



Original Research Article

Drug utilization evaluation of the antiretroviral regimen: A prospective observational study

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ABSTRACT

Background: An estimated 36.7 million people are infected with HIV. Despite the availability of free ART services, deaths due to AIDS still exist, and the prevalence of HIV is still high. The aim of the present study was to evaluate the utilization pattern, safety, efficacy and adherence to the ART regimen and to determine the prevalence of OIs in HIV infected patients.

Subject and Methods: A prospective observational study was conducted in a tertiary care hospital on subjects who were prescribed ART. Prescribed treatment was co-related with NACO guidelines. MMAS questionnaire was used for the assessment of adherence. Multivariate and univariate logistic regression was used to assess the factors influencing treatment co-relation of the given regimen and adherence of ART. ADRs were also assessed for their causality, severity, and preventability as per the standard algorithm and bivariate analysis with odds ratio.

Results: Out of patients evaluated, prescriptions of 76% were complying with guidelines. On the MMAS scale, 72 % of patients were adherent and most common reason for non-adherence was forgetting to take medications (38.3%). Tuberculosis (54.1%) was the most common opportunistic infection, most common regimen which caused ADR's was ZLN and most common ADR was rash (56%). On the evaluation of the causality of ADRs, the majority were probable, the severity assessment showed most patients with ADRs were of level 3 and the preventability assessment showed all observed ADRs were non-preventable.

Conclusion: Most patients were prescribed initial treatments in agreement with the guideline to achieve maximal and durable suppression of viral load. The prevalence of commonly reported OIs HIV-infected individuals demands the need for early screening and to increase awareness in healthcare providers in order to improve decisions regarding prophylaxis for prevention and adequate therapeutic planning. A healthcare professional must monitor adverse effects and adherence efficiently.

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INTRODUCTION

An estimated 33 million people are infected with HIV (Human Immunodeficiency Virus) worldwide (Anonymous, 2013). With the advent of HAART (Highly Active Antiretroviral Therapy), HIV-1 infection is now manageable as a chronic disease in patients who have access to medication. HAART provides effective treatment options for treatment-naïve and treatment-experienced patients (Suarez-Lozano et al., 2009).

The use of ART (Antiretroviral therapy) in clinical practice is mainly based on the ease or complexity of use, side-effect profile, efficacy based on clinical evidence, practice guidelines, and clinician preference of the drugs. The study of the correlation between prescribing patterns and guidelines is essential for recommendations that inform physicians what not to do so as to avoid harm and for recommendations that inform physicians what to do so as to improve efficacy (Holodny et al., 2007).

Adherence to ART is well recognized to be an essential component of individual and programmatic treatment success. In order for ART to work, clients have to stringently stick to the regime of medications. Higher levels of adherence are associated with improved virological and clinical outcomes (Suarez-Lozano et al., 2009). Therefore adherence can be improved by counseling patient and keeping a regular check on his drug use (Steele and Grauer, 2003). Failure to do so can undermine the effectiveness of the treatment and viral load can increase faster than it would have, otherwise. The expected results were to provide evidence what to address and/or promote to scale up the adherence (Steele and Grauer, 2003).

Our study aimed to assess the correlation between prescription and standard prescribing guidelines, coinfections prevalence in HIV infected patients, ADRs (Adverse drug reactions) associated with the ART medication and patient adherence to the medication. This study would serve as a resource for further research and for developing new protocols for improvement in future.

SUBJECTS AND METHODS

The study and Participants

The study protocol was approved by the Institutional Ethical Committee (MCP/PD/PR/08) before starting the study. Informed consent was obtained from the patient in English, Urdu, and Telugu. A prospective observational study was conducted in the tertiary care hospital, Hyderabad, India. A total of 150 cases were studied. The duration of the study was 6 months. Subjects of all age groups on antiretroviral therapy with HIV infection and HIV with opportunistic infections in outpatient and inpatient department were enrolled in the present study with or without symptoms of HIV infection with their respective CD4 (Cluster of Differentiation 4) counts. Patients attending the outpatient clinic for regular follow-up and to take medicine were approached for interview who gave an active consent in the study. Patients who were not willing to participate in the study, pregnant, lactating women and patients <10 years of age were excluded from the study.

