

A cross-sectional study of the factors influencing adherence to antiretroviral therapy among adults with human immunodeficiency virus infection in a tertiary care hospital in Puducherry, India

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Abstract

Context: Combating human immunodeficiency virus/acquired immunodeficiency syndrome epidemic has been possible due to advances in prevention strategies and Antiretroviral therapy (ART). Optimal adherence to ART is a major factor in achieving the desired immunological, virological, and patient well-being outcomes. Several socio-demographic, patient, treatment, and health-care system-related factors influence nonadherent behavior to ART. **Aims:** This study was planned to assess (1) ART adherence level, (2) factors and reasons associated with nonadherence, and (3) impact of suboptimal adherence on treatment outcomes. **Settings and Design:** This was a cross-sectional analytical study of 300 patients in a tertiary care hospital in Puducherry, India. **Methods:** Random sampling was used to collect data from patient treatment cards and a predesigned structured questionnaire. The pill count method was used to calculate adherence level. **Statistical Analysis Used:** Nonadherence was chosen as a dependent variable and factors affecting adherence were chosen as independent variables. Test for significance was carried out by Chi-square test and Fisher's exact test. **Results:** Optimal adherence was seen in 68.3%. Factors significantly associated with nonadherence were lower education level, high prior CD4 count, irregular follow-up, missing doses in the past, and being late for pharmacy pill refills. Adherence was positively associated with mean increase in CD4 count over 6 months. **Conclusions:** In our study, the adherence rate is suboptimal which can lead to failure of ART. Nonadherence was associated with a decrease in CD4 count overtime. Most of the factors significantly affecting ART adherence were patient behavior related. These factors can be used for target intervention during reinforcement adherence counseling.

Key words: Adherence, adults, anti-retroviral therapy, CD4 count, factors, human immunodeficiency virus

Introduction

As per UNAIDS estimates in 2017, 36.9 million people are living with human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) globally with an adult HIV prevalence of 0.8%.^[1] Although India has a low prevalence of 0.22% adult HIV infections, in absolute numbers it is 2.14 million people living with HIV. This amounts to the third highest burden of HIV in the world.^[2] Combating HIV/AIDS has been possible due to advances in the prevention and treatment of the disease. Antiretroviral therapy (ART) has contributed to a significant change

in the course of the disease, making AIDS a manageable chronic illness.^[3,4] In India, the impact of lifesaving ART is seen with adult HIV prevalence decreasing from 0.38% in 2001 to 0.22% in 2017 and AIDS-related deaths going down by 71% since its peak in 2005. To consolidate these gains National AIDS Control Organization, India, has highlighted some key priority areas which include:

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reaching the unreachable, early diagnosis, retention across the continuum of HIV care, and maintaining a high level of adherence.^[5]

Among several factors that can affect ART outcome, suboptimal adherence to ART has been cited as a major factor associated with poor treatment outcomes.^[6-8] Adherence is defined as “Extent to which a person’s behaviour-the taking of medication and the following of a healthy lifestyle including a healthy diet and other activities-corresponds with the agreed recommendation of healthcare providers” (WHO, 2003).^[5] National guidelines for ART in India stipulate that >95% adherence to treatment is required for optimal viral load suppression. A lesser degree of adherence can be associated with low CD4 count, virological failure, drug resistance, transmission of these resistant viral strains in the population, and poor health outcomes.^[5,9,10]

Studies have shown that multiple factors influence adherence to ART in developing countries, such as patient and family/caregiver, medication, health-care delivery system, and social/environmental related factors. Optimizing adherence and minimizing loss to follow-up are two major challenges of ART program up-scaling in India.^[11] A systematic review and meta-analysis study^[12] has shown varying estimates of ART adherence in India, from 57%^[13] to 94%^[14] with an overall adherence of around 70%. Several studies from India have highlighted various factors leading to suboptimal adherence among those on ART. This may be due to the variations in socioeconomic status and the diversity of the population and the regions in India.^[10-12,15-18] At present the National ART Programme has been upscaled to provide free-of-cost ART to all persons diagnosed with HIV infection regardless of CD4 count or WHO clinical staging (test and treat). Furthermore, the introduction of tenofovir + lamivudine + efavirenz as fixed-dose combination in a single pill as the recommended choice of first-line regimen in ART has reduced the pill burden on the patient.^[5]

