



## Association between Medication Adherence Outcomes and Adverse Drug Reactions to Highly Active Antiretroviral Therapy in Indian Human Immunodeficiency Virus-Positive Patients

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### ABSTRACT

In India, interruptions to highly active antiretroviral therapy (HAART) are due to adverse drug reactions. This study was aimed to assess the association between HAART adherence and adverse drug reactions (ADRs) in human immunodeficiency virus (HIV) patients. This prospective study was conducted at a Medicine department in a South Indian tertiary care teaching hospital. HIV-positive patients were interviewed for adherence using ACTG adherence questionnaire and intensively monitored for ADRs to HAART. The percentage of adherence was calculated based on missed doses, and graded as less than 80%, 80–95%, and >95%. The World Health Organization (WHO) probability scale was used for causality assessment. Logistic regression analysis as well as univariate analysis was used to assess the association ( $P$  value < 0.05). A total of 105 HIV-positive patients had been taking HAART out of whom 50 (47.6%) patients agreed for adherence assessment, and 23 (21.9%) refused due to social stigma. Upon evaluation of the patient characteristics in the reported adherence, 78% were in males (53.8%) and 22% were in females (46.2%) with the level of adherence greater than 95%. Six (12%) patients had a regular alcoholic intake with adherence less than 80% compared to 31 (62%) patients who never had any alcoholic intake ( $P$  < 0.05). A significant association between ADRs and adherence was found ( $P$  < 0.05). Causality found by the WHO scale was “probable.” Clinicians must focus on education regarding the need for adherence, possible adverse effects, and early detection and prevention of ADRs to HAART.

**Key words:** Adverse drug reaction, highly active antiretroviral therapy, human immunodeficiency virus, medication adherence

### INTRODUCTION

Human immunodeficiency virus (HIV)-infected patients require a combination of three to four antiretroviral drugs, termed highly active antiretroviral therapy (HAART). Adherence to HAART is increasingly recognized as the key factor to prevent treatment failure in most people with HIV infection. There is a significant association between medication adherence and virological suppression in the treatment of HIV infection.<sup>[1,2]</sup> India stands at the third position in having the highest burden of HIV/acquired

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immunodeficiency syndrome<sup>[3]</sup> (AIDS). In India, National AIDS Control Organization (NACO) offers free HAART for HIV and related opportunistic infections. According to NACO guidelines,<sup>[3]</sup> adherence should be maintained at a minimum of 95% in order to maintain clinical effectiveness and to minimize the development of drug-resistant strains of HIV. In resource-limited countries like India, failure in HIV treatment is due to drug intolerance or adverse drug reactions (ADRs); unfortunately, 84% of HIV patients discontinue their initial HAART within the first 8 months of therapy due to ADRs, which leads to non-compliance.<sup>[4]</sup> In addition, the transmission of drug-resistant viruses is a major health concern. Although many methods have been used in clinical practice to measure adherence, self-reports of the taken medication is the most reasonable, accurate, and ideal to an Indian setup because it promotes a candid exchange between the treating clinician and the treated patient. A number of strategies can be used to improve adherence that include education, simplification of regimen with regard to timing, pill burden and food requirements, avoidance of ADR, and involvement of health care team, family, and friends. The safe and effective management of HIV infection requires understanding of adverse effects associated with HAART because ADRs negatively affect confidence in antiretroviral therapy and medication adherence. HIV-infected patients may stop taking lifelong HAART as a strategy to manage unpleasant symptoms or to avoid adverse health outcomes associated with HAART. Hence, adherence may be compromised, leading to treatment failure, increased hospitalization, and to morbidity and mortality, which significantly affects the quality of life. To date, no study has been published from India on the effects of adverse drug reaction on medication adherence and its outcome in HIV-infected patients. The study was aimed to assess the association between self-reported HAART adherence outcomes and ADRs in Indian HIV-positive patients.

## MATERIALS AND METHODS

This was a prospective study conducted from October 2010 to June 2011 among HIV-infected patients by a clinical pharmacist at a Medicine department in a teaching hospital where ADR reporting exists. The study was approved by the institutional ethics committee. HIV-infected hospitalized patients of either sex who were on HAART were included in the study; HIV-positive patients who refused for medication adherence interview, patients with traditional medicines alone, and pregnant women were excluded from medication adherence assessment. Based on the study criteria, the study procedure was explained and

informed consent was taken from the patients. The AIDS Clinical Trial Group (ACTG) adherence questionnaire<sup>[5]</sup> was used for medication adherence assessment. Demographic details, information on sociodemographic factors, psychological factors, disclosure of status, social habits, time of diagnosis of HIV, health care system and health care professional-related factors, HAART-related factors, knowledge and belief related to HAART, and reasons for lack of adherence<sup>[6]</sup> were documented in adherence assessment. Agreed patients for adherence assessment were interviewed and asked to recall and report the number of missed antiretroviral doses in the last one month (each missed medication regarded as one dose). The percentage of adherence from self-report was calculated by using the following formula:<sup>[7]</sup>

$$\text{Percentage of adherence} = \frac{\text{No. of doses the patient should have taken} - \text{No. of doses missed}}{\text{No. of doses the patient should have taken}} \times 100$$