Data collection forms based on the study objectives were prepared to look into patient's socio-demographics, ART adherence, as well as ART side effects information, were made by taking into consideration all ART medications which were prescribed by the physician to the patient. The proforma contained patient identification data, personal history, family history, risk factor details, Antiretroviral treatment history, Antiretroviral treatment, laboratory investigations, ADR details & its assessment and patient follow-up details. Essential laboratory investigations such as hemoglobin (Hb), total leukocyte count, differential leukocyte count, erythrocyte sedimentation rate, serum creatinine, blood urea, serum bilirubin, SGOT (Serum Glutamic Oxaloacetic Transaminase), SGPT (Serum Glutamic Pyruvic Transaminase), blood sugar, VDRL (Venereal

Disease Research Laboratory), HBsAg (Hepatitis B Surface Antigen), anti-HCV (Anti-Hepatitis C Virus Test) and CD4 count. Additional laboratory investigations like chest X-ray was done, whenever needed. Data were also evaluated for patient demographics, risk factors for ADRs and type of ADR. Treatment given to HIV patients was correlated with standard NACO guidelines. Cases of HIV with Pre-ART, ART and other drug therapy for co-infections were also documented. Medication adherence was evaluated using eight questions of MMAS (Morisky Medication Adherence Scale) in HIV patients and was reported.

Finally, the observed results were calculated statistically and reported.

Assessment

Assessment of treatment co-relation

The treatment given to the patient was correlated with the standard NACO (National AIDS Control Organisation) Guidelines based on the: CD4 cell count, Complete Blood picture (especially Hemoglobin), the presence of OIs especially Tuberculosis or any adverse effect of the drugs in the given treatment regime. Patient's present complaints were co-related with the drugs that were prescribed by the physician to evaluate the treatment being given.

Assessment of adherence

Adherence was measured using self-reported data, pill counts and attendance and pharmacy records. Eligible patients were interviewed for 10-20 minutes. In addition, a proforma was used to collect data regarding a number of medications taken, the number of doses missed, socio-demographic information, family support and reasons for not taking medications as prescribed.

Adherence Rate was calculated by dividing the number of pills actually taken by the number of pills prescribed during one month multiplied by 100. Adherence was defined as value > 95 %. Adherence rate is equal to

The eight questions Morisky Medication Adherence Scale with scores ranging from 1 to 13 was used to measure adherent behavior. Score > 11 indicates adherence to medication.

Assessment of opportunistic infections in HIV

In this study, the most commonly included measurement is CD4 cell count the assessment of the prevalence of opportunistic infections in HIV patients. OIs were diagnosed on the basis of clinical evaluation supported by appropriate lab investigations. Demographic and clinical data were captured at each follow-up visit. Patients with baseline CD4 counts of <200cells/mm³ were six times more likely to develop OIs compared to those with CD4 counts of >350cells/mm³

Assessment of adverse reaction

The study evaluated the suspected adverse drug reactions based on the patient's symptoms from the Case study forms. This tool included sections on the patient's demographics, ADR description, treatment, the outcome of the reaction, suspected drug details and the concomitant medicines. ADRs were also assessed

for their causality, severity, and preventability using Naranjo's algorithm, Hartwig scale (and Shumock and Thornton criteria respectively). The reported ADRs were assessed for causality by using Naranjo's algorithm scale, once complete data of patient was taken, ADRs were classified as "definite", "probable", "possible" and "doubtful" based on Naranjo causality assessment scale for ADRs. The probability scale is based on the total score; ≤ 0 doubtful, 1 to 4 possible, 5 to 8 probable and ≥ 9 definite causality assessment scale criteria are based on the score ranging from +2 to -1 given for each. To study the severity of ADR's, Hartwig's scale was used. This scale categorizes the reported adverse drug reactions into different levels. The preventability assessment was done by using modified Shumock and Thornton criteria. Any answer of "yes" to any question suggests that the ADR might have been preventable.

Statistical analysis

The information collected from the respondents were sorted, coded and entered in datasheet created in Statistical Package for Social Science (SPSS).

RESULTS

The subjects were studied in the in-patient and ART Centre (i.e. out-patient) setting of the hospital. The study was initiated in order to study the utilization pattern, safety and efficacy of antiretroviral drugs, adherence of patient to the antiretroviral therapy and prevalence of co-infection in HIV infected patients.

Distribution of patient pool as per age and gender

All the HIV patients studied were classified as per age group and gender. A total of 150 patients receiving ART were evaluated in the in-patient and ART centre (i.e. out-patient) setting of the tertiary care hospital. Majority of the patients in study belonged to the age group 31-40 years (46%), followed by age group of 20-30 years (28%). Only few patients of age group 61-70 years (0.6%) and 10-19 years (1%) were included. The study had predominance of adults (92%) over children (1%) and geriatrics (5%). Among the subjects studied, 44% were male subjects and 56% were female subjects.

Table 1. Distribution of patient pool as per age.

S. No.	Age	No. of patients observed	Percentage
1.	10-19	2	1%
2.	20-30	42	28%
3.	31-40	69	46%
4.	41-50	28	18%
5.	51-60	8	5%
6.	61-70	1	0.6%
7.	71-80	0	0%

Table 2. Distribution of patient's pool as per gender.