Therefore in this current scenario of upscaling of ART program in India, varying estimates of ART adherence and factors leading to suboptimal adherence reported in different studies, this study was planned in a tertiary care center in Puducherry, South India to assess the (1) ART adherence level, (2) factors influencing suboptimal adherence, (3) reasons attributed by patients for suboptimal adherence, and (4) impact of suboptimal adherence on treatment outcome.

Methods

Study design

The present study was a hospital-based cross-sectional, analytical type study.

Study settings

The study was conducted at the ART center attached to the Department of Dermatology and STD of Indira Gandhi Government General Hospital and Post Graduate Institute (IGGGH and PGI), Puducherry, India. Puducherry is situated on the eastern coast of South India and has an estimated adult HIV prevalence of 0.15% (2017).^[2] In August 2015, 751 patients on ART (685 adults and 66 children) attended the ART center with an average daily attendance of 27 adults per day. The ART center provides drugs and investigations free of charge and has the relevant facilities for CD4 count estimation, counseling sessions (pre-ART and during each visit), and regular check-ups as per the National ART guidelines.

Inclusion and exclusion criteria

HIV-positive patients attending the ART center aged 18 years or above, who had received ART for 6 months or longer, received a CD4 count in the last 6 months and able to provide informed consent are included in the study. Patients who were unwilling, unable to communicate, or seriously ill were excluded from the study.

Sample size

Assuming nonadherence level as 30%^[12] and an absolute precision of 5%, the total sample size required was calculated to be 322 (formula: $n = z^2pq/e^2$; where n = sample size, z = value of standard normal deviate = 1.96 at 95% confidence interval, p = prevalence of nonadherence, $q = 1 - p$, and e = absolute precision).^[19]

Sampling method

The study period was from August 2015 to August 2016. Data were collected every week on one randomly selected day to reduce day-specific patient attendance bias. Considering the interview duration of 30 min required, we interviewed six consecutive patients per day and reached a sample size of 300 patients at the end of the study.

Ethical clearance

The study was approved by the General Hospital Institution Ethics Committee of IGGGH and PGI, Puducherry. Informed written consent was obtained from the patients interviewed after briefing the purpose of the study and assuring the confidentiality of the data collected.

Data collection

Instruments for data collection consisted of records from ART treatment card of the patient (having treatment information and laboratory investigation results), pill count in the ART pill bottle on the day of interview, and a pre-designed, prestructured questionnaire prepared in the local language (Tamil). The questionnaire was used to acquire socio-demographic, patient-related, ART-related, and health system-related information on adherence. Socio-economic factors such as education, occupation, and monthly family income of the participants were classified using modified Kuppusamy’s scale.^[20] Furthermore, adherence-related information by patient recall was obtained by asking the patient if he/she missed doses in the past 6 months and the past 1 month. Information on the clinical and immunological treatment outcome by: (1) CD4 count – 6 months prior and present, (2) change in body mass index (BMI) – 6 months prior and present, and (3) opportunistic infections and hospitalizations in the past 6 months was obtained from ART treatment records of the patient.

Assessment of nonadherence

Adherence percentage in the past 1 month was assessed using the pill count method.

