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Prospective study of spectrum of adverse effects of highly active antiretroviral therapy among HIV infected individuals

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Abstract
Aim: To study prospectively various HAART drugs induced adverse reactions among HIV patients within six months of therapy.
Methodology: The study was a prospective, observational and descriptive study done at Siddhartha Medical College, Vijayawada from December 2015 to November 2016.
Results: All patients underwent disease staging as per WHO staging and underwent evaluation as per NACO guidelines. 200 patients which consisted of male and female patients (M:F=1.2:1) with an mean age of 34.9+9.6 yrs (16 to 70 yrs) were recruited for the study. The mean age of female was lower than that of male [32.1+10.1yrs (16 to 70yrs) Vs 37.2+8.5yrs (23 to 66yrs)]. Nearly 3/4thof the study population was between 3rd to 4th decades. 3.5% of our patients were under 20 yrs of age (16yr to 20yrs). One third of our population was illiterates and more than 80% were unskilled workers. Loss of weight and appetite was reported by 2/3rd of our patients as a presenting symptom. More than 1/3rd had BMI<18.5. Those who had loss of weight at the time of recruitment also showed a positive trend towards higher prevalence of ADR (p=0.088). Most of our patients had advanced disease with 37.5% having stage IV followed by stage I (22.5%), stage II (2.5%) and stage III (18.5%). However, within six months of HAART therapy, nearly half of the patients with stage IV changed over to lower stage of the disease demonstrating the efficacy of treatment even within shorter duration. The major opportunistic infection in our study population was caused by M. Tuberculosis with pulmonary manifestations (50%). Nevirapine base regime was instituted in nearly 2/3rd of our patients. Almost one third were on Efavirenz base regime and only 3% were on Stavudine base regime. Unlike other Indian studies, the compliance was 100% which may suggest more efficacies in the health care system. Less than one third required interchange of regime due to ADR or drug interactions. Almost 2/3rd of our patients (60%) manifested with the adverse drug reactions within six months of HAART. Gastrointestinal manifestations were the most common ADR in our patients (40.8%) which was followed by fatigue (25.9%). Other ADR included hematological (17.3), dermatological (7.1%), head ache (5.1%), IRIS (1.6%), lactic academia (0.8%), peripheral neuropathy (0.8%) and vivid dreams (0.4%). Dermatological manifestations such as skin rashes and nail hyperpigmentation correlated significantly with the nevirapine use (p=0.008). Peripheral neuropathy was significantly more with the stavudine base regime (p=0.05). Although the mean CD4 count was lower in patients with opportunistic infection, this was not statistically significant (153.96+112.55 Vs 166.25+83.81 cells/cmm; p=0.392).
Conclusion: More research is needed to develop low-cost investigations and algorithms for prediction of adverse drug reactions to existing regimes, along with the generations of more efficacious and less toxic drugs.

Keywords: HIV, HAART, ADR, CD4 count, BMI, Nevirapine, Stavudine base regime

Introduction
Human immunodeficiency virus (HIV) disease was first described in 1981 among 2 groups one in San Francisco and the other in New York City. In India, in 1986 [1], the first known case of HIV was diagnosed by Dr. Suniti Solmon amongst female sex workers in Chennai. At that time, foreigners in India were traveling in and out of the country. It is thought that these foreigners were the ones responsible for the first infections. By 1987, about 135 more cases came to light. Among these 14 had already progressed to AIDS. Prevalence in high-risk groups reached above 5% by 1990. As per UNDP's 2010 report, India had 2.395 million people living with HIV at the end of 2009, up from 2.27 million in 2008.

Adult prevalence also rose from 0.29% in 2008 to 0.31% in 2009. As per 2009 estimates, adult HIV prevalence in Andhra Pradesh was 0.9%, accounting to 4,99,620 people [2].