Gender	No. of Patients observed	Percentage of patients observed
Male	66	44%
Female	84	56%

Frequency of various ART regimens prescribed to HIV infected patients at the ART centre

From the total number of prescriptions studied, maximum number of prescriptions contained ZLN (Zidovudine + Lamivudine + Nevirapine) (55%) as the treatment regimen. Followed by TLE (Tenofovir + Lamivudine + Efavirenz) (27%) ranking a second place. The rest of the regimens like ZLE (Zidovudine + Lamivudine + Efavirenz), TLN (Tenofovir + Lamivudine + Nevirapine), SLN (Stavudine + Lamivudine + Nevirapine), SLE (Stavudine + Lamivudine + Efavirenz) were rare in the prescriptions collected. It was observed that ZLN regimen (31%) was mostly prescribed in females patients when compared to male patients with 23% of ZLN. Then followed by TLE regimen, (16%) was prescribed in male patients when compared to female patients with 14% of TLE. There was no significant difference in regimen with respect to gender.

Treatment correlation with guidelines

The treatment was correlated with NACO (National AIDS Control Organisation) guidelines. Out of 150 cases collected, we found prescriptions of 114 (76%) cases complying with guidelines and prescriptions of 36 (24%) cases not complying with guidelines. The treatment was correlated with haemoglobin values; CD4 and any co-infection present (especially TB).

Table 3. Distribution of ART regimen in prescriptions collected.

S. No.	Drug regimen used	Frequency of drug prescription	% of Drug regimen prescribed
1.	ZLN	83	55%
2.	ZLE	10	6%
3.	TLE	41	27%
4.	TLN	7	4%
5.	SLN	6	4%
6.	SLE	1	0.6%
7.	PRE ART	2	1.3%

ZLN=Zidovudine+Lamivudine+nevirapine
 ZLE=Zidovudine+lamivudine+efavirenz
 TLE=Tenofovir+lamivudine+efavirenz
 TDF/3TC=Tenofovir+lamivudine
 SLN=Stavudine+lamivudine+nevirapine
 SLE=Stavudine+lamivudine+efavirenz
 TLN=Tenofovir+lamivudine+nevirapine
 PRE ART=Sepran DS
 NVP=Nevirapine

Table 4. Distribution of ART regimen in patients with respect to gender.

S. No.	Drug regimen used	Frequency of regimen in prescription		% of regimen in prescription	
		Males	Females	Males	Females
1.	ZLN	35	46	23%	31%
2.	ZLE	7	6	5%	4%
3.	TLE	24	21	16%	14%
4.	TLN	1	2	0.6%	1%
5.	SLN	0	4	0%	3%
6.	NVP	0	0	0%	0%
7.	TDF/3TC	0	2	0%	1%
8.	PRE-ART	1	1	0.6%	0.6%

Table 5. Percentage of Prescriptions complying & not complying with the guidelines.

S. No.	Prescriptions observed	No. of prescriptions	% of prescriptions
1.	Prescriptions complying with guidelines (PCG)	114	76%
2.	Prescriptions not complying with guidelines (PNCG)	36	24%

CD4: Most of the patients (except some TB patients) were started therapy when the CD4 count was below 350. CD4 before initiation of treatment and 6 months after treatment initiation was analyzed using student t-test (paired) and was found to be significantly different with a p-value of <0.0001 ($p < 0.0005$).

Logistic regression for factors associated with treatment: The variables associated with treatment were analyzed using univariate analysis and

multivariate analysis. By univariate analysis, it was found that Hemoglobin with a p-value of 0.0004 ($p < 0.05$) was found to be statistically significant with the treatment. By multivariate analysis, it was found that Hemoglobin with a p-value of 0.0004 ($p < 0.05$) was found to be statistically significant with the treatment. The variable hemoglobin was more strongly influencing the treatment than the variable Co-infection.

Table 6. Logistic regression for factors associated with treatment.

Univariate analysis				
S. No.	Variable	P-value	Odds Ratio	95% Confidence interval(CI)
1.	Co-infection	0.0598	0.2685	0.0683-1.0557
2.	Hemoglobin	0.0004	38.7333	5.0433-297.4767
Multivariate analysis				
S. No.	Variable	P-value	Odds Ratio	95% Confidence interval(CI)
1.	Co-infection	0.0511	0.2406	0.0575-1.0068
2.	Hemoglobin	0.0004	40.0365	5.1887-308.9248

Medication Adherence: The MMAS adherence questionnaire was used for data collection.

Percentage of patients adhering to medication regimen from the start of treatment: Out of 150 patients enrolled in the study, the percentage of

patients adhering to medication regimen from the start of treatment was found as 2 (1.3%) patients showed a range 1-20% of adherence, 8(5.3) patients showed a range of 20-40%, 21(14%) patients showed a range of 40-60%, 26 (17.3%) patients showed a range of 60-80% , 93(62%) patient showed a range of 81-100%.

