[3]

Adherence to an optimal ART regimen is fundamental to reducing the likelihood of ART failure and also the emergence and spread of drug-resistant HIV.^[4] Adherence is a shared responsibility of not only the patient, but also the health care providers, the patient’s family and community.^[5] In India, HIV treatment and therapy are complicated by the fact that although a majority of PLHIV receive their medications from the government sector, about 25,000 – 30,000 patients are receiving free ART in the Private sector.^[6] There is a paucity of data from private clinics.

Materials and Methods

Study area and sampling

The study population included those patients with ART failure who presented to a private clinic in Nagpur. It was a convenience sample.

Inclusion criteria

Patients included in the study presented with first-line ART failure – clinical, immunological and virologic failure as defined by the WHO (given below).

Study type

Retrospective cross-sectional observational study.

Collection of data, data entry and statistical analysis

A total of 139 patients that fit the inclusion criteria were included in the study.

The data were collected from the patients using a questionnaire method which was administered on a one on one basis and maintained in a database by a team of doctors at the Nagpur clinic. Patient consent was obtained for use of data for the study. All data obtained were anonymous and without identifiers. The data were collected over a period of 7 years from 2010 to 2017.

Questions were pertaining to the demographic profile of the patient population, ART and first-line failure related information and information regarding adherence and the factors affecting it. Data were then moved to Microsoft Excel. Data were cleaned and subjected to statistical analysis using IBM SPSS Statistics v20.

Defining terms

Adherence is defined as “the ability to follow a treatment plan, take medications at prescribed times and frequencies, and follow

restrictions regarding food and other medications.”^[7] Adherence has been classified as optimal and suboptimal, defined by the WHO as “... while adherence of >95% is accepted as optimal adherence. Levels of adherence below 95% are considered to be sub-optimal.”^[8] In this study, adherence was assessed over a period of one month and evaluated based on memory and where possible, pill counting was utilised.

First-line ART failure is defined as those patients on first-line ART medications and belonging to any of the types of ART failure categories as described by the WHO: (a) Clinical failure: New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4) after 6 months of effective treatment, (b) Immunological failure: CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm³ and (c) Virologic failure: Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support.^[9]

Results

Baseline characteristics

A total of 139 patients were included in the study. The socio-demographics of the patient population have been described in Table 1. The patients were on ART for an average duration of 4.97 years with 50% of patients being on treatment for 2-4 years. The features of the patients’ treatment regimen and the type of ART failure have been listed in Table 2.

Adherence to ART

Factors influencing adherence like receiving pre-treatment and adherence counselling, patients’ knowledge of ART medications and social factors like support systems and avoidance of family have been detailed in Table 3. Reasons for suboptimal level of adherence (due to missed doses or stopping treatment) listed by the patients have been summarized in Table 4. On statistical analysis, several significant associations were found between factors influencing adherence and the level of adherence. This has been elucidated in Table 5. Adherence leading to ART failure has been demonstrated as a flow chart in Figure 1.