To control the spread of the virus, the Indian government set up the National AIDS Control Programme in 1987 to co-ordinate national responses such as blood screening and health education. In 1992, the government set up the National AIDS Control Organisation (NACO) to oversee policies and prevention and control programmes relating to HIV and AIDS and the National AIDS Control Programme (NACP) for HIV prevention [3]. The State AIDS Control Societies (SACS) was set up in 25 societies and 7 union territories to improving blood safety.

Although highly active antiretroviral therapy (HAART) has reduced HIV mortality significantly; it is clear now that prolonged treatment that maintains suppression of plasma viremia is unlikely to eradicate HIV. Therefore, therapy must be life-long for most HIV-infected individuals. Unfortunately long term HAART may lead to broad array of significant toxicities. Unfortunately up to 25% of individuals discontinue HAART due to treatment failure, toxic effects or noncompliance [4]. Moreover adverse drug effects have been increasingly recognized recently as the incidence of opportunistic infections have significantly reduced.

The risk of specific adverse effects varies from drug to drug, regimen to regimen and patient to patient. Common but mild adverse effects occurring early in most antiretroviral regimens include gastrointestinal effects such as bloating, nausea and diarrhea, which may be transient or may persist throughout therapy. Other common adverse effects are fatigue and headache caused by AZT, nightmares associated with EFV, AZT-associated anemia, d4T-associated peripheral neuropathy, PI-associated retinoid toxicity (exemplified by pruritus and ingrown toe nails) and NNRTI-associated hypersensitivity reactions. There are subtle but serious natures of other adverse effects which includes lactic acidosis, hepatic steatosis, hyperlactatemia, hepatotoxicity, hyperglycemia, fat maldistribution, hyperlipidemia, bleeding disorders, osteoporosis and skin rash.

Due to the ongoing development of newer antiretroviral drugs it becomes much more important to understand and recognize the various adverse effects for better management. Despite HAART therapy has been introduced in India since many years, there are only very few studies which have comprehensively looked into various adverse effects and majority of the studies have been limited to certain aspects of whole spectrum of adverse effects. In this study, various adverse effects related to HAART drugs among Indian patients have been studied prospectively.

Haart in India

India's reasonably successful tactics of interventions owe much to the vision and pioneering leadership of the Indian council of medical research(ICMR).In 1985 ICMR centre of excellence in virology at Christian medical college, Vellore, established a laboratory for HIV until the national AIDS control organization (NACO)set up under the ministry of health and family welfare took over in 1992, ICMR functioned as the public health agency to spread messages of awareness and prevention, train physicians, ensure safe blood transfusions, and prevent nosocomial transmission.

On April 1, 2004, NACO launched the supply of the fixed drug combination in eight government hospitals in Bangalore, Chennai, Hyderabad, impala, kohima, New Delhi, and Mumbai. NACO has also initiated training of physicians in the correct use of HAART.

Aims and objectives

1. To study prospectively various HAART drugs induced adverse reactions among HIV patients within six months of therapy.
2. To evaluate the adverse drug reactions with various demographic factors, clinical symptoms at the time of initiation of treatment, CD4 count at baseline and various HAART regimens.

Materials and Methods

We conducted a prospective, observational and descriptive study on pattern of various adverse drug reactions to HAART therapy. The study was conducted during the period from December 2015 to November 2016 at ART center, Siddhartha Medical College, Vijayawada.

During the study period 200 HIV patients who fulfilled the NACO guidelines for HAART therapy were started on treatment and recruited for the study with the following inclusion and exclusion criteria.

Inclusion criteria

All HIV positive individuals irrespective of associated opportunistic infections who fulfilled the NACO criteria for HAART therapy were recruited. In addition those patients who were started on HAART therapy within 6 months of initiation of study were also recruited.

Exclusion criteria

None of the patients were excluded unless they are not willing to participate in the study.

All the patients who were attending the ART center out-patient department were interviewed by a single investigator and the details were entered in the predesigned profroma for the subsequent analysis of the data. All the newly recruited patients were followed up for six months from the data of inclusion. However, those patients who were started on within six months of beginning of the study period were enquired about the ADR's at the time of inclusion and followed upon.