The level of adherence was graded as less than 80%, 80%–95%, and greater than 95% as per NACO guidelines.<sup>[3]</sup> As HAART is a life-long therapy in an HIV-infected patient, it is more meaningful to evaluate long-term and short-term ADRs associated with HAART; hence, during the study period, adherence interview for HIV-infected, hospitalized in-patients was intensively monitored for ADRs by active follow-up after treatment, and adverse events were detected by asking patients directly or screening patient records in order to correlate medication adherence and ADRs to HAART. Treatment charts and patient case notes were made; CD4 count, HAART status, occurrence of ADRs, HAART regimen implicated in ADRs, duration of therapy, route of administration, dosage, with frequency, complementary treatment, patient's allergic status to food and drugs, and use of oral contraceptives were also documented. Naranjo's algorithm<sup>[8]</sup> and World Health Organization's ADR probability scale<sup>[9]</sup> were used for the causality assessment of ADRs. If there was a history of allergy or reactions to the medication during previous exposure, the ADR was considered "predictable." Modified Shumock and Thornton criteria<sup>[10]</sup> were used to assess the preventability of ADRs. The severity of suspected ADRs was assessed using the modified Hartwig and Siegel scale.<sup>[11]</sup> The ADR was considered as "not predictable" if the drug had previously been well tolerated by the patient at the same dose and route of administration. WHO adverse reaction terminologies (WHO-ART) for system organ class codes<sup>[12]</sup> were used to code the suspected ADR. ADR with a literature

incidence of  $\geq 1/100$  was considered “predictable.” Any suspected ADR documented with HAART was reviewed and assessed by a senior academic clinical pharmacist and was reported to the treating clinicians.

### Statistical analysis

Logistic regression analysis as well as univariate analysis was used to find an association between self-reported medication adherence and ADRs. A classification and regression tree was used to establish continuous variable cut points. All statistical calculations were performed using Statistical Package for Social Science (SPSS), version 17.0. A *P*-value of  $<0.05$  was considered as statistically significant.

## RESULTS

During the study period, a total of 105 HIV positive patients were taking HAART. Of these, 50 (47.6%) patients agreed to participate and agreed to be interviewed, 23 (21.9%) refused for adherence assessment interview, and 32 (30.5%) did not meet the inclusion criteria. Majority of the patients were males, 68 (64.8%), compared to females, 37 (35.2%). Majority of patients were greater than 48 years of age (44.8%). Most of the patients were unemployed (68, 64.8%) and married (86, 81.9%). Over 62.9% of the patients were HAART experienced, 29.5% of the patients were HAART new, i.e., naïve, and 7.6% of the study patients were HAART defaulters. Patients’ demographic details are shown in Table 1.

Out of 50 patients for adherence assessment interview, 78% were males with a 53.8% level of adherence, greater than 95%, compared to females (22%) with a 46.2% adherence level. A level of adherence greater than 95% was seen in the age group of 39–48 years (6, 46.2%) and married patients (11, 84.6%). Most of the patients were unemployed (29, 58%) with secondary school education (37, 74%); employed patients had an average monthly income of INR 5000–10,000 (US\$96.15–192.30). Among the psychological factors for adherence assessment in our study, results showed that patients reported that they had disclosed their HIV status to the spouse (33, 66%;  $P = 0.040$ , i.e.,  $P < 0.05$ ) and 43 (86%) of the patients reported that they had received help from family members in taking their medication regularly ( $P = 0.049$ , i.e.,  $P < 0.05$ ). A total of 40 (80%) patients felt that support from family was needed strongly in order to have good adherence. Table 2 depicts the details of socio-demographic and psychological factors for adherence.

A total of 49 (98%) patients reported that they were aware

about the significance of HAART therapy and 15 (30%) patients were following all instructions regularly provided by the treating clinician. A total of 8 (16%) patients reported that they had never followed instructions and left the treatment in between due to various reasons such as feeling better, financial problem, alcohol intake, or busy schedule. Following the instructions as per the treating clinician was found to be statistically significant ( $P = 0.001$ , i.e.,  $P < 0.05$ ). The reason for difficult follow-up of HAART was due to cost (25, 50%) followed by financial discomfort (14, 28%). We found that 6 (12%) patients with regular alcoholic intake had poor adherence (less than 80%) compared to 31 (62%) patients who never