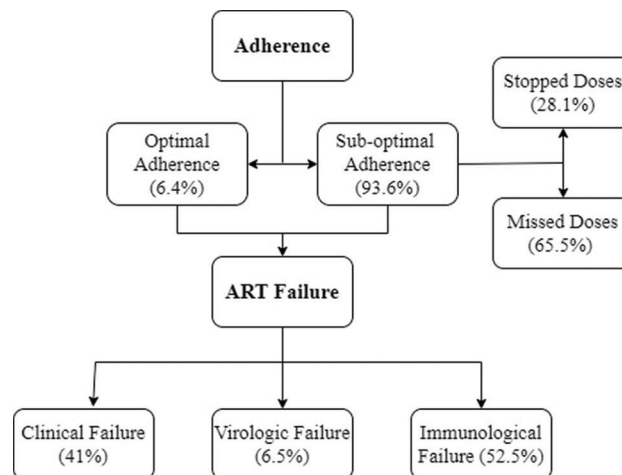


Figure 1: Adherence to ART failure flowchart

Table 1: Socio-demographic characteristics of the patients

Characteristics	Frequency (n=139)	%
1. Gender		
a. Male	118	84.9
b. Female	21	15.1
2. Age (in years)		
a. 18-20	8	5.8
b. 20-29	72	51.8
c. 30-39	44	31.7
d. 40-49	14	10
e. 50-59	1	0.7
3. Income (in rupees)		
a. <10,000	33	23.7
b. 10,000-25,000	46	33
c. 25,000-50,000	34	24.5
d. >50,000	26	18.7
4. Locality		
a. Urban	93	66.9
b. Rural	46	33.
5. Marital status		
a. Married	134	96.4
b. Unmarried	3	2.2
c. Separated/Widow/Widower	2	1.4
6. Education		
a. None	1	0.7.
b. Primary	23	16.6
c. Secondary	30	21.9
d. University/College	85	61.2

Table 2: ART regimen and the type of failure

Features	Frequency (n=139)	%
1. Initial treatment by		
a. Government	17	12.2
b. Private practitioners	122	87.8
2. Regimen before ART failure was detected		
a. SLN (Stavudine + Lamivudine + Nevirapine)	53	38.1
b. TLE (Tenofovir + Lamivudine + Efavirenz)	11	7.9
c. ZLN (Zidovudine + Lamivudine + Nevirapine)	36	25.9
d. Other 3 drug regimens	35	25.2
e. 2 drug regimens (Example: SL _n /TL/ZL)	4	2.9
3. Type of ART failure		
a. Immunological	73	52.5
b. Clinical	57	41
c. Virologic	9	6.5

Discussion

Paucity of data and the significance of our study

With about 50% of its 2.1 million HIV infected population, India is rapidly scaling up its ART program to reach the 90%-on-medication target set by UNAIDS.^[1] But with increasing access to medications comes an increasing threat of drug resistance.^[3] With reports from multiple countries indicating 30% drug resistance to first-line therapy and about 10% transmitted drug resistance, India is at the brink of a new epidemic fuelled

by drug resistant HIV.^[10] Thus, it becomes especially important to determine the extent of practices that lead to ART failure and to better prepare our healthcare force to recognize and anticipate drug resistance earlier.

Very little data exists on adherence of HIV patients to ART in India, especially those receiving care and/or treatment under private physicians in India. Thus, although it is estimated that only about 25,000–30,000 patients are receiving free ART in the private sector and are likely receiving on-going care from private clinics, the standard and quality of care is mostly unregulated.^[6]

What can be inferred from the profile of patients in our study population?

Over 40% of people living with HIV (PLHIV) in India are women.^[11] Our study, in congruence with other studies from India, includes a greater number of male patients,^[12-15] indicating that a sizable percentage of women do not get sufficient treatment possibly due to a lack of resources or greater difficulty in overcoming stigma.

Most studies associate lower levels of education with ART failure.^[16-18] In contrast, 60% of patients of our study population received education at a university level. While our study sample was skewed in terms of education, education alone seems like a weak factor to assess adherence, especially in India with people receiving education whose quality varies widely with population and location.

Our study population was roughly evenly distributed across all income groups. Although income is a commonly studied factor, a review by Karl Peltzer and Supa Pengpid on the socioeconomic factors related to adherence to ART found that 20 of the 36 papers reviewed found no association between income and adherence.^[16] This is in congruence with our own study.

Gaps in HIV care

It was found that the majority of patients with ART failure in our study were identified on immunological and clinical grounds, measures that tend to delay detection of treatment failure. Programs that have used viral load testing are more likely to detect treatment failure earlier.^[19-21] High costs and inaccessibility of viral load tests could be major reasons for the sparse use of this for early diagnosis of treatment failure.