Study tools

1. Details about various demographic information.
2. Details about clinical features with regard to HIV with or without associated opportunistic infections.
3. All patients underwent detail clinical examination as per proforma.
4. All newly recruited patients came for the follow up at 1,3 and 6 months. At follow up visit patient underwent detailed clinical evaluation with special emphasis on any new symptoms that have been observed after initiation of HAART or any worsening of the preexisting symptoms.
5. Details regarding concomitant use of drugs for opportunistic infection were recorded.
6. Specialists opinion was taken regarding various clinical features such as presence of peripheral neuropathy, nightmares, dermatological manifestations etc.,
7. All the investigations were done as per the NACO guidelines and local ART center protocol. All the investigations were done at our central laboratory and

only some investigations such as lactate and nerve conductions studies were out sourced due to lack of facility at our center.

8. We grouped the HAART regimen basically into 3 types base on the use of

Nevirapine base regimen-
Zidovudine+Lamivudine+Nevirapine
Efavirenz base regime-
Zidovudine+Lamivudine+Efavirenz
Stavudine base regimen-
Stavudine+Lamivudine+Nevirapine/Efavirenz

Investigations

1. Complete hemogram which include hemoglobin, RBC indices, total leukocyte count, differential counts, platelet count, peripheral smear morphology was done at baseline, 1 month, 3months and 6 months.
2. Blood sugar- at baseline and was repeated at 3 and 6 months if patient was on protease inhibitors.
3. Urea and creatinine- at baseline and was repeated if any clinical suspicion of renal dysfunction is considered.
4. Liver function tests- complete panel which included bilirubin, proteins, ALT, AST, GGT was done at baseline and only enzymes were repeated at 3 and 6 months.
5. Lipid profile-at baseline for all patients and repeated at 6monts for those patients who are no protease inhibitors.
6. Serum lactate, anion gap estimation, arterial blood gas analysis was done in those who presented with clinical signs and symptoms suggestive of lactic acidosis.
7. CD4 counts, VDRL, HBsAg, HCV was one as per NACO guidelines.

Ethical Issues

All the investigations were carried out after obtaining informed consent from the participants. The investigations that were planned in this study are essential in monitoring of patients who are on HAART as per NACO guidelines. No financial or other forms of incentives were provided for the participants. No invasive procedures were carried out as a part of the study. All the data obtained was kept confidential.

Statistical Methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean+/-SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups.

Results and Observations

This is a prospective, observational and descriptive study on pattern of various adverse drug reactions to HAART therapy. The study was conducted during the period from December 2015 to November 2016 at ART center, Siddhartha Medical College, Vijayawada.

During the study period 200 newly diagnosed HIV patients who fulfilled the NACO guidelines were recruited and followed up for 6 months for any adverse reactions.

Demographic Characteristics

Age

The mean age of our study population was 34.9+/-9.6 yrs with a range 16 to 70 yrs. Majority of the patients were young adults belonging to 3rd and 4th decades (72.5%). Interestingly 3.5% our study group was between 16-20 yrs.

The mean age of male patient was 37.2+/-8.5yrs (23 to 66yrs). The mean age among females was 32.1+/-10.1yrs (16 to 70yrs).

Table 1: Age distribution

Age in years	Number of patients	%
16-20	7	3.5
21-30	73	36.5
31-40	72	36.0
41-50	38	19.0
51-60	5	2.5
61-70	5	2.5
Total	200	100.0

Gender

Although there was slight male preponderance [M=109 (54.5%); F=91
(45.5%)], the male to female ratio was not significantly different (M:F=1.2:1).