Table 7. Percentage of patients adhering to medication regimen from the start of treatment.

S. No.	% Range of the Adherence from the start of treatment	No of patients adhering	% of patients adhering
1.	1-20%	2	1.3%
2.	20-40%	8	5.3%
3.	40-60%	21	14%
4.	60-80%	26	17.3%
5.	80-100%	93	62%

Percentage of patients adhering to medication regimen (previous month) MMAS

On the MMAS scale the number patients who were adherent to the treatment regimen was 108 (72%)

having a summary score of >11 (i.e. adherent) and patients with low adherence were 42 (28%) with score of 5-8. The range of summary score was from 5 to 13, with a mean summary score of 11.04 (sd = ± 1.7).

Table 8. Percentage of patients adhering to medication regimen (previous month) MMAS scale.

S. No.	MMAS Adherence scale	MMAS score	No. of patients	% of Patients
1.	Low Adherence	5-10	42	28%
2.	Adherent	11-13	108	72%

Table 9. Assessment of Morisky scale.

S. No.	QUESTIONS	No. of patients	% of patients
1.	Ever forget to take medicine?	50	38.3%
2.	Miss medication for reason other than forgetting, over the past 2 weeks there any day days when you did not take medicine?	55	36.6%
3.	Have cut back medicine without the doctor's knowledge?	24	16%
4.	Have forgotten medicine while travelling?	27	18%
5.	Missed medicine previous day?	6	4%
6.	When feel like symptoms under control do sometime stop taking medicine?	12	8%
7.	Feel hassled about sticking to treatment?	45	30%
8.	Difficulty in remembering treatment		
	▪ Never	84	56%
	▪ Rarely	12	8%
	▪ Once in a while	26	17.3%
	▪ Sometimes	23	15.3%
	▪ Usually	5	3.3%
	▪ All the time	0	0

Table 10. No of patients showing adherence or low adherence with respect to factors.

S. No.	Factors	Adherent	Low Adherence	
1.	Age	≤ 40 years	50	27
		>40 years	55	18
2.	Sex	Male	42	23
		Female	63	22
3.	Occupation	Employed	44	20
		Unemployed	61	25
4.	Income	>8000	43	18
		≤8000	62	27
5.	Education	Secondary school and above	52	23
		Up to primary	53	22
6.	Marital status	Married	86	41
		Single	19	4
7.	Locality	Urban	72	21
		Rural	33	24
8.	CD4	<200	31	17
		>200	74	28
9.	Regimen	ART	84	21
		ART +others	37	8
10.	Problems in remembering	Yes	41	38
		NO	64	7
11.	Find treatment to be difficult	Yes	33	34
		No	72	11
12.	Have told about medicines	Yes	58	24
		No	47	21

Assessment of Morisky medication adherence scale (MMAS)

Out of 150 patients, observation of the patient's responses on individual questions in the MMAS scale, suggested that 38.3 % of the respondents confessed to have sometimes forgotten medications, 36.6% had forgotten pills in the 2 weeks before interview. A total of 27 patients (18%) had not taken medication while they were travelling, 6(4%) patients had not taken medications a day before being interviewed, 24(16%) stopped medications without telling their doctor, 12(8%) patients did not take medications because they felt better and thought that disease was now under control, while 45(30%) of patients felt hassled about sticking to treatment.

Logistic regression for adherence

The socio- demographic factors that are associated with adherence was analyzed using the univariate analysis and multivariate analysis. By univariate analysis, it was found that CD4 with a p-value of 0.0124 ($p < 0.05$), problems in remembering treatment with a p-value of 0.00 ($p < 0.05$) and finding treatment to be difficult with a p-value of 0.000 ($p < 0.05$) was found to be statistically significant with the adherence. By multivariate analysis, it was found that CD4 with a p-value of 0.0019 ($p < 0.05$), problems in remembering treatment with a p-value of 0.00 ($p < 0.05$) and finding treatment to be difficult were found to be statistically significant with the adherence.

Table 11. Univariate analysis for adherence.

S. No.	Factor	Chi square	P-value	Odds Ratio	95% interval(CI)	Confidence
1.	Age	1.9347	0.1661	0.6061	0.2983-1.2312	
2.	Gender	1.5761	0.2096	0.6377	0.3157-1.2879	
3.	Occupation	0.0829	0.7732	0.9016	0.4458-1.8235	
4.	Income	0.0119	0.9133	1.0403	0.5104-2.1203	
5.	Education	0.0317	0.8586	0.9385	0.4667-1.8871	
6.	Locality	2.2427	0.1601	0.4416	0.1411-1.3815	
7.	CD4	6.3139	0.0124	2.4935	1.2185-5.1026	
8.	Marital status	0.9711	0.3218	0.6900	0.3311-1.4377	
9.	Regimen	0.1010	0.7523	0.8649	0.3511-2.1304	
10.	Problems in remembering treatment	28.1353	0.000	0.1180	0.0482-0.2892	
11.	Find treatment to be difficult	25.4586	0.000	0.1483	0.0670-0.3284	
12.	Have told about medicines	0.0461	0.8300	1.0798	0.5358-2.1759	

Table 12. Multivariate Analysis for adherence.