**Table 1: Demographic characteristic of patients on highly active antiretroviral therapy**

Characteristic	Total number of patients on HAART <i>n</i> = 105 (%)
Gender	
Male	68 (64.8)
Female	37 (35.2)
Age group (years)	
18–28	8 (7.6)
29–38	23 (21.9)
39–48	47 (44.8)
49–58	19 (18.1)
59–68	8 (7.6)
BMI(kg/m <sup>2</sup> )	
18.4	37 (35.2)
18.5–24.5	53 (50.4)
$\geq 25$	6 (5.8)
$\geq 30$	9 (8.6)
Marital status	
Single	6 (5.7)
Married	86 (81.9)
Widowed	8 (7.6)
Separated	5 (4.8)
Occupation	
Employed	37 (35.2)
Unemployed	68 (64.8)
Alcoholic	
Yes	31 (29.5)
No	74 (70.5)
Smoker	
Yes	27 (25.7)
No	78 (74.3)
Complementary treatment	
Yes	9 (8.6)
No	96 (91.4)
Status of HAART	
HAART naïve	31 (29.5)
HAART experienced	66 (62.9)
HAART defaulter	8 (7.6)
Adherence assessment status	
Interviewed and assessed	50 (47.6)
Refused to be Interviewed	23 (21.9)
Non-eligible	32 (30.5)

HAART = highly active antiretroviral therapy

**Table 2: Sociodemographic and psychological factors for adherence**

Sociodemographic factors for adherence	n =50 (%)	Percentage of adherence			P-value
		<80%	80-95%	>95%	
		n=23	n=14	n=13	
Gender					
Male	39 (78)	20 (87)	12 (85.7)	7 (53.8)	0.05
Female	11 (22)	3 (13)	2 (14.3)	6 (46.2)	
Age group (years)					
18–28	3 (6)	1 (4.3)	1 (7.1)	1 (7.7)	0.147
29–38	13 (26)	7 (30.5)	2 (14.3)	4 (30.8)	
39–48	23 (46)	12 (52.2)	5 (35.7)	6 (46.2)	
49–58	10 (20)	2 (8.7)	6 (42.9)	2 (15.3)	
59–68	1 (2)	1 (4.3)			
Marital status					
Single	4 (8)	2 (8.7)	1 (7.1)	1 (7.7)	0.048
Married	37 (74)	16 (69.6)	10 (71.5)	11 (84.6)	
Widowed	4 (8)	2 (8.7)	1 (7.1)	1 (7.7)	
Separated/divorced	5 (10)	3 (13)	2 (14.3)		
Level of education					
Primary school	4 (8)	2 (8.7)	1 (7.1)	1 (7.7)	0.362
Secondary school	37 (74)	18 (78.3)	8 (57.1)	11 (84.6)	
College level Illiterate	9 (18)	3 (13)	5 (35.7)	1 (7.7)	
Occupation					
Employed	21 (42)	12 (52.2)	6 (42.9)	3 (23.1)	0.235
Unemployed	29 (58)	11 (47.8)	8 (57.1)	10 (76.9)	
Income in per month (INR)					
<5000 <sup>a</sup>	13 (26)	6 (26.1)	3 (21.4)	4 (30.8)	0.180
5000–10,000 <sup>b</sup>	19 (38)	9 (39.1)	4 (28.6)	6 (46.2)	
10,000–20,000 <sup>c</sup>	15 (30)	8 (34.8)	4 (28.6)	3 (23.0)	
>200,000 <sup>d</sup>	3 (6)		3 (21.4)		
Psychological factors for adherence					
Disclosed to spouse					
Yes	33 (66)	8 (34.8)	13 (92.8)	12 (92.3)	0.040
No	17 (34)	15 (65.2)	1 (7.2)	1 (7.7)	
Help from family members in taking medicines regularly					
Yes	43 (86)	21 (91.3)	12 (85.7)	10 (76.9)	0.049
No	7 (14)	2 (8.7)	2 (14.3)	3 (23.1)	
Moral support from family					
Yes	40 (80)	17 (74)	11 (78.5)	12 (92.3)	0.032
No	10 (20)	6 (26)	3 (21.5)	1 (7.7)	

n = Number of patients; INR = Indian Rupees. A P-value of <0.05 was considered as statistically significant with Fisher's exact test. <sup>a</sup><US\$96.15; <sup>b</sup>US\$96.15–192.30; <sup>c</sup>US\$192.30–384.60; <sup>d</sup>>US\$384.60

had alcoholic habits which resulted in good adherence (greater than 95%;  $P = 0.027$ , i.e.,  $P < 0.05$ ). The overall adherences to HAART in case of smokers (10, 20%) and nonsmokers (33, 66%) were poor (less than 80%). In our study, none of them reported the use of IV drugs. Table 3 summarizes health care and social factors for adherence.