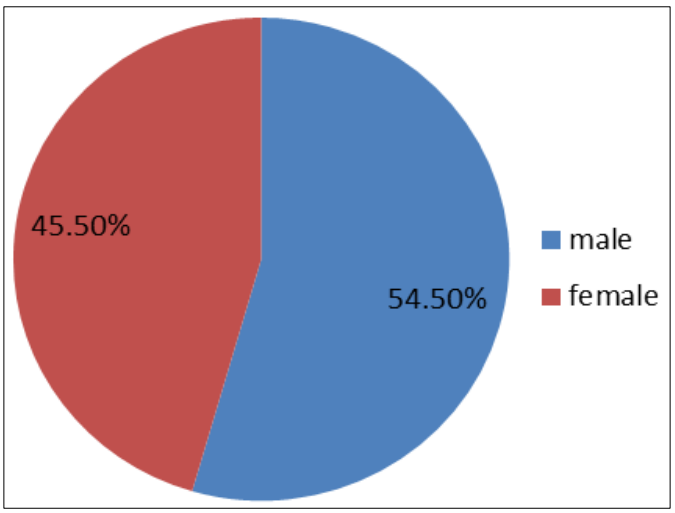

Fig 1: Gender distribution

Education

More than 1/3rd of our study group was illiterates who have not attended the school (36%). Nearly 50.5% of the study group was educated up-to primary class and or class X. Only 13.5% were educated upto degree.

Table 2: Education level of patients studied

Education	Number of patients	%
Illiterate	72	36.0
Primary	43	21.5
SSLC	58	29.0
College and Above	27	13.5
Total	200	100.0

Occupation

Eighty-two percent of our study population was unskilled workers (164 of 200) which were followed by semiskilled workers (25 of 200; 12.5%). There were only 3 (1.5%) professionals who were on HAART at our center.

Table 3: Occupation

Occupation	Number of patients	%
Professional	3	1.5
Skilled	8	4.0
Semiskilled	25	12.5
Unskilled	164	82.0
Total	200	100.0

Marital Status
Except 14 (7%) patients, rest of our study population (93%) was married.

Income Status
In our study we sub-grouped the study population based on the monthly per-capita income as mentioned in the table below. More than 2/3rd of our population had monthly per-capita income less than Rs 2000 (35.5% were <1000 and 37.0% were 1001 to 2000). This was followed by 1.5% of study population having income between Rs 2001 and 3000.Only 24 patients (12%) had income >Rs 3000.

Table 4: Income distribution

Income distribution (per-capita per month)	Number of patients	%
Income (Rs)		
<1000	71	35.5
1001-2000	74	37.5
2001-3000	31	15.5
3001-4000	14	7.0
4001 & above	10	5.0
Total	200	100.0

Diet and Other Habits
Most of our study population (83.5%) consumed non – vegetarian diet at least once a month. There were 33 patients (16.5%) who were pure vegetarians.
Smoking habit was prevalent in 58 of 200 patients (29%) and an equal number also had habitual consumption of various forms of alcohol preparations (59 of 200; 29.5%). Some of these individuals had overlap of smoking as well as alcohol consumption.

Table 5: Habits of patients studied

Habits	Number of patients (n=20)	%
Diet		
Vegetarian	33	16.5
Non- Vegetarian	167	83.5
Smoking		
Yes	58	29.0
No	142	71.0
Alcohol		
Yes	59	29.5
No	141	70.5

HIV Transmission Risk Factors
None of our patients had homosexual practices.
None of our patients were IV drug abusers.
Blood transfusion and surgery related HIV prevalence was not found in any of the study population.

Contraception Use and Spouse HIV Status
All our patients reported unprotected sex with their partners. Around 47% (94 of 200) of the spouse population have not got their HIV testing during our study period. Among those who underwent voluntary testing, 64.4% were found to be positive and 33.7% were negative. Two (1.9%) of them reported that their HIV testing status unknown.

CO-morbid conditions
Only 43 (21.5%) reported previous history of co-morbid illness. Anemia was the major co-morbid illness which was prevalent in our study population (27 of 43). Interestingly all of them were treated with oral supplementation and none received blood transfusion. Previous sexual transmitted disease was seen in 5 of 43. Pulmonary tuberculosis was prevalent in 3 of 43 patients. Other co-morbid conditions were pregnancy (4 of 43), epilepsy (2 of 43), previous drug related adverse effect (1 of 43) and only one of them reported diabetes mellitus.