S. No.	Factor	P-value	Odds Ratio	95% interval(CI)	Confidence
1.	Age	0.1509	0.4813	0.1775-1.3054	
2.	Gender	0.3132	0.5662	0.1875-1.7101	
3.	Occupation	0.5079	0.6751	0.2109-2.1605	
4.	Income	0.7165	1.2178	0.4205-3.5267	
5.	Education	0.7837	1.1533	0.4166-3.5267	
6.	Locality	0.0932	0.2986	0.0728-1.2245	
7.	CD4	0.0019	5.4476	1.8728-15.8454	
8.	Marital status	0.5970	1.3137	0.4778-3.6118	
9.	Regimen	0.52726	0.6840	0.2094-2.2342	
10.	Problems in remembering treatment	0.000	0.0972	0.0317-0.2987	
11.	Find treatment to be difficult	0.000	0.1163	0.0413-0.3276	
12.	Have told about medicines	0.8004	1.1287	0.4416-2.8852	

Reasons for non adherence

The reasons for non adherence were evaluated, it was found that forgetting (38.3%), being away from home (27%), fear of side effects (6%), did not want others to

know (40%), no improvement on medications (10%), too busy in other work (20%), felt better hence did not take pills (8%), too many pills (9%) and others (13%) were the most common causes of missing the pills.

Table 13. Reasons for non-adherence.

S. No.	Reasons for non-adherence	No of patients	% of patients
1.	Were out of home/were traveling	27	18%
2.	Too busy in other work	30	20%
3.	Forgot to take pills	50	38.3%
4.	Felt better hence did not take pills	12	8%
5.	Did not want others to know	40	26%
6.	No improvement on medications	15	10%
7.	Fear of side effects	10	6%
8.	Too many pills	14	9%
9.	Others	20	13%

Co-infections observed in HIV patients

From the total number of patients observed, it was noted that tuberculosis was the most common opportunistic infection with an incidence of 54.1%, followed by herpes z genitalis (29.1%), inguinal lymphadenopathy (8.3%), pruritic folliculitis (4.1%) and lower respiratory tract infection (4.1%). It was observed that 37.5% of male patients were suffering from most common tuberculosis opportunistic infection when

compared with female patients (16.6%). Then herpes z genitalis infection was observed in 16.6% of male patients when compared with female patients (12.5%). We found that ZLN was most commonly prescribed in individuals suffering from co-infections, followed by ZLE, TLE and least is PRE-ART regimen (Septran DS).

Table 14. Percentage of co-infections observed.

S. No.	Co-infections Observed	No. of co-infections	% of co-infections
1.	Lower Respiratory Tract Infection	1	4.1%
2.	Tuberculosis	13	54.1%
3.	Inguinal Lymphadenopathy	2	8.3%
4.	Pruritic folliculitis	1	4.1%
5.	Herpes Z genitalis	7	29.1%

Table 15. Percentage of co-infections observed in patients with respect to gender.

S. No.	Type of co-infections	Frequency of co-infections observed		% of co-infections observed	
		Male	Female	%male	%female
1.	Lower respiratory tract infection	0	1	0%	4.16%
2.	Tuberculosis	9	4	37.5%	16.6%
3.	Inguinal lymphadenopathy	1	1	4.16%	4.16%
4.	Pruritic folliculitis	0	1	0%	4.16%
5.	Herpes Z genitalis	4	3	16.6%	12.5%

ADRs**Percentage of ADRs observed with ART regimen:**

Out of 150 patients studied, 16 ADRs were observed in the ART regimens. Most common regimen which caused ADRs was ZLN (68%), followed by TLN (18%). Less number of ADRs was due to ZLE, TLE (i.e. 6% each). Most common types of ADRs were rash (56%) and anemia (25%).

Type of ADR and its assessment

On evaluation of the causality of ADRs, majority of it were found to be probable (81%). The severity assessment showed that most of the patients with ADRs were of level 3 (68%). The preventability assessment showed that all observed ADRs were non-preventable.

Bivariate regression analysis was performed to analyze the relationship between ADRs observed and ART regimen used. The statistical analysis indicates a negative relationship between ART regimens used and the frequency of ADRs observed (P value=0.2).