Majority of the patients (29, 58%) were able to identify their ART medication by brand name and were on HAART for more than a year. Most (45, 90%) of the patients knew that HAART had been prescribed to them to slow down the progression of HIV; 30 (60%) patients found the HAART treatment difficult to afford. A total of 31 (62%) of patients

showed the behavior of skipping medication regularly which resulted in poor adherence (less than 80%). Regarding the knowledge and beliefs related to HAART, our results were found to be statistically significant ( $P < 0.05$ ) for timings of medication; 33 (66%) believed that antiretroviral treatment should be taken on time as prescribed by the clinician, 34 (68%) felt that special instructions given along with HAART are important to be followed, 29 (58%) felt that the treatment should not stopped and should be continued, and 44 (88%) patients agreed that HAART is life saving. Fisher's exact test revealed that the occurrence of ADRs to antiretroviral therapy was significantly associated and significantly predicted with the percentage of adherence

**Table 3: Health care and social factors for adherence**

Health care- system and health care team-related factors	Number of patients <i>n</i> = 50 (%)	Percentage of adherence			<i>P</i> -value
		<80%	80-95%	>95%	
		<i>n</i> = 23	<i>n</i> = 14	<i>n</i> = 13	
Knowledge about importance of taking medicines needed?					
Yes	49 (98)	22 (95.7)	14 (100)	13 (100)	0.549
No	1 (2)	1 (4.3)			
How often do you follow instructions provided by the clinician?					
Never	8 (16)	8 (34.8)			0.001
Sometime	12 (24)	11 (47.8)	1 (7.1)		
Most of the time	15 (30)	4 (17.4)	8 (57.1)	3 (23.1)	
All the time	15 (30)	0	5 (35.8)	10 (76.9)	
Difficulty in follow-up					
Yes	30 (60)	16 (69.6)	7 (50)	7 (53.8)	0.435
No	20 (40)	7 (30.4)	7 (50)	6 (46.2)	
Reason for difficult follow-up					
Cost					
Yes	25 (50)	13 (56.5)	6 (42.9)	6 (46.2)	0.686
No	25 (50)	10 (43.5)	8 (57.1)	7 (53.8)	
Discomfort					
Yes	14 (28)	7 (30.4)	4 (28.6)	3 (23.1)	0.893
No	36 (72)	16 (69.6)	10 (71.4)	10 (76.9)	
Lack of time					
Yes	7 (14)	3 (13)	3 (21.4)	1 (7.7)	0.580
No	43 (86)	20 (87)	11 (78.6)	12 (92.3)	
Distance to center					
Yes	2 (4)	1 (4.3)	1 (7.1)	13 (100)	0.635
No	48 (96)	22 (95.7)	13 (92.9)		
Social factors for adherence					
Alcohol					
Regular	6 (12)	5 (21.7)	1 (7.1)	1 (7.7)	0.027
Occasional	4 (8)	3 (13.1)	4 (28.6)	1 (7.7)	
Rare	1 (2)	1 (4.3)	9 (64.3)	11 (84.6)	
Reformed	8 (16)	3 (13.1)			
Never	31 (62)	11 (47.8)			
Smoking					
Regular	10 (20)	7 (30.5)	2 (14.3)	1 (7.7)	0.391
Occasional	1 (2)	1 (4.3)	3 (21.4)	1 (7.7)	
Rare	1 (2)	1 (4.3)	9 (64.3)	11 (84.6)	
Reformed	5 (10)	1 (4.3)			
Never	33 (66)	13 (56.6)			

A *P*-value of <0.05 was considered as statistically significant

being less than 80% ( $P < 0.001$ ). Table 4 highlights the HAART-related factors, knowledge, beliefs related to ART, and ADRs reported.

Out of 50 HIV-infected patients for adherence assessment, patients with ADRs were 32 (27 males, 84.4%, and 5 females, 15.6%) in number. The majority of patients with ADR were in the age group of 39–48 years. Most of the patients with ADRs were agriculturists (37.5%). Four patients (12.5%) were on both HAART and complementary treatment. The majority (93.7%) of patients with ADRs were HAART experienced. The CD4 count in the majority of patients (78.1%) with ADRs was  $\leq 200$  cells/ $\mu$ l. In the majority of ADRs, occurrence was reported at the time of hospital

admission (37.6%) followed by previous exposure to ADRs, and during hospital stay (31.2%). During the study, 37.5% ADRs to HAART were observed due to polypharmacy (four to five drugs). A higher rate of ADRs was noted with the zidovudine + lamivudine + nevirapine combination (31.5%), while the lowest rate of ADRs was noted with atazanavir + ritonavir + tenofovir + emtricitabine (3.1%). Table 5 represents the demographic details of the patients with ADRs.