Adherence rate

$$= \frac{\text{Total number of tablets or doses actually taken}}{\text{Total number tablets or doses actually prescribed}} \times 100$$

All patients with an adherence rate of <95% were denoted as “nonadherent” for further analysis as per the National ART guidelines.^[5]

Data analysis

Nonadherence to ART was selected as a dependent variable and socio-demographic, patient-related, treatment-related, and clinical/immunological outcome-related factors were chosen as independent variables to identify the association between them. Data were compiled and analyzed using

Statistical Packages for the Social Sciences software version 20. Relevant means and standard deviations were calculated. Test of significance was carried out by Chi-square test and Fisher's exact test. A $P \leq 0.05$ was assumed to be statistically significant.

Results

Among the 300 patients enrolled in the study, the mean age was 42.1 ± 8.9 years and the majority was in the middle age group of 31–45 years. By gender females were predominant (55.7%) and there was one transgender in the study population. Most of the patients were married, living with a nuclear family and with caregivers from the family. While considering socioeconomic factors, most of them were educated up to the primary level or illiterate, were either unskilled workers or unemployed and had a monthly family income below 5546 rupees [Table 1]. In terms of treatment, 93.3% of study participants were living <50 km from the ART

Table 1: Sociodemographic attributes of the study participants (n=300)

| Variables | Frequency, n (%) |
|---------------------------------|------------------|
| Age (years) | |
| 18-30 | 32 (10.7) |
| 31-45 | 164 (54.7) |
| 46-60 | 104 (34.6) |
| Gender | |
| Male | 132 (44) |
| Female | 167 (55.7) |
| Transgender | 1 (0.3) |
| Marital status | |
| Married | 172 (57.3) |
| Unmarried | 21 (7) |
| Widow/widower | 96 (32) |
| Separated/divorced | 11 (3.7) |
| Type of family | |
| Living alone | 36 (12) |
| Nuclear | 264 (88) |
| Education | |
| Professional | 12 (4) |
| Graduate/postgraduate | 14 (4.7) |
| Intermediate | 16 (5.3) |
| High school | 44 (14.7) |
| Middle school | 45 (15) |
| Primary | 86 (28.6) |
| Illiterate | 83 (27.7) |
| Occupation | |
| Professional | 6 (2) |
| Semiprofessional | 7 (2.3) |
| Clerical, shop owner, farmer | 39 (13) |
| Skilled worker | 53 (17.7) |
| Semiskilled worker | 46 (15.3) |
| Unskilled worker | 68 (22.7) |
| Unemployed | 81 (27) |
| Monthly family income in rupees | |
| ≥36,977 | 4 (1.3) |
| 18,498-36,996 | 5 (1.7) |
| 13,874-18,497 | 6 (2) |
| 9249-13,873 | 4 (1.3) |
| 5547-9248 | 33 (11) |
| 1866-5546 | 136 (45.3) |
| ≤1865 | 112 (37.3) |

center, 98.7% had received pre-ART counseling, 90.3% were on ART for more than 4 years and the current ART regimen was tenofovir, lamivudine, and efavirenz for 45% and zidovudine, lamivudine, and nevirapine for 44.3% of the participants.

Rate of adherence

By pill count method, optimal adherence level of >95% in the past 1 month was seen in 205 patients (68.3%). 100% adherence level was seen in 155 patients (51.7%). 20.3% patients had adherence of 80%–95%, 3.3% patients had <80% adherence, while 8% patients had no adherence (missed all doses). The overall mean adherence was $86.5\% \pm 3.19\%$.

Factors associated with nonadherence

Of the various factors studied [Table 2], lower level of education (below high school or illiterate), irregular visits in the past 3 months, history of missing medications in the past and attending later than the day of appointment for pharmacy refill of ART were significantly associated with nonadherence. Nonadherence by patient recall in the past 6 months and past 1 month was 20% and 19% respectively while nonadherence rate by pill count method was 31.7%. The common reasons given for nonadherence were feeling depressed, too busy, and forgetfulness. 24.2% nonadherent patients declined to give any reason [Table 3].