Table 6: Co-morbid conditions

Co-morbid conditions	Number of patients (n=200)	%
No	157	78.5
Yes	43	21.5
Anemia	27	13.5
STDs	5	2.5
Pregnancy	4	2.0
Pulmonary Koch's	3	1.5
Epilepsy	2	1.0
Previous ADR	1	0.5
Diabetes	1	0.5

Clinical Characteristics
All the patients were enquired about their presenting symptoms before they were diagnosed to have HIV infection. Loss of weight and appetite was the most common presenting symptom reported by almost 2/3rd. This was followed by fever and cough in 1/5th, and chronic diarrhea in 1/10th of the study population

Table 7: Distribution of chief complaints

Chief complaints	Number of patients (n=200)	%
Fever	45	22.5
Loss of weight	122	61.0
Loss of appetite	144	72.0
Diarrhea	29	14.5
Cough	45	22.5

Physical examination at the time of initiation of HAART therapy during recruitment showed abnormality in 124 of 200 patients (62%). Clinical evidence of mucosal pallor was the most common general physical examination finding (71 patients; 35.5%) which was followed by generalized lymph node enlargement (27 patients; 13.5%). Skin lesions such as healed herpes zoster eruptions, seborrheic dermatitis, icthyosis, etc, was seen in 13 of them (6.5%). Nine had dependent lower limb edema and three had clinical evidence of jaundice.

Table 8: Physical Findings

Physical examination	Number of patients (n=124 of 200)	% (out of200)
Pallor	71	35.5
Lymphnode enlargement	27	13.5
Skin lesion	13	6.5
Edema	9	4.5
Icterus	3	1.5
Clubbing	1	0.5
Cyanosis	0	0.0

All the patients were evaluated for the BMI (Body Mass Index). Seventy-four (37%) patients had severe malnutrition at the time of recruitment with BMI less than 18.5. BMI of 18.5 to 24.9 was observed in 114 patients (57%). Only 11(5.5%) were overweight and (0.5%) was obese.

HIV Disease Staging

At the time of initiation of the HAART therapy in the study group, majority of them were in stage IV (75 of 200; 37.5%). This was followed by stage I (45 of 200; 22.5%), stage II (43 of 200; 2.5%) and stage III (37 of 200; 18.5%), suggesting that most of them had advanced disease.

However, within six months of HAART therapy disease staging showed significant changes. Nearly half of the patients with stage IV disease changed over to lower stages within six months of therapy (43%).

Table 9: Stage of disease at baseline and at 6 months

Stage of disease at baseline	At Baseline (no and %)		At 6 months of follow up (no and %)	
Stage I	45	22.5	51	25.5
Stage II	43	21.5	54	27
Stage III	37	18.5	52	26
Stage IV	75	37.5	43	21.5

Opportunistic Infections

Out of 200 patients 111 (55.5%) had some form of the opportunistic infections either at the recruitment or developed during the course of study period. The major opportunistic infection in our population was tuberculosis in its various forms (80 of 111; 72%). Among them pulmonary tuberculosis constituted 50% (40 of 80) which was followed by extra-pulmonary tuberculosis 32.5% (26 of 80). Tubercular meningitis was prevalent in 11.3% (9 of 80) and tubercular lymphadenitis in 6.3% (5 of 80).

Other opportunistic infections included candidiasis in 14 of 111 (12.6%), herpes zoster in 7 of 111 (6.3%), scabies in 4 of 111 (3.6%) and cytomegaloviral retinitis in 1 of 111 (0.9%).

Table 10: Opportunistic infections

Opportunistic Infection	Number of Patients (n=200)	%
Nil	89	44.5
Yes	111	55.5
PTB	40	20.0
ETB	26	13.0
OC	13	6.5
TBM	9	4.5
HZ	7	3.5
TBL	5	2.5
PCP	8	4.0
SCABIES (SCA)	4	2.0
OEC	2	1.00
CMV	1	0.50

Drugs for the Opportunistic infections

All the patients were on drugs for the opportunistic infections. Hundred-eleven of two hundred patients were on treatment for specific treatment for the opportunistic infection and the rest of them were on prophylaxis for opportunistic infections. Majority of them were on both cotrimoxazole and fluconazole combination (115 of 200; 57.5%). Antitubercular drugs were used in 8 of 200 (40.5%) patients along with coadministration of other drugs for opportunistic infections such as cotrimoxazole and fluconazole. fluconazole was given in 4 patients (2%).