The WHO probability scale was “probable” (50%) and “possible” (31.2%) and by Naranjo’s algorithm, causality was “probable” (68.8%) and “possible” (25%). Most of the ADRs that were “moderate” in severity on Hart -wig *et al.*’s scale

**Table 4: Highly active antiretroviral therapy-related factors, knowledge, and beliefs related to ART and ADRs reported**

Highly active antiretroviral therapy-related factors	Number of patients <i>n</i> = 50 (%)	Percentage of adherence			<i>P</i> -value
		<80%	80-95%	>95%	
		<i>n</i> = 23	<i>n</i> = 14	<i>n</i> = 13	
<b>ART identification</b>					
By brand name	29 (58)	13 (56.5)	10 (71.4)	6 (46.2)	0.293
By medication wrapper	16 (32)	7 (30.4)	3 (21.5)	6 (46.2)	
By color, shape, size	2 (4)	–	1 (7.1)	1 (7.6)	
Cannot identify	3 (6)	3 (13)	–	–	
<b>Frequency</b>					
Once/day	15 (30)	7 (30.4)	1 (7.1)	7 (53.8)	0.031
Twice/day	35 (70)	16 (69.6)	13 (92.9)	6 (46.2)	
<b>No. of pills/day</b>					
One	12 (24)	6 (26.1)	1 (7.1)	5 (38.5)	0.147
Two	22 (44)	11 (47.8)	5 (35.7)	6 (46.1)	
Three	16 (32)	6 (26.1)	8 (57.2)	2 (15.4)	
<b>Duration of ART</b>					
6 months	21 (42)	7 (30.4)	5 (35.7)	9 (69.2)	0.06
More than a year	29 (58)	16 (69.6)	9 (64.3)	4 (30.8)	
<b>Reason of taking ART</b>					
To prevent progression of HIV	45 (90)	21 (91.4)	14 (100)	10 (76.9)	0.080
To increase CD4 count	1 (2)	1 (4.3)	–	–	
Both	3 (6)	–	–	3 (23.1)	
Don't know	1 (2)	1 (4.3)	–	–	
<b>Attitude of treatment to ART</b>					
Very well	13 (26)	5 (21.7)	2 (14.2)	6 (46.2)	0.373
Okay	18 (36)	8 (34.8)	6 (42.9)	4 (30.8)	
Not well	19 (38)	10 (43.5)	6 (42.9)	3 (23.0)	
<b>Frequency of skipping medication</b>					
Yes, very often	17 (34)	16	1	–	0.487
Sometimes	18 (36)	7	9	2	
No	15 (30)	–	4	11	
<b>Behavior of skipping</b>					
Skip regularly	31 (62)	21 (91.3)	9 (64.3)	1 (7.7)	0.487
Take when remember	3 (6)	2 (8.7)	1 (7.1)	–	
Skip if it's time for the next dose	1 (2)	–	–	1 (7.7)	
Double the dose	15 (30)	–	4 (28.6)	11 (84.6)	
<b>ART affordable?</b>					
Yes	30 (60)	13 (56.5)	10 (71.4)	7 (53.8)	0.582
No	20 (40)	10 (43.5)	4 (28.6)	6 (46.2)	
<b>Knowledge and belief related to ART</b>					
<b>Medications to be taken for whole life?</b>					
Yes	49 (98)	22 (95.7)	14 (100)	13 (100)	0.549
No	–	–	–	–	
Don't know	1 (2)	1 (4.3)	–	–	
<b>Time of medication will affect the effectiveness of treatment?</b>					
Yes	33 (66)	8 (34.8)	12 (85.7)	13 (100)	0.001
No	3 (6)	3 (13)	–	–	
Don't know	14 (28)	12 (52.2)	2 (14.3)	–	
<b>Do you think special instructions are necessary to be followed?</b>					
Yes	34 (68)	9 (39.1)	12 (85.7)	13 (100)	0.001
No	3 (6)	3 (13)	–	–	
Don't know	13 (26)	11 (47.8)	2 (14.3)	–	
<b>Once after getting better Can you stop drugs?</b>					
Yes	29 (58)	5 (21.7)	11 (78.6)	13 (100)	0.001
No	6 (12)	4 (17.4)	2 (14.3)	–	

Contd...

**Table 4: Contd...**

Highly active antiretroviral therapy-related factors	Number of patients <i>n</i> = 50 (%)	Percentage of adherence			<i>P</i> -value
		<80%	80-95%	>95%	
		<i>n</i> = 23	<i>n</i> = 14	<i>n</i> = 13	
Don't know	15 (30)	14 (60.9)	1 (7.1)	–	
Do you know ART is life saving?					
Yes	44 (88)	17 (73.9)	14 (100)	13 (100)	0.091
No	1 (2)	1 (4.3)	–	–	
Don't know	5 (10)	5 (21.7)	–	–	
Adverse drug reactions					
Present	32 (64)	13 (56.5)	12 (85.7)	7 (53.8)	<0.001
Absent	18 (36)	10 (43.5)	2 (14.3)	6 (46.2)	

ART = Antiretroviral therapy; A *P*-value of <0.05 was considered as statistically significant

(71.8%) were required discontinuation of suspected drug (s). Of the 32 ADRs, 69 (87.5%) were “predictable” and 4 (12.5%) were “non-predictable.” The majority of ADRs (53.1%) were “non-preventable,” 18.1% “probably preventable,” and 28.1% were “definitely preventable,” as found by the modified Schumock and Thornton scale. The suspected drug was withdrawn in 62.5% of patients with ADRs.