Impact of nonadherence on treatment outcome

An increasing trend of CD4 count in 6 months was found in the majority of patients (81%). A decrease in CD4 count was significantly associated with nonadherence [Table 4]. When mean CD4 count trends over 6 months were analyzed, the nonadherent group had a higher prior mean CD4 count compared to the adherent group. However, the mean increase in CD4 count in 6 months was higher in the adherent group. These findings were statistically significant [Table 5]. Nonadherence had no impact on BMI, hospitalization, and severe opportunistic infections in the past 6 months [Table 4].

Discussion

In our study, optimal adherence level of >95% in the past 1 month was seen in 68.3% of patients. This level of adherence is similar to that described in other studies from South India.^[16-18] A study of 30 ART centers^[15] and a systematic review meta-analysis study^[12] have estimated an overall adherence rate of 76% and 70%, respectively. Our level of adherence is better than the pooled estimate of 55% adherence in North American studies and lesser than 77% adherence in studies from Africa.^[21] Such suboptimal adherence levels can contribute to ineffective control of HIV viremia and emergence of viral resistance. Furthermore, it is alarming that 8% of our patients showed no adherence skipping all the doses in a month. Adherence remains a problem in chronic diseases with an average nonadherence rate of 24.8% reported and it may drop as early as after the first 6 months of ART.^[22,23]

Among the socio-demographic factors studied, only lower level of education was significantly associated with nonadherence. However, studies have shown varying associations between education and adherence. Higher education may have positive,^[24] negative^[25] or no effect^[11] on adherence. Most of the Indian studies have highlighted financial constraints as major reasons for nonadherence.^[12,17] In our study, none of the patients

Table 2: Analysis of factors associated with nonadherence (n=300)

| Variables | Category | Adherent (n=205), n (%) | Nonadherent (n=95), n (%) | P |
|--|---|-------------------------|---------------------------|-------|
| Age | 18-30 | 25 (12.2) | 7 (7.4) | 0.26 |
| | 31-45 | 114 (55.6) | 50 (52.6) | |
| | 45-60 | 66 (32.2) | 38 (40) | |
| Gender | Male | 89 (43.4) | 43 (45.3) | 0.68 |
| | Female | 115 (56.1) | 51 (53.7) | |
| | Transgender | 1 (0.5) | | |
| Marital status* | Married | 115 (56.1) | 57 (60) | 0.40 |
| | Single | 90 (43.9) | 38 (40) | |
| Type of family | Living alone | 27 (13.2) | 9 (9.5) | 0.36 |
| | Nuclear | 178 (86.8) | 86 (90.5) | |
| Education | Professional/postgraduate/graduate | 24 (11.7) | 2 (2.1) | 0.01 |
| | Intermediate/post high school | 9 (4.4) | 7 (7.4) | |
| | High school and below | 172 (83.9) | 86 (90.5) | |
| Occupation | Professional/semiprofessional | 11 (5.4) | 2 (2.1) | 0.43 |
| | Clerical/shop owner/farmer/skilled/semiskilled worker | 93 (45.4) | 45 (47.4) | |
| | Unskilled worker/unemployed | 101 (49.3) | 48 (50.5) | |
| Family income | ≥32,050-8010 | 15 (7.3) | 4 (4.2) | 0.07 |
| | 8009-1601 | 122 (59.5) | 47 (49.5) | |
| | ≤1600 | 68 (33.2) | 44 (46.3) | |
| Distance from home (km) | <50 | 192 (93.7) | 88 (92.6) | 0.74 |
| | 50-200 | 13 (6.3) | 7 (7.4) | |
| HIV status disclosed to spouse | Yes | 198 (96.6) | 88 (92.6) | 0.13 |
| | No | 7 (3.4) | 7 (7.4) | |
| Caregiver | Family | 191 (93.1) | 89 (93.7) | 0.87 |
| | Friend | 14 (6.8) | 6 (6.3) | |
| Alcohol consumption | Yes | 34 (16.6) | 10 (10.5) | 0.38 |
| | No | 171 (83.4) | 85 (89.4) | |
| Smoking | Yes | 19 (9.3) | 10 (10.5) | 0.76 |
| | No | 186 (90.7) | 85 (89.4) | |
| Pre-ART counseling | Yes | 203 (99) | 93 (97.9) | 0.59 |
| | No | 2 (1) | 2 (2.1) | |
| Regular visits in the past 3 months | Yes | 204 (99.5) | 90 (94.7) | 0.006 |
| | No | 1 (0.5) | 5 (5.3) | |
| Visited traditional healer | Yes | 16 (7.8) | 12 (12.6) | 0.18 |
| | No | 189 (92.2) | 83 (87.4) | |
| Duration on ART (years) | <1 | 4 (1.9) | 7 (7.4) | 0.06 |
| | 1-4 | 95 (46.3) | 39 (41.1) | |
| | >4 | 106 (51.7) | 49 (51.6) | |
| Current ART regimen** | AZT + 3TC + NVP | 89 (43.4) | 44 (46.3) | 0.41 |
| | AZT + 3TC + EFV | 11 (5.4) | 3 (3.2) | |
| | TDF + 3TC + NVP | 15 (7.3) | 3 (3.2) | |
| | TDF + 3TC + EFV | 90 (44) | 45 (47.4) | |
| Switch in regimen | Yes | 159 (77.6) | 72 (75.8) | 0.73 |
| | No | 46 (22.4) | 23 (24.2) | |
| Number of pills per day | One | 90 (44) | 45 (47.4) | 0.25 |
| | Two | 89 (43.4) | 44 (46.3) | |
| | Three | 26 (12.6) | 6 (6.3) | |
| Missed medication in the past 6 months | Yes | 20 (9.8) | 40 (42.1) | <0.05 |
| | No | 185 (90.2) | 55 (59.8) | |
| Missed medication in the past 1 month | Yes | 14 (6.8) | 43 (45.3) | <0.05 |
| | No | 191 (93.2) | 52 (54.7) | |
| Time of refill | Exact day | 125 (61) | 11 (11.6) | <0.05 |
| | Prior days | 38 (18.5) | 13 (13.7) | |
| | Later days | 42 (20.5) | 71 (74.7) | |