Immune status with respect to cd4 counts

All the patients underwent CD4 counts at the entry into the study and at 6 months to look for the effect of HAART in the improvement of immune status. At the initiation of HAART therapy less than 100 CD4 count was seen in 66 of 200 (33%) and almost equal number had CD4 of 101 to 200 (64 of 200; 32%). Fifty-seven (28.5%) had 201 to 300 and eleven (5.5%) had CD4 of 301 to 500. Only two patients had CD4 above 500 at the initiation of HAART. The mean CD4 count at the time of recruitment was 159.42+100.73.

At the end of six months of therapy CD4 count was done in 198 patients. Only 4 were having CD4 less than 50cells/cmm and 12 had 51 to 100. One fourth had between 101 and 200 (49 of 200; 24.7%). CD4 was 201 to 300 in 57 patients (28.8%). There was noticeable increase in number patients who had CD4 count 301 to 500 (62 of 198; 31.3%) and fourteen patients had CD4 count above 500 cells in contrast to entry level. The mean CD4 count at six months of the study was 280.40±144.98.

Table 11: CD4 count at Presentation and 6 months

CD4count at presentation	At presentation (n=200)		At 6 months (n=198)	
	No	%	No	%
1-50	30	15.0	4	2.0
5-100	36	18.0	12	6.1
101-200	64	32.0	49	24.7
201-300	57	28.5	57	28.8
301-500	11	5.5	62	31.3
>500	2	1.0	14	7.1
Mean + SD	159.42±100.73		280.4.±144.98	

CD4 counts and opportunistic infections

We had 111 patients with various forms of opportunistic infections. Out of 111 with opportunistic infections, 76 (68.5%) had CD4 count< 200 cells/cmm and 35 (31.5%) had > 200 cells/cmm. Severe immunodeficiency with CD4 count <100 cells/cmm was seen in 45 of 76 (59.2%). There was significant correlation between lower CD4 counts and higher prevalence of opportunistic infections.

Table 12: Correlation of Opportunistic infection with CD4 counts

Opportunistic infection	CD4: <100 (n=66)	CD4: 101-200 (n=64)	CD4: >200 (n=70)
Nil	21(31.8%)	33(51.6%)	35(50%)
Yes	45(68.2%)	31(48.4%)	35(50%)
PTB	14(21.2%)	14(21.9%)	12(17.1%)
ETB	12(18.2%)	2(3.1%)	12(17.1%)
OC	6(9.1%)	4(6.3%)	3(4.3%)
TBM	3(4.5%)	3(4.7%)	3(4.3%)
HZ	2(3.0%)	3(4.7%)	1(1.4%)
TBL	1(1.5%)	1(1.6%)	3(4.3%)
PCP	6(9.1%)	2(3.1%)	0
SCABIES	1(1.5%)	3(4.7%)	0
OEC	2(3.0%)	0	0
CMV	1(1.5%)	0	0

Adverse drug reactions with hart

We had 131 (65.5%) on NVP based regime, 63 (31.5%) on EFV based regime and 6 (3%) on d4T based regime. As all of them were treated as per NACO guidelines, the compliance was 100%. Although the interchange of regime

was done in 29% of patients for various reason such as reactions, drug interactions etc., all our patients showed good tolerance.

Table 13: Regimen, tolerance, Compliance, Change of regimen due to any reason

Regimen	Number of patients (n=200)	%
NVP	131	65.5
EFV	63	31.5
d4T	6	3.0
Tolerance		
Good	200	100.0
Poor	0	0.0
Compliance		
Good	200	100.0
Poor	0	0.0
Change of regimen		
No	142	71.0
Yes	58	29.0

Prevalence and pattern of adverse drug reactions in the study population

In our study, the overall prevalence of early adverse reaction within six months of initiation of HAART was 60% (120 of 200).