Symptomatic treatment was instituted in 34.3% of the ADR cases. Most (78.1%) of the patients were recovered while 15.7% had ADRs till the day of discharge. A total of 6.2% of patients with ADRs were discharged from the hospital against medical advice, resulting in an unknown outcome of ADRs. The ADR reported was zidovudin-induced anemia (22%), zidovudin-induced pancytopenia (18.9%), and tenofovir-induced renal failure (12.6%). The organ system affected was red blood cell disorders (43.8%) followed by urinary system disorders (12.5%) as per system organ class codes. Table 6 represents the causality assessment of ADRs. The reasons for the lack of adherence to antiretroviral therapy in our study include ADR/toxicity/side-effects (64%); forgetting to take medication (44%); being too ill (46%); social stigma, disclosure, and privacy issues (14%); drug stock out (8%); patient losing/running out of pill (10%); delivery/travel problems (4%); inability to pay for HAART (70%); depression (8%); and alcohol usage (4%).

## DISCUSSION

This is the first study conducted on Indian HIV-infected patients that explores the association of medication adherence outcomes based on self-report and the occurrence of ADRs to HAART. We found that most (26%) of our patients had good adherence to HAART (greater than 95%) because most of them were married ( $P = 0.048$ , i.e.  $P < 0.05$ ), as marriage favors the disclosure of HIV-positive status to the spouse ( $P = 0.040$ , i.e.  $P < 0.05$ ) and the spouse acts as a great source of social support

(reminding about pill taking, etc.). Our results were comparatively low with other studies Amberbir *et al.*<sup>[13]</sup> and Gifford *et al.*<sup>[14]</sup> Interestingly, in our study, 21.9% of HIV-infected patients refused for interview for adherence assessment due to social stigma and illiteracy.

Most of our patients were well educated, but unable to express their symptoms of adverse drug effects to clinicians due to fear and their personal beliefs regarding intentional non-adherence. This finding is consistent with various studies.<sup>[15-17]</sup> Most of our patients were non-alcoholics ( $P = 0.027$ , i.e.  $P < 0.05$ ) and non-smokers ( $P = 0.039$ , i.e.  $P < 0.05$ ), the traits being positively associated with adherence to antiretroviral therapy. This finding is consistent with various study reports.<sup>[18,19]</sup> In our study, factors such as unemployment and low income (less than INR 5000; less than US\$96.15) were negatively associated with adherence. This might be due to the fact that most of our patients were below the poverty line, even unable to afford their daily food and inability to pay for antiretroviral therapy. This is in accordance with published studies.<sup>[20]</sup>

Our study shows that HIV disclosure to spouse ( $P = 0.04$ , i.e.,  $P < 0.05$ ) was significantly and positively correlated with getting help in taking medicines regularly from family and gaining overall moral support ( $P = 0.03$ , i.e.,  $P < 0.05$ ) from them in order to have good adherence, and significantly indicates that HIV disclosure avoids depressive illness and also psychological stress associated with HIV infection. Similar results have been reported from various studies.<sup>[21-23]</sup>

Patients' knowledge and belief related to antiretroviral therapy in our study was statistically significant ( $P < 0.05$ ) for good adherence with a higher self-efficacy belief, i.e., confidence about one's ability to maintain a behavior regarding their antiretroviral medications. This finding was in accordance with another study<sup>[14]</sup> where it was reported that patients with self-efficacy beliefs were found to have

**Table 5: Demographic details of the patients with adverse drug reactions**

Characteristic	Total number of patients with adverse drug reactions <i>N</i> = 32 (%)
Gender	
Male	27 (84.4)
Female	5 (15.6)
Age group (years)	
18–28	2 (6.3)
29–38	8 (25)
39–48	13 (40.6)
49–58	9 (28.1)
BMI (kg/m <sup>2</sup> )	
18.4	13 (40.7)
18.5–24.5	17 (53.1)
≥25	1 (3.1)
≥30	1 (3.1)
Marital status	
Single	3 (9.3)
Married	23 (71.9)
Widowed	2 (6.2)
Separated	4 (12.6)
Occupation	
Housewife	4 (12.5)
Agriculturist	12 (37.5)
Employed	11 (34.4)
Selfemployed	4 (12.5)
Student	1 (3.1)
Alcoholic	
Regular	4 (12.5)
Occasional	3 (9.4)
Rare	1 (3.1)
Reformed	7 (21.9)
Never	17 (53.1)
Smoker	
Regular	8 (25)
Occasional	--
Rare	1 (3.1)
Reformed	5 (15.6)
Never	18 (56.3)
Complementary treatment	
Yes	4 (12.5)
No	28 (87.5)
HAART status	
HAART experienced	30 (93.7)
HAART defaulter	2 (6.3)
CD4 count (cells/μl)	
≤200	25 (78.1)
>200	7 (21.9)
Occurrence of ADRs	
ADRs during hospital stay	10 (31.2)
ADRs at the time of admission	12 (37.6)
Previous exposure of ADRs	10 (31.2)
Polypharmacy	
Minor (two to three drugs)	4 (12.5)
Moderate (four to five drugs)	12 (37.5)
Major (greater than five drugs)	16 (50)
Highly active antiretroviral therapy implicated in ADRs	