*Single=Unmarried, widow, separated, divorced; **AZT - Zidovudine, 3TC - Lamivudine, NVP - Nevirapine, TDF - Tenofovir, EFV - Efavirenz. HIV=Human immunodeficiency virus; ART=Anti-retroviral treatment

mentioned cost as a limiting factor and adherence was not affected by occupation and family income [Table 2]. This may be due to the free-of-cost drugs and services provided under the national program.

In the patient-related factors, adherence to ART was found to be strikingly behavior dependent. Regular clinic visits were significantly associated with adherence and in fact, in one study, it was the only statistical factor

affecting medication adherence.^[16] Among the nonadherent group significant number of patients (74.7%) collected their pills later than the scheduled day of appointment. Program evaluation studies have similarly revealed missing the scheduled appointments as an important factor for nonadherence.^[15,26] Furthermore, pharmacy-based time to refill has been found to correlate with pill count adherence, increase in CD4 count, and decrease in viral load.^[27,28] Among those who accepted by self-recall to missing doses in the past 6 months and 1 month, nonadherence rate was 20% and 19%, respectively, and this behavior of missing doses was significant among the nonadherent group [Table 2]. However, the nonadherence rate of 31.7% derived from pill count method was higher than the patient recall method in our study. This drawback of patient recall method has been highlighted in several studies and the use of more than one adherence measure will capture more accurate information.^[11,12,23] The common reasons given for nonadherence were depression, being too busy, and forgetfulness. In addition, many patients (24.2%) did not attribute any reason for missing the doses. This may be due to a behavioral attitude among patients with chronic diseases where long-term adherence is a problem.^[22,23]