Table 14: Overall adverse reactions to HAART

Overall drug reactions	Number of patients (n=200)	%
Yes	120	60.0
No	80	40.0

Overall, there were 255 ADR events in these 120 patients. The events were counted as mentioned here. Some of the patients had various system involvement when they first manifested with ADR e.g. a patient presenting with gastrointestinal symptoms such as nausea, vomiting, pain abdomen etc., also had associated skin rashes. In these situations we considered them as two events. Similarly, in the other case if patient who had ADR involving gastrointestinal system recovers from the same and later manifest with headache was also considered as two separate events.

Table 15: Pattern of adverse reactions to HAART

Pattern of adverse reactions	Number of events (n=255)	%
Fatigue	66	29.5
Nausea/Vomiting	57	22.4
Gastritis	44	17.3
Anemia	44	17.3
Rashes	18	7.1
Headache	13	5.1
ISRS	4	1.6
Hepatitis	3	1.2
Lacticacidosis	2	0.8
Peripheral neuropathy	2	0.8
Nightmare	1	0.4
ADR with drugs for OI	1	0.4

Correlation between ADR with cd4 counts at the baseline: We attempted to look at the hypothesis that whether the severe immunodeficiency with respect to lower CD4 count at the initiation of HAART therapy is associated with the higher prevalence of various types of ADR.

In our study, there was no significant correlation between baseline CD4 count and the prevalence of ADR within first six months. However, the hematological manifestation such as severe anemia showed a trend towards statistical significance with lower CD4 count at the time of initiation of HAART.

Hematological profile in the study group

As per NACO guidelines we performed complete hemogram in all the patients at the time of recruitment, at 1 month, 3 months and 6 months of the study. The tests included estimation of hemoglobin, RBC indices which included MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration), total leukocyte count, differential leukocyte count, platelet count, ESR (erythrocyte sedimentation count) and morphology of peripheral smear.

Table 17: Hematological profile of patients studied

Hematological profile	Criteria	Number of patients (n=200)	%
Hb	<8.0 gm%	30	15
	8.0-12.0 gm%	117	58.5%
	>12.0 gm%	53	26.5
MCV	<70 fl/dl	53	26.5
	70-90 fl/dl	75	37.5
	>90 fl/dl	72	36.0
ESR	<10 mm/hr	11	5.5
	>10 mm/hr	189	94.5
TLC	<4100 cells/mm^3	113	56.5
	4100-11000 cells/mm^3	80	40
	>11000 cells/mm^3	7	3.5
Platelet counts	<1.40 lakh/mm^3	32	16.0
	>1.40 lakh/mm^3	168	84.0

We grouped our patients as severe anemia with Hb% <8gm%, moderate anemia with Hb%-8 to 12gm% and normal with Hb %> 12 gm %. Severe anemia was prevalent in 15% of our patients at the time of recruitment. Moderate anemia was seen in 58.5% and 26.5% had hemoglobin greater than 12 gm%.

On follow-up, estimation of hemoglobin did not show any significant changes at 15 days (range-3.60 to 16.00; 10.97+1.78), 1 month (range 3.80 to 16.40; 10.8+2.04), 3 months (range 3.40 to 16.70; 11.28+1.68) and 6 months (range 6.20 to 17.00; 11.75+1.17) of the study.

Biochemical investigations in the study group

In our study group, normal triglycerides (range 100 to 256; 149.88±18.35), total cholesterol (range:130 to 300; 175.15±25.39), very low density cholesterol (range: 30 to 60; 44.31±5.36) and low density cholesterol (range: 78 to 140; 108.29±11.44). However, majority of our patients showed lower high density cholesterol (range: 20 to 43; 29.97±5.26).

Blood glucose levels and renal functions in our study remained within normal limits.

