

DOES PROVIDING FREE ANTIRETROVIRAL THERAPY ENSURE OPTIMAL ADHERENCE AMONG PEOPLE LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME?

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ABSTRACT

Objective: The present study was carried out with the objective of determining the level of adherence and factors affecting it among patients receiving free antiretroviral therapy (ART).

Methods: A cross-sectional study design was adopted and 320 human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome positive patients receiving free ART from a district hospital in Udupi were interviewed using a semi-structured questionnaire. Adherence to ART >95% of the prescribed medication was used as the cutoff for deciding on the treatment adherence.

Results: An encouragingly high 96.9% of the individuals were adherent to the medication over the past month. However, 41.8% of the participants reported to have ever missed doses of ART. On univariate analysis, having ever consumed alcohol, absence of side effects such as fatigue and tingling/numbness, having a feeling of sadness and sleep disturbances, being on efavirenz-based regimen, non-disclosure HIV status, being unsure of continuing lifelong treatment were significantly associated with non-adherence ($p < 0.05$).

Conclusion: Although non-adherence was of concern among a small proportion of participants, a large number of them reported to have ever missed doses of ART. This finding suggests that adherence rate may be lower over longer periods of time. Hence, periodic assessments may address patient specific barriers and help to improve the adherence rate among this population.

Keywords: Adherence, Adults, Antiretroviral therapy, Determinants.

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INTRODUCTION

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) continues to be a global public health concern, and world over, an estimated 2 million people became newly infected with HIV in 2014 [1]. India has the third-largest number of people living with HIV/AIDS. The free antiretroviral therapy (ART) program of India under the National AIDS Control Program has been providing treatment support to people infected with HIV since 2004. One of the biggest challenges of this program is maintaining the adherence levels among patients on ART; as the provision of no cost ART does not ensure optimal adherence to therapy. Studies have traditionally used a threshold of 95% or more to distinguish between optimal and suboptimal adherence [2,3]. Although studies have shown that adherence to ART improves the quality of life among HIV-positive patients, the requisite lifelong treatment affects its compliance [4,5]. Continuous monitoring of levels and patterns of adherence in different settings and addressing the factors and circumstances that lead to suboptimal adherence are vital for the success of the ART program as well as for the prevention of HIV drug resistance. Although free ART has been available for a considerable period, studies determining adherence to ART and factors affecting it are essential to assess the success of the program. Considering the lack of data pertaining to this issue in the current population, this study was planned to address the same among patients receiving no cost ART under the program.

METHODS

Using a cross-sectional design, 320 patients living with HIV/AIDS were interviewed at the ART center, district hospital, Udupi, when they came for a routine monthly check up and collection of drugs during the year 2011. Patients above 18 years and on first-line ART for more than 3 months were included in the study. Seriously ill patients who were

not able to respond to the questions were excluded. Considering a 60% prevalence of complete adherence to ART [6], relative precision of 10% and 20% non-response rate for a finite population, the sample size was calculated to be 320. Following informed consent, those consenting and willing to participate in the study were interviewed using a modified, pretested, and validated questionnaire [7].

Apart from socio-demographic information, responses related to disclosure of HIV status, alcohol, and drug abuse were collected. Adverse drug effects based on patient-reported symptoms were recorded. Adherence was measured based on self-reports of missed doses. Those not willing to participate in the study were considered as non-respondents. Anthropometric variables such as height and current weight as well as the weight during initiation of ART were noted from the records. Disease was staged as per the World Health Organization (WHO) criteria and the current cluster of differentiation 4 (CD4) levels besides that at the time of treatment initiation was documented. Risk factors for HIV and diagnosed opportunistic infections if any were accessed from the case records for both respondents and non-respondents. Socio-economic status was assessed using modified Kuppuswamy scale.

Information pertaining to monthly, weekly, and daily adherence to ART was queried from the participants. Data concerning treatment interruption since initiation of ART was also obtained. Monthly and weekly adherence to antiretroviral agents was computed by dividing the number of pills consumed daily over the past 1 month and week by the number of pills prescribed during the particular period and presented as a percentage. Only self-reported data were used for calculating the adherence to ART. Adherence levels were further classified based on the number of missed doses. Individuals were considered to have >95% adherence level if they had missed <3 doses, 80-95% if they missed

3-12 doses, and <80% if they missed more than 12 doses in the past 1 month. Participants with adherence more than 95% over the past month were considered as adherent to ART.