Odds ratio was also carried out to compare the prevalence of ADR with the use of a particular treatment regimen in males and females. Odds ratio for ZLN was found to be 0.62. This concluded that there is 0.6% chances of ADR with ZLN in males compared to females. Similarly the ratio was carried out for ZLE, TLN, TLE which showed similar chances of developing ADRs with the regimens in males and females.

Table 16. Distribution of characteristics of patients on ART who had the ADRs.

S. No.	Characteristic	Frequency	Percentage
1.	Gender		
	Male	7	50%
	Female	7	50%
2.	Age		
	11-20	1	6%
	21-30	4	25%
	31-40	7	43%
	41-50	2	12%
3.	Regimen		
	ZLN	11	68%
	ZLE	1	6%
	TLN	3	18%
	TLE	1	6%

Table 17. Type of ADR and its assessment.

S. No.	ADR type & assessment	N=16	Percentage
1.	ADR Type		
	Rash	9	56%
	Anemia	4	25%
	Lactic Acidosis	1	6%
	Peripheral neuropathy	1	6%
	Acute kidney injury	1	6%
2.	Causality assessment		
	Possible	3	18%
	Probable	13	81%
3.	Severity assessment		
	Level 1	2	12%
	Level 3	11	68%
	Level 4	4	25%
4.	Preventability assessment		
	Preventable	0	0%
	Non preventable	16	100%

Table 18. Odds ratio.

Odds ratio for ZLN (N=83)		
	With ADR	Without ADR
Males	3	33
Female	6	41
The ratio was found to be 0.62. This concluded that there is 0.6% chances of ADR with ZLN in males compared to females.		
Odds ratio for ZLE (N=10)		
	With ADR	Without ADR
Males	1	3
Female	0	6
Odds ratio for TLN (N=7)		
	With ADR	Without ADR
Males	3	0
Female	0	4
Odds ratio for TLE (N=41)		
	With ADR	Without ADR
Males	0	16
Female	1	24

*remaining 9 (of 150 sample size) patients were prescribed different regimen.
Similarly the ratio was carried out for ZLE, TLN, TLE which showed similar chances of developing ADRs with the regimens in males and females.

DISCUSSION

This prospective study was conducted in General Medicine department of a tertiary care, teaching hospital for about 6 months. The subjects were studied in the inpatient and out-patients (i.e. ART Centre) setting of the hospital. The study was initiated in order to study the utilization pattern, safety and efficacy of Anti-retroviral drugs, adherence of patients to the Anti-retroviral therapy and prevalence of co-infections in HIV infected patients. CPG (Clinical practice guidelines) are important sources of information used to disseminate advances in scientific knowledge, to help doctors make clinical decisions and to minimize variability in clinical practice (Suarez-Lozano et al., 2009). The co-relation between prescribing patterns and guidelines was greatest for recommendations that inform physicians what not to do so as to avoid harm rather for than recommendations that inform physicians what to do so as to improve efficacy (Holodniy et al., 2007).

In our study, the Anti-retroviral regimen was appropriate in most of the cases. Most patients were prescribed initial Anti-retroviral drug combinations in agreement with the NACO guideline recommendations, in accordance with the study performed by Suarez Lozano et al. (2009), who also found that initial treatments were prescribed mostly according to guidelines. The most commonly prescribed ART regimen in our study for adult patients was ZLN (55%) and the second most commonly prescribed was TLE (27%). 76% of the prescriptions of ART given to patients were complying and 24% of the prescriptions were not complying with the guidelines. The percentage of prescriptions which were not complying with the guidelines were mostly given TLE due to its less side effect profile.

Our study found that almost all patients (96%) were started ART below the CD4 cell count threshold (<350 cells/mL) except some patients with co-infection TB (2.6%), which was in accordance with the study performed by Holodniy, et al. (2007), in US showed that on average, 60% had a CD4 count 350 cells/mL when treatment was initiated. Our study also found that the patients who were on Pre-ART (1.3%) did not receive any Antiretroviral therapy. The student's t-test analysis showed a significant difference of CD4 count before initiation of the ART and 6 months after initiation of the ART. CD4-T-cell count and hemoglobin were the more accurate surrogate marker for clinical outcome and were increasingly used to assess prognosis before starting treatment and to monitor the progress of disease during treatment according to the study performed by Kalokoni (2010). In univariate and multivariate analysis hemoglobin was found to be strongly influencing the treatment than co-infection (TB).

The MMAS adherence questionnaire was used to check the adherent behavior of the patients. On the MMAS scale the number patients who were adherent to the treatment regimen were 108 (72%) having a summary score of >11 (i.e. adherent), in accordance with the

study performed by Gokarn et al. (2009), on Adherence to Antiretroviral Therapy in the Department of Medicine in a tertiary care hospital which concluded the adherence to ART was high. The most common reasons for missing pills were found to be forgetting and being busy in some other work, in contrast, to study performed by Gokarn, et al. (2009), who found that the most common reasons for missing pills were being out of home or travelling, being busy in some other work and side effect and correlates with the study conducted by Shigdel et al. (2012), who concluded that the main reasons accounted for non-adherence were patients simply forgetting to take ART and having a busy schedule.