An analysis of 6 months trend in CD4 count revealed significantly higher prior mean CD4 count and a lesser mean increase in CD4 count associated with nonadherence. The association between optimal adherence and lower baseline CD4 count,^[28] improved immunological^[27,28] and virological^[29-30] outcome has been documented in previous studies. While decrease in CD4 count was associated with nonadherence, treatment outcome factors such as BMI, hospitalization and severe opportunistic infection in the past

6 months had no impact on adherence. Although a study by Chi *et al.* showed that the WHO clinical stage, hemoglobin, BMI, and tuberculosis status were not predictive of poor adherence,^[28] the 6-month trend of the treatment outcome factors we analyzed may be too short to conclude on these outcomes.

Limitations

This study has the inherent limitations of a cross-sectional hospital-based study. Due to the inclusion criteria, patients on ART for <6 months and those who were lost to follow-up could not be included. Majority of the nonadherent patients cited depression as a reason but depression scoring mechanisms were not included in the study design. The trends of treatment outcome measures studied were short-term in nature.

Conclusions

HIV infection/AIDS has transitioned into a chronic manageable disease with improved survival due to advances in ART. Suboptimal adherence to treatment is one of the major factors leading to ART failure. The level of adherence in our study (68.3%) is suboptimal but comparable to other studies from South India in similar settings. A significant proportion of nonadherent patients had a decrease in CD4 count and optimal adherence was positively associated with better immunological outcome (mean increase in CD4 count) over 6 months. The significant factors associated with nonadherence were lower education level, higher prior CD4 count, irregular follow-up, missing doses in the past and being late for pharmacy pill re-fill. Most of these factors are behavior dependent as seen in the management of any chronic illness. National guidelines lay special emphasis on adherence counseling both pre-ART and during each of the patient's visits to the ART center. The factors identified in our study can be used for target intervention during reinforcement adherence counseling to overcome the challenge of achieving optimal adherence levels.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Table 3: Reasons for nonadherence to anti-retroviral treatment (n=95)

| Reason | Frequency, n (%) |
|-------------------------|------------------|
| Feeling depressed | 33 (34.7) |
| Too busy | 21 (22.1) |
| Forgot to take medicine | 17 (17.9) |
| Drug allergy | 1 (1.1) |
| Declined to give reason | 23 (24.2) |

Table 4: Impact of nonadherence on treatment outcome (n=300)

| Variables | Category | Adherent (n=205), n (%) | Nonadherent (n=95), n (%) | P |
|--|-----------------|-------------------------|---------------------------|--------|
| CD4 count in 6 months | Increased | 177 (86.3) | 66 (67.4) | 0.0005 |
| | Decreased | 28 (12.7) | 29 (32.6) | |
| BMI in 6 months | Increased | 146 (71.2) | 61 (64.2) | 0.39 |
| | No change | 35 (17.1) | 18 (18.9) | |
| | Decreased | 24 (11.7) | 16 (16.8) | |
| Hospitalization in the past 6 months | No | 194 (94.6) | 87 (91.6) | 0.31 |
| | Once | 7 (3.4) | 5 (5.3) | |
| | Twice and above | 4 (2) | 3 (3.1) | |
| Opportunistic infection in past 6 months | Yes | 3 (1.5) | 4 (4.2) | 0.21 |
| | No | 202 (98.5) | 91 (95.8) | |

BMI=Body mass index

Table 5: Trends in mean CD4 count in 6 months and adherence

| Variable | Adherent (n=205) | Nonadherent (n=95) | P |
|--|------------------|--------------------|-----------------|
| Mean CD4 count 6 months before study | 337.57±255.27 | 401.27±276.27 | <0.05 |
| Mean CD4 count during the study period | 574.83±274.17 | 519.13±286.52 | Not significant |
| Mean increase in CD4 count in 6 months | 237.26±258.18 | 117.85±302.82 | <0.05 |

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