*Contd....***Table 5: Contd...**

Characteristic	Total number of patients with adverse drug reactions <i>N</i> = 32 (%)
Zidovudine + lamivudine + nevirapine	10 (31.5)
Zidovudine + lamivudine + efavirenz	7 (22)
Tenofovir + lamivudine + efavirenz	2 (6.2)
Tenofovir + efavirenz +emtricitabine	2 (6.2)
Nevirapine + stavudine + lamivudine	2 (6.2)
Stavudine + lamivudine + efavirenz	2 (6.2)
Atazanavir + ritonavir + tenofovir	2 (6.2)
Zidovudine + lamivudine	1 (3.1)
Stavudine + lamivudine	1 (3.1)
Atazanavir + ritonavir + tenofovir + emtricitabine	1 (3.1)
Atazanavir + tenofovir + emtricitabine	1 (3.1)
Indinavir + abacavir + tenofovir	1 (3.1)

good adherence to HAART. We found that short- and long-term adverse drug reactions to HAART such as red blood cell disorders, urinary system disorders, skin and appendages disorders, and gastrointestinal system disorders had contributed to non-adherence due to adverse side effects and affected quality of life during HIV treatment.

In our study, the occurrence of anemia and pancytopenia in HIV-infected patients due to the use of zidovudine-containing HAART regimen impacts greatly with its associated symptoms of weakness, fatigue, nausea, and severe vomiting within 4–8 weeks of initiation of zidovudine-containing HAART regimen which leads to medication non-adherence in our patients. These data are in agreement with other studies<sup>[4,24]</sup> demonstrating that either discontinuation of zidovudine to improve the hemoglobin level or a definite need of a change to some other HAART regimen is required for adherence.

In our study, the occurrence of moderate to severe renal dysfunction (12.6%) was highly associated with the use of tenofovir-containing HAART regimen with the signs of proteinuria, fatigue, glucosuria, nausea, and weight loss within 5–12 months of initiation resulting for non-adherence. The renal function test and other laboratory values returned to normal within a few months after tenofovir discontinuation.

Our study highlights the use of tenofovir-containing HAART regimen which was associated with a small,



**Table 6: Causality assessment of adverse drug reactions**

Assessment of adverse drug reactions	Number of ADRs, n = 32 (%)
Causality of ADRs	
WHO probability scale	
Certain	6 (18.8)
Probable	16 (50)
Possible	10 (31.2)
Naranjo's scale	
Definite	2 (6.2)
Probable	22 (68.8)
Possible	8 (25)
Severity (Hartwig <i>et al.</i> 's scale)	
Mild	9 (28.2)
Moderate	23 (71.8)
Severe	Nil
Predictability	
Predictable	28 (87.5)
Non predictable	4 (12.5)
Preventability (Modified Schumock and Thornton's scale)	
Definitely preventable	9 (28.1)
Probably preventable	6 (18.8)
Not preventable	17 (53.1)
Management of ADRs	
Drug withdrawn	20 (62.5)
Dose altered	Nil
No change	12 (37.5)
Treatment given	
Specific	13 (40.7)
Symptomatic	11 (34.3)
No change in treatment	8 (25)
Outcome of management of ADRs	
Recovered	25 (78.1)
Continuing	5 (15.7)
Unknown	2 (6.2)
Dechallenge	
No dechallenge	11 (34.3)
Definite improvement	19 (59.5)
Unknown	2 (6.2)
Rechallenge	
No rechallenge	30 (93.8)
No occurrence of symptoms	1 (3.1)
Unknown	1 (3.1)
Adverse drug reactions reported	
Anemia	Zidovudine 7 (22)
Pancytopenia	Zidovudine 6 (18.9)
Leucopenia	Zidovudine 1 (3.1)
Renal failure	Tenofovir 4 (12.6)
SJS and TEN	Nevirapine 3 (9.3)
Sensory neuropathy	Stavudine 2 (6.2)
Hepatitis	Stavudine 2 (6.2)
Hyperbilirubinemia	Atazanavir 1 (3.1)
Maldistribution	Atazanavir 1 (3.1)
Insomnia	Efavirenz 1 (3.1)
Vomiting	Zidovudine 1 (3.1)
IRIS	Efavirenz 1 (3.1)

Contd...