The proposal was approved by the Institutional Ethics Committee. Permission was also obtained from the district surgeon before initiating the study. Data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 15.0. Continuous data were summarized using mean (standard deviation [SD]) or Median (interquartile range [IQR]) depending on the skewness of the data. The frequency with percentages was used to summarize categorical data. Associations were assessed using Chi-square or Fisher's exact test for categorical data. Paired *t*-test or Wilcoxon's signed rank test was used to compare weight and CD4 count at treatment initiation and current levels. Risks have been estimated as odd's ratio (OR). Graphical presentations are done using error bar and box plot. A $p < 0.05$ was considered significant.

RESULTS

Socio-demographic profile of the participants

The study had a response rate of 99.3% with 318 individuals consenting to participate. As shown in Table 1, a significant proportion of the participants were in the productive age group of 31-50 years (79.2%) with a mean age of 40.81 years (± 7.96). A significant 97.7% were living with their family members.

Disease profile of the participants

Of the study participants, 198 (62.3%) were having the WHO stage 4 disease at the time of ART initiation. The median (IQR) time since diagnosis of HIV infection and ART initiation was 35.1 (18.5, 58.45) months and 23.96 (12.3, 35.15) months, respectively. Heterosexual route of transmission was the only mode of transmission reported by the participants at the time of enrollment in the ART center. Tuberculosis (43.4%) and herpes zoster (33.3%) were the two most common opportunistic infections observed at any point among the participants. Of the enrolled participants, complete data pertaining to pre-ART and current CD4 count were available for 297 participants. Almost 316 (99.3%) of the participants had a CD4 count < 500 cells/ mm^3 at the time of starting ART.

Median CD4 count recovery following administration of ART was 197 (IQR 81,330) cells/ mm^3 , which was significant ($p < 0.001$) (Fig. 1). A significant ($p < 0.001$) improvement in the mean (SD) body weight was observed after initiation of the treatment (46.9 [± 9.47] kg vs. 50.0 [± 10.3] kg) (Fig. 2).

Treatment profile of the participants

Nearly, 77.4% of the respondents were on a first line nevirapine-based regimen either in combination with zidovudine or stavudine (d4T) consuming two pills per day. The remaining were administered efavirenz (EFV)-based regimen requiring them to consume a total of 3 pills/day. Almost half the participants were on cotrimoxazole/dapsone prophylaxis, and another 4.4% were on antitubercular treatment at the time the investigator interviewed them. A large proportion of participants reported either neurological (73.3%) or gastrointestinal (69.2%) related adverse events with ART intake.

Adherence to ART

The majority (96.9%) of the participants had an adherence rate $> 95\%$ over the past 30 days as depicted in Table 2. However, 41.8% reported to have ever missed doses of ART. The median number of doses missed by the non-adherent participants over the past month was 21 (IQR 6, 67.5). Treatment interruption for a period of 1-week or more was seen among 10.1% of the participants.

Factors affecting adherence

There was no statistically significant association between adherence and socio-demographic characteristics and disease-related variables such as time since diagnosis or duration of ART. It was observed that with increasing age, the adherence levels declined; however, the trend

Table 1: Socio-demographic characteristics of the study participants (N=318)

Variables	N (%)
Age group (years)	
<30	30 (9.4)
31-40	148 (46.5)
41-50	104 (32.7)
>50	36 (11.3)
Gender	
Male	179 (56.3)
Female	139 (43.7)
Education	
Illiterate	58 (18.2)
1-5 years of schooling	88 (27.7)
6-10 years of schooling	151 (47.5)
>10 years of schooling	21 (6.6)
Employment	
Employed	220 (69.2)
Unemployed	98 (30.8)
Occupation	
White collar	6 (1.9)
Skilled/semi-skilled	90 (28.3)
Unskilled	124 (39.0)
Never worked/ unemployed	98 (30.8)
Economic status	
Low	201 (63.2)
Middle	117 (36.8)
Marital status	
Currently married	153 (48.1)
Widowed	94 (29.6)
Single (never married)	44 (13.8)
Divorced/separated	26 (8.1)
Cohabiting	1 (0.3)
Habits	
Ever consumed alcohol	144 (45.3)
Ever smoked	73 (22.9)
Ever consumed drugs	8 (2.5)