The univariate and multivariate logistic regression analysis of socio-demographic factor, socio-economic and other factors related to adherence were studied. In univariate analysis as well as multivariate analysis CD4, Problems in remembering treatment and finding treatment to be difficult were found to be statistically significant with the adherence, in contrast to the study by Gokarn, et al. (2009), who concluded that on univariate analysis, age and marital status were significantly associated with adherence and on multivariate analysis, age was significantly associated with adherence. The patient was counseled for improving the adherence.

The most frequent Co-infection in HIV patients was tuberculosis (54.1%) followed by herpes Z genital disease (29.1%) in our study which was in accordance with the study performed by Ghatge et al. (2009), who also found that Tuberculosis was the most common OI followed by herpes z genitals. Since the epidemiology, clinical manifestations and management of both HIV and TB infections are of more complex in co-infected patients, thus the effort to control HIV related TB and herpes Z genital disease, its prevention are matters of great urgency.

Our study found the age group of 31-40 years (43%) more prone to ART-induced ADRs, in contrast to the study performed by Srikant et al. (2012), performed in Kadapa, India who found age group of 17-40 years was more affected. and Agu and Oparah (2013) performed the study in Nigeria and found age group of 16-45 years was more affected.

The incidence of ADRs to ART in males and females did not show any difference (males 50%, females 50%), in contrast to the study performed by Srikant et al. (2012) which showed the majority of ADRs were observed in males (60%). ZLN was the most common regimen which caused ADRs like the study from Nigeria, and in contrast to the study performed by Singh et al. (2010), Chhattisgarh that found SLN was the most common regimen which caused ADRs. Our study observed that majority of ADRs were due to drug regimens containing Nevirapine in contrast to the study conducted by Agu and Oparah (2013) which concluded that ADRs were less likely to occur in patients on stavudine-based and

tenofovir-based regimens compared to zidovudine-based regimens.

Various ADRs observed include skin rash and anemia due to nevirapine and in rare cases due to efavirenz (EFV), tenofovir-induced AKI and zidovudine-induced lactic acidosis, ZLN induced peripheral neuropathy. In our study, rash (56%) and anemia (25%) were found to be the most common type of ADR. A study by Sharma et al. (2008), Vadodara, India unlike our study, found that cutaneous ADR was most common (44.4%), then next was hematological ADR (32.2%). In another study by Kumarasamy et al. (2003), the most common ADRs were peripheral neuropathy, anemia, and nail hyperpigmentation. A study by Sivadasan et al. (2009), clearly showed that adverse effects of various drugs of the HAART regimen were one of the major reasons for treatment change. Anemia (25%) was seen with ZLN/TLE/TLN regimen, an improvement in the Hb level was observed on discontinuation of the regimen, which was similar to other studies. Rash (56%) was seen with the Nevirapine (NVP) based regimen and rarely with EFV based regimen. It was treated conservatively and regimen of AZT/TDF + 3TC + NVP was substituted with AZT/TDF+3TC+EFV regimen when an improvement was observed on discontinuation of NVP and substituted with EFV. And in cases (rarely) where the rash observed was due to EFV the regimen was substituted to AZT/TDF+3TC+NVP.

Carrying out the causality assessment using standard methods is one of the best ways to establish the relationship between a drug and its effect. The Naranjo algorithm was widely used in carrying out causality assessment of ADRs (Naranjo et al., 1981). It is based on the scores calculated on the basis of points given for each of ten questions that comprise the algorithm. In our study, if the score was >9, then the adverse reaction was categorized as definitely caused by the particular drug. A score of 5-8 was categorized as probably caused by the drug and a score of 1-4 was categorized as possibly caused by the drug. On the evaluation of the causality of ADRs, the majority was found to be probable (81%).

In order to take proper initiatives toward the management of ADRs, it is necessary to study the

REFERENCES

- Agu KA, Oparah AC. Adverse drug reactions to antiretroviral therapy: Results from spontaneous reporting system in Nigeria. *Perspectives in Clinical Research*. 2013;4(2):117-124.
- Anonymous. Global report 2013: UNAIDS report on the global AIDS epidemic 2013. UNAIDS Web site. [http://www.unaids.org/en/media/unaids/contentasset/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf.] [Accessed 9 April 2015].
- Ghate M, Deshpande S, Tripathy S, Nene M, Gedam P, Godbole S et al. Incidence of common opportunistic infections in HIV-infected individuals in Pune, India: analysis by stages of immunosuppression represented by

severity of ADRs. Hartwig's scale was widely used for this purpose (Hartwig et al., 1992). This scale categorizes the reported adverse drug reactions into different levels. The severity assessment showed that most of the patients ADRs were of level 3 (68%). The preventability assessment done by using modified Shumock and Thornton (1992) criteria showed that all observed ADRs was non-preventable. This study may require further study and evaluation.