**Table 6: Contd...**

Assessment of adverse drug reactions	Number of ADRs, n = 32 (%)
Gastritis	Efavirenz 1 (3.1)
Fever	Zidovudine 1 (3.1)
System organ class codes WHO-ART	
Red blood cell disorders (1210)	14 (43.8)
Urinary system disorders (1300)	4 (12.5)
Skin and appendages disorders (0100)	3 (9.3)
Gastrointestinal system disorders (0600)	2 (6.3)
Central and peripheral nervous system disorders (0410)	2 (6.3)
Liver and biliary system disorders (0700)	2 (6.3)
White cell and RES disorders (1220)	1 (3.1)
Psychiatric disorders (0500)	1 (3.1)
Metabolic and nutritional disorders (0800)	1 (3.1)
Body as a whole – general disorders (1810)	1 (3.1)
Resistance mechanism disorders (1830)	1 (3.1)

SJS = Steven Johnson syndrome; TEN = Toxic epidermal necrolysis; IRIS = Immune reconstitution inflammatory syndrome

increased risk of grades 3–4 nephrotoxicity. In one of the four cases of tenofovir-induced renal failure, even after tenofovir discontinuation, the renal function test was abnormal and dialysis was performed. Our study findings are similar to a study<sup>[25]</sup> where a similar type of nephrotoxicity with tenofovir usage was observed in HIV-infected patients.

In our study of HIV-infected patients (9.3%), cutaneous drug eruptions, i.e., Steven–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) were observed with protease inhibitors and most commonly nevirapine. This adverse drug reaction was presented in our patients with symptoms of painful swallowing, fever, stinging eyes, followed by the development of erythematous macules that progressed to flaccid blisters. SJS and TEN were managed by discontinuation of nevirapine and with supportive measures of intravenous fluid administration, antimicrobial therapy, electrolyte maintenance, and skin care. These observations are in agreement with the previously published study.<sup>[26]</sup>

In our study, we found that antiretroviral, toxic sensory neuropathy was observed in 6.2% of patients who were on nucleoside reverse transcriptase inhibitors (NRTIs), especially stavudine-containing HAART. Two patients who exhibited stavudine-induced sensory neuropathy were also suffering from depression due to chronic pain associated with neuropathic symptoms such as numbness, burning pain, and hyperesthesia resulting for nonadherence to antiretroviral therapy. Sensory neuropathy was managed by discontinuation of stavudine therapy, and the patient was

also started on amitriptyline, 10 mg HS, for relief of pain and depression management. Our findings are similar to those of other studies<sup>[27,28]</sup> conducted elsewhere.

In our study, a patient with stavudine-containing HAART developed symptoms of liver disease during the first 2–3 months of HAART initiation, but the patient did not tell the physician about symptoms of adverse effects which resulted intentional non-adherence to HAART for a period of 10 days. Further, the patient was then presented to our HIV clinic with hepatomegaly with a fatty liver and lactic acidosis. Liver biopsy and an abnormal liver function test confirmed acute hepatitis. The offending drug stavudine was withdrawn and treatment was continued along with atazanavir + ritonavir + tenofovir combination. This finding is concurrent with another study.<sup>[29]</sup>

During this study, hyperbilirubinemia was observed in one patient who was on atazanavir-containing HAART regimen. A total of 3.1% of patients developed elevated indirect bilirubin levels, and after discontinuation of atazanavir, we found that indirect bilirubin levels and liver function tests were normal, similar to the finding of a study.<sup>[30]</sup> In our study, fat maldistribution was reported in one patient within first 6 months of atazanavir-containing HAART regimen. This finding is concurrent with the study carried out by Paterson *et al.*<sup>[2]</sup> Similar to other studies,<sup>[31-33]</sup> central nervous system effects such as insomnia were reported in our patient during the first 3 days of efavirenz therapy. The patient who experienced insomnia due to efavirenz therapy was tolerable to the adverse effect, when the daily dose of efavirenz was administered on an empty stomach, at bed-time.

In our study, gastrointestinal effects such as vomiting and anorexia were observed as a cause for non-adherence to antiretroviral therapy in one patient with asymptomatic HIV infection who was on zidovudine therapy during the first week. Gastrointestinal symptoms and HIV disease are more common in developing countries while opportunistic infection such as mycobacterium avium complex and cytomegalovirus are more in developed countries. However, these gastrointestinal symptoms were self-limiting. These findings are in agreement with another study.<sup>[34]</sup>

During the present study, one patient experienced immune reconstitution syndrome during initial treatment with combination antiretroviral therapy, including efavirenz and zidovudine. This patient developed an inflammatory response to opportunistic infections with *Pneumocystis carinii* pneumonia and cytomegalovirus infection. Our

findings are similar to those of other studies<sup>[35,36]</sup> conducted elsewhere.

## CONCLUSION

Our study shows that the level of antiretroviral medication adherence in HIV patients was less than 80% in 46%, 80%–95% in 28%, and greater than 95% in 26% patients. Clinicians need to pay attention to make the HIV patient understand about the importance of good adherence to antiretroviral therapy. The need for awareness of possible side effects of antiretroviral therapy will be an essential method for the early prevention of ADRs.

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