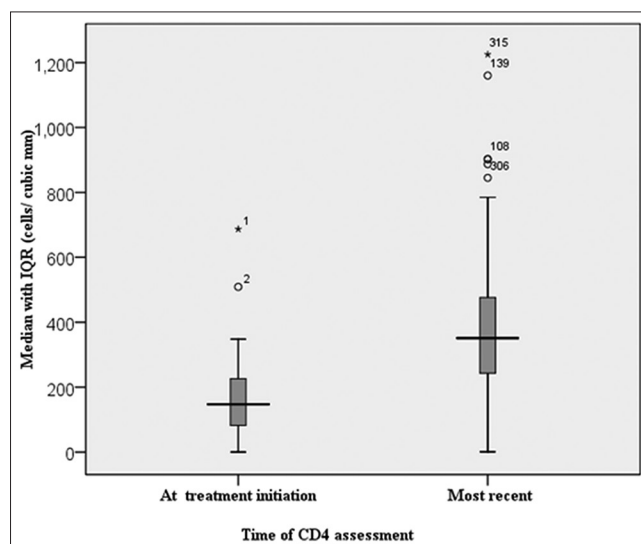


Fig. 1: Change in cluster of differentiation 4 (CD4) count following antiretroviral therapy initiation (N=297). As the CD4 count at treatment initiation was available for only 297 individuals, the change in CD4 was only computed for the before mentioned number

was not statistically significant. Non-adherence was significantly higher among those who ever consumed alcohol (OR: 5.05; confidence interval [CI]: 1.05-24.21; $p = 0.047$). Being on EFV-based regimens,

which translate to consuming three pills per day, were found to be significantly associated with non-adherence (OR: 0.18; CI: 0.50-0.66; p=0.011).

A sense of well-being (OR: 0.16; CI: 0.03-0.79; p=0.018) and not experiencing any drug-related side effects such as pain or tingling, numbness in hands and feet (OR: 1.05; CI: 1.01-1.08; p=0.016) was found to be significantly associated with non-adherence. Conversely, feeling sad or depressed (OR: 5.55 CI: 1.49-20.70; p=0.020) and disturbed sleep (OR: 4.44, CI: 1.12-17.54; p=0.038) were some of the other predictable factors affecting non-adherence. Not disclosing the HIV status was statistically significantly associated with non-adherence (OR: 0.09; CI: 0.01-0.52; p=0.029). Seven participants were unsure of continuing lifelong treatment, and this was another significant factor associated with non-adherence (OR: 0.06; CI: 0.01-0.393; p=0.017). Multivariable analysis did not show any significant predictors for non-adherence.

DISCUSSION

An encouraging high proportion (96.9%) of adherence to ART over a 30 day period was observed among the participants in this study which is consistent with the results of the study done by Gokarn *et al.* (97%) and Bam *et al.* (94.8%) [8,9]. The reported adherence in the literature varies widely, ranging from 43.2% to 97% [8-14]. In contrast to the findings of the present study, a study by Sarna *et al.* observed that adherence levels were lower among patients receiving free ART compared to patients paying out of pocket for medication [15]. A study by Achappa *et al.* observed that, among those who received free ART, 64 (76.2%) had high adherence and only 10 (31.3%) patients who paid for ART had high adherence [16]. However, another study by Lal *et al.* reported that 90% patients receiving free ART were adherent over the past 4 days. The study also showed that 30% of the

patients reported to have ever missed doses of medication which is lower than the present study [17]. The method of measurement, as well as the type of resource settings, could be attributed to the wide variation in adherence rates. Findings similar to the present study were reported by Safren *et al.*, wherein no association was found between demographic variables and adherence [18]. However, a study by Uzochukwu *et al.* showed that demographic factors such as age <35 years, being female, and having higher education status were significantly associated with non-adherence [19]. Results akin to the present study were reported by Sarna *et al.* wherein adherence levels were not related to time since diagnosis and duration of time patients had been receiving ART [15]. Participants showed a significant response to ART which was reflected in their improved CD4 count and body weight. Similar improvements in CD4 count were reported by Bachani *et al.* in which the median increase in CD4 count at 6 months after initiation of treatment was 142 (IQR 57-750; n=616), and at 1 year, it was 184 cells/mm³ (IQR 102-299; n=582) [20].