CONCLUSION

With the advent of HAART, HIV-1 infection is now manageable as a chronic disease in patients who have access to medication. The goal of HAART is to achieve maximal and durable suppression of virus replication. We conclude in our study that the guidelines for treatment correlation are intended to reflect 'best practice'. Guidelines designed to maximize efficacy were followed almost stringently. Most patients were prescribed initial treatments in agreement with the guideline recommendations which included two NRTIs (Nucleoside Analogue Reverse Transcriptase Inhibitor) and one NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitor) mostly. The most commonly prescribed ART regimen for adult patients was ZLN and the second most commonly prescribed ART regimen was TLE. Most of the patients (except Pre-ART and some TB patients) were initiated Anti-retroviral therapy when the CD4 count was below 350. The change in CD4-T-cell count after six months from the initiation of therapy showed a significant change.

In this study the adherence to Anti-retroviral treatment in the ART center was high. The definition of adherence used by the World Health Organization (WHO) is, "the extent to which a person's behavior-taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider". CD4, problems in remembering treatment and finding treatment to be difficult was found to be statistically significant with adherence.

CONFLICT OF INTEREST

None declared.

CD4 counts. *International Journal of Infectious Diseases*. 2009. 13(1):e1-e8.

Gokarn A, Narkhede MG, Pardeshi GS, Doibale MK. Adherence to antiretroviral therapy. *Journal of The Association of Physicians Of India*. 2012;60:16-20.

Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *American Journal of Health-System Pharmacy*. 1992;49(9):2229-2232.

Holodniy M1, Hornberger J, Rapoport D, Robertus K, MacCurdy TE, Lopez J et al. Relationship between antiretroviral prescribing patterns and treatment guidelines in treatment-naive HIV-1-infected US veterans

(1992-2004). *Journal of Acquired Immune Deficiency Syndromes*. 2007;44(1):20-29.

Kalokoni E. Prescribing patterns of antiretroviral (ARV) drugs at Sekgoma Memorial Hospital ARV therapy clinic in Botswana. 2010.

[http://dspace.nwu.ac.za/bitstream/handle/10394/4855/Kalokoni_E.pdf?sequence=2] [Accessed 10 May 2015].

Kumarasamy N, Solomon S, Chaguturu SK, Mahajan AP, Flanigan TP, Balakrishnan P, et al. Safety, tolerability and effectiveness of locally produced generic antiretroviral drugs in persons with HIV disease in Southern India. *Acquired Immune Deficiency Syndromes*. 2003 17(15):2267-2269.

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology and Therapeutics*. 1981;30(2):239-245.

Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hospital Pharmacy*. 1992;27(6):538.

Sharma A, Vora R, Modi M, Sharma A, Masfatia Y. Adverse effects of antiretroviral treatment. *Indian Journal of Dermatology, Venereology and Leprology*. 2008;74(3):234-237.

Shigdel R, Klouman E, Bhandari A, Ahmed LA. Factors associated with adherence to antiretroviral therapy in HIV-

infected patients in Kathmandu District, Nepal. *HIV/AIDS (Auckland)*. 2014;6:109-116.

Singh H, Dulhani N, Kumar BN, Singh P, Tewari P, Nayak K. A Pharmacovigilance Study in Medicine Department of Tertiary Care Hospital in Chhattisgarh (Jagdalpur), India. *Journal of Young Pharmacists*. 2010;2(1):95-100.

Sivadasan A, Abraham OC, Rupali P, Pulimood SA, Rajan J, Rajkumar S, et al. High rates of regimen change due to drug toxicity among a cohort of South Indian adults with HIV infection initiated on generic, first-line antiretroviral treatment. *Journal of the Association of Physicians of India*. 2009;57:384-388.

Srikanth BA, Babu SC, Yadav HN, Jain SK. Incidence of adverse drug reactions in human immune deficiency virus-positive patients using highly active antiretroviral therapy. *Journal of Advanced Pharmaceutical Technology & Research*. 2012;3(1):62-67.

Steele RG, Grauer D. Adherence to Antiretroviral Therapy for Pediatric HIV Infection: Review of the Literature and Recommendations for Research. *Clinical Child and Family Psychology Review*. 2003;6(1):17-30.

Suarez-Lozano I, Viciano P, Lacalle JR, Teira R, Lozano F, Lopez-Aldeguer J et al. The relationship between antiretroviral prescription patterns and treatment guidelines in treatment-naïve HIV-1-infected patients. *HIV Medicine*. 2009;10(9):573-579.