Counselling is the cornerstone of ART adherence which in turn is the key to prevent ART failure.^[22] A review analysis by Yesenia Musayón-Oblitas *et al.* breaks down the methods of counselling followed in various studies.^[23] While the quality, duration and frequency of counselling were not analysed in our study, statistically significant association was established between individuals who received pre-treatment counselling, knew the name of the ART and counselled on the importance of life long treatment and the decreased likelihood of complete stoppage of treatment. This is supported by a study by Varadharaj

Table 3: Counselling, knowledge and social factors related to adherence

Factors	Frequency (n=139)	%
1. Pretreatment counselling		
Yes	64	46
No	75	54
2. Knowledge about the ART medications		
Yes	104	74.8
No	35	25.2
3. View on ART		
Cure	2	1.4
Reduces pain	3	2.2
Reduces progression of HIV	99	71.2
4. Adherence counselling		
Yes	64	46
No	74	53.2
Unknown	3	2.2
5. Was told about the importance of lifelong treatment		
Yes	54	38.9
No	85	61.2
6. Was told about the side effects		
Yes	58	41.7
No	81	58.3
7. Avoidance of friends and family		
Yes	65	46.8
No	74	53.2
8. Support of family/community members		
Yes	102	73.4
No	37	26.6
9. If yes, who was it?		
Spouse/family member	71	69.6
Self-help groups	2	1.9
Nurse	8	7.8
Doctor	18	17.6
Friend	3	2.9

Sakthivel *et al.* on factors associated with adherence in a tertiary care hospital in South India. Patients who were knowledgeable about their illness were more likely to be adherent to ART.^[24]

Counselling includes pre-test counselling, adherence counselling, pre-conceptual counselling, stigma reduction counselling, reproductive counselling as well as financial counselling. The effectiveness of counselling can be enhanced by: (a) using an approach based on the principles of shared decision-making (b) involving a family member, especially the spouse or partner; and (c) discussing punctuality and strategies to support.^[25]

Our study also showed a large number of patients avoided friends and family and a fourth of the patients did not receive support from family/community. This is similar to other studies which demonstrated that those who did not disclose their HIV status to family members were more likely to be poorly-adherent to ART compared to those who enjoyed a greater level of family support.^[26-29]

Table 4: Reasons for suboptimal adherence

Suboptimal adherence due to	Frequency (n=139)	%
1. Stopped treatment	39	28.1
Reasons		
a. High cost	14	35.9
b. No identifiable reason	12	30.7
c. Alcoholism	10	25.7
d. Choosing non-allopathic medications	10	25.6
e. Depression	7	17.9
f. ART side effects	3	7.7
g. Feeling healthy	13	3.3
h. Deterioration following Immune Reconstitution Inflammatory Syndrome (IRIS)	1	2.6
2. Missed doses	91	65.5
Reasons		
a. Feeling healthy	37	40.7
b. Depressed	30	32.9
c. Forgetfulness	29	31.9
d. Busy	26	28.8
e. Travelling	22	24.2
f. Too many pills	15	16.5
g. Alcoholism	15	16.5
h. Drug side effects	12	13.2
i. Work timings	12	13.2
j. No stocks of ART	11	12.1

Suboptimal adherence and ART failure

Adherence levels evaluated in a meta-analysis carried out by Rahul Mushkar *et al.* in PLHIV reported adherence levels varying between 59% (0.53, 0.66) to 94% (0.90 to 0.96) in various studies. The calculated pooled ART adherence was 0.70 (95% CI: 0.59–0.81). However, there was a statistically significant heterogeneity for the outcome of overall ART adherence (I² = 96.3%) among the included studies.^[30] Other studies conducted in Indian setting (most using self-reporting) show high level of adherence of up to 90-98.6%.^[12,31,32] The contrasting results might be due to recall bias, poor monitoring or severe under-reporting.^[4,33] Studies carried out by Shah *et al.* and Sarna *et al.* in a private clinic and hospital respectively showed adherence levels of 73% (0.68–0.79) and 94% (0.90–0.96).^[30]