However, non-adherence was also of concern among a small proportion of the participants. Behavioral factors such as consumption of alcohol, not disclosing the HIV status, and being unsure of continuing ART for life were found to be significant predictors of non-adherence. On the other hand, the absence of side effects such as having no fatigue, pain, or numbness was also observed to be associated with non-adherence. This could reflect a non-chalant behavior, which is commonly experienced during a feeling of wellness among patients on long-term medication. Treatment-related factors such as being on the EFV-based regimen, having to consume more than 2 pills/day, and encountering adverse drug events such as psychological disturbances were significantly associated with non-adherence. A study by Mitiku *et al.* found that there was no significant association between the presence and absence of side effects on adherence (COR: 0.94; 95 CI: 0.39, 2.23) [21]. In analogy to the findings of our study, a study done by Joshi *et al.* showed that non-disclosure of HIV status (OR: 1.549; CI: 1.176-2.039) and being on EFV-based regimens (OR: 1.479; CI: 1.190-1.837) were found to be significant predictors of non-adherence [22]. Another study by Wasti *et al.* also showed that alcohol consumption (OR: 12.89; p<0.001) and non-disclosure of HIV status (OR: 17.99; p=0.014) were associated with non-adherence [23]. A study by Silva *et al.* showed that time since diagnosis (p=0.002) and alcohol use (p=0.030) were significantly associated with non-adherence [24].

There are certain limitations to the study. Self-reported disclosure may have led to overestimation of the adherence rates. As the study was conducted among patients at a single ART center, the determinants of adherence reported in the study may not be generalizable. The study also does not address the concerns of those lost to follow-up.

CONCLUSION

Despite a high level of adherence among patients receiving free ART, a large proportion of them also reported to have missed doses at some point during treatment. Sustaining adherence over a long period is, therefore, a great challenge for the successful implementation of the ART program. Periodic assessment of adherence and addressing patient-specific barriers could go a long way in ensuring optimal adherence. Prospective follow-up studies could further explore the factors associated with long-term adherence to ART.

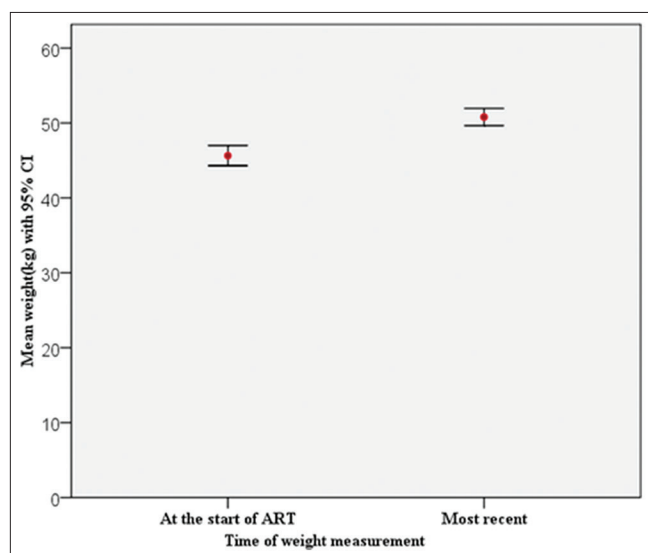


Fig. 2: Change in weight following antiretroviral therapy initiation (N=309). As weight at treatment initiation was available for only 309 individuals, the change in weight was only computed for the before mentioned number

Table 2: Adherence to ART over past month (N=318)

Adherence levels	N (%)					
	Yesterday	Day before yesterday	3 days ago	4 days ago	Last 7 days	Last 30 days
>95% (<3 doses missed)	312 (98.1)	310 (97.5)	309 (97.2)	308 (96.9)	304 (95.6)	308 (96.9)
80-95% (3-12 doses missed)	-	-	3 (0.9)	5 (1.6)	9 (2.8)	4 (1.3)
<80% (>12 doses missed)	6 (1.9)	8 (2.5)	6 (1.9)	5 (1.6)	5 (1.6)	6 (1.9)

ART: Antiretroviral therapy

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