In our study 6.45% of the patients who failed first-line ART showed good adherence. The occurrence of first-line treatment failure despite good adherence raises the concern of possible transmitted drug resistance. Patients therefore have pre-treatment resistance and fail the ART regimen. A study by Woldelessie M. Bezabhe *et al.* suggest the use of viral load monitoring in resource limited settings to enhance treatment outcomes.^[34] Over 93% of our study population reported suboptimal adherence. The most commonly cited reasons for stopping treatment included high cost, alcoholism, opting for non-allopathic medications and depression. The top reasons for missing doses were feeling healthy, depression, forgetfulness and busy schedules. Financial strains imposed by a chronic illness like HIV has been studied by N. Kumaraswamy *et al.* Private practices are often unregulated

Table 5: Optimal and suboptimal adherence (stopped and missed) vs factors of adherence

Variables	Response	Stopped doses n (%)	Missed doses n (%)	Optimal adherence n (%)	Total n (%)	Chi-square test P (significant <0.05)
Pre-treatment counselling	Received	18 (28)	38 (59)	8 (13)	64 (46)	0.03
	Not received	21 (28)	53 (71)	1 (1)	79 (54)	
	Total	39 (28)	91 (65)	9 (6)	139 (100)	
Know the name of current ART	Yes	21 (20)	74 (71)	9 (9)	104 (75)	0.00
	No	18 (51)	17 (49)	0 (0)	35 (25)	
	Total	39 (28)	91 (65)	9 (6)	139 (100)	
Received counselling on the importance of lifelong treatment	Yes	4 (7)	45 (83)	5 (9)	54 (39)	0.00
	No	35 (41)	46 (54)	4 (5)	85 (61)	
	Total	39 (28)	91 (65)	9 (6)	139 (100)	
Type of failure	Virologic failure	1 (11)	6 (67)	2 (22)	9 (6)	0.00
	Immunological failure	14 (19)	53 (73)	6 (8)	73 (53)	
	Clinical failure	24 (42)	32 (56)	1 (2)	57 (41)	
	Total	39 (28)	91 (65)	9 (6)	139 (100)	

leading to increased prescriptions of unnecessary investigations and inappropriate testing.^[35] We believe that data from private ART centres and practices should be analysed to assess the compliance with national guidelines for the same. In addition, financial counselling and planning can help alleviate the burden of ART health care costs thereby increasing adherence.

Depression is another major factor for suboptimal adherence in our study. It is known to influence adherence by creating a sense of hopelessness, reducing motivation and interest to pursue treatment.^[36] Identification and treatment of depression together with an increased focus on mental health has been known to improve adherence to ART.^[37,38]

We believe most reasons for suboptimal adherence can be tackled by frequent counselling and developing a support system that includes not only family, friends and members of the community but the health care providers as well.

Relevance in primary care practice

With the high prevalence of HIV positive cases in India and an increasing number of them receiving ART, the likelihood of a primary care physician coming across HIV positive cases on ART is high. There is a high preference for HIV positive patients to have a one stop HIV care as well as primary care.^[39] Successful HIV therapy is built on optimal adherence, which can be handled at a primary care level. This paper highlight barriers to adherence and primary care physicians should utilise the findings in this paper to forestall the same.

Key points

- ART failure can be prevented by ensuring adherence to ART regimen
- Most common reasons for suboptimal adherence include high cost, alcoholism, feeling healthy, depression and forgetfulness
- Most reasons for reduced adherence can be tackled by pre-treatment followed by regular and repeated counselling by the practitioner

- Counselling should stress the importance of lifelong therapy and educate the patient about the disease and treatment
- A support system comprising of the doctor, family and community members can enhance adherence to ART.

Limitations

- The quality and frequency of adherence counselling was not evaluated
- The quality of the study could have been improved if a control group of those who hadn't failed first-line was included.

Conclusion

This study adds to the literature on predictors of ART failure from a private clinic in India. Adherence to therapy calls for a multi-faceted approach to tackle the numerous reasons for disrupted treatment. It is imperative that HIV care be delivered in an individualised, patient centred manner with adequate attention to counselling and identification of underlying reasons for reduced adherence.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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