Table 18: Bio chemical parameters (mean values)

Bio-chemical parameters	Min-Max	Mean ± SD
RBS	77 -150	116.88 ± 10.19
Urea	12 – 56	27.53 ± 7.32
Creatinine	0.24 - 73	1.20 ± 5.17
Bilirubin	0.12 – 65	0.83 ± 4.6
AST	4.5 - 234	41.48 ± 30.31
ALT	3.2 - 211	33.98 ± 24.17
Total Protein	4 – 8.2	5.73 ± 0.63
Albumin	2.6 -5.5	3.97 ± 0.56
Globulin	2 – 3.6	2.59 ± 0.43
HDL-C	20 – 43	29.97 ± 5.26
LDL-C	78 – 140	108.29 ± 11.44
VLDL-C	30 – 60	44.31 ± 5.36
Triglycerides	100 – 256	149.88 ± 18.35
Total Cholesterol	130 – 300	175.15 ± 25.39

Discussion

We conducted a prospective, observational and descriptive study on adverse drug reactions within six months of HAART therapy during December 2015 and November 2016.

Our study population included 200 patients. Various studies from within India and outside have included different study size and follow up period. Dyer *et al*. (1997) [11], Schroder *et al*. (2002) [10] and Mellors *et al*. (1997) [9] studied 3154, 64 and 79 patients respectively. We followed up our patients for 6 months after the initiation of HAART with an intention of evaluating the early adverse drug reactions to HAART therapy. The mean age reported by Mellors *et al*. (1997) [9] was 31.16+8.39 yrs.

In our study, male to female ratio was 1.2:1. Mellors *et al*. (1997) reported similar gender proportion (M=44; F=35; M: F=1.2:1). The author also concluded that the female gender correlate with higher and more severe form of ADR (p=<0.001) based on the hypothesis of lower body mass index and influence of female sex hormones in the drug metabolism.

The overall prevalence of adverse drug reaction to HAART in our study was 60% (120 of 200) as against 86% by Mellors *et al*. (1997), [9] and 71.1% by Schroder *et al*. (2002). [10] There were 255 adverse drug reactions in 120 patients in our study. Similar to our study, Mellors *et al*. (1997) [9] reported 120 events in their 68 patients who manifested with ADR.

We found the most common ADR was related to involvement of gastrointestinal system manifesting as acute gastritis, nausea, vomiting, as well as few had drug induced hepatitis (105events of 255; 40.8%). In contrast to our observation, Mellors *et al*. (1997) [9] reported peripheral neuropathy as the most common ADR (31.64%). Dyer *et al*. (1997) [11] and Schroder *et al*. (2002) [10] reported cutaneous manifestations due to HAART as the most common ADR (15.2% and 44.4% respectively). This difference in the various studies could be due to different periods of follow up period and differences in the drugs used during the initiation of HAART. Most of the HAART drugs from NRTI (Neucleoside Reverse Transcriptase Inhibitor) and PI (protease inhibitor) are associated with gastrointestinal and hepatic toxicities. But, cutaneous adverse reactions are more common with NNRTI's (Non-Neucleoside Reverse Transcriptase Inhibitor). Nevirapine based regime was used in 93% of patients by Mellors *et al*. (1997) [9] and 70% by Dyer *et al*. (1997). This could explain the reason for higher cutaneous adverse drug reactions in these two studies. Although we had 65.5% of our patients on NVP base regime, cutaneous adverse drug reactions was noticed in 7.1% only. But interestingly all our patients were also on NVP. There was a statistically significant correlation between prevalence of cutaneous manifestations and use of NVP (p=0.008).

Mellors *et al*. (1997) [9] Dyer *et al*. (1997) [11] and Schroder *et al*. (2002) [10] reported anemia as ADR in their 13.3%, 5.4% and 20% of their patients respectively.

The prevalence of peripheral neuropathy in our cohort (0.8%) was lower compared to other studies. Mellors *et al*. (1997) reported it as the most common ADR (20.8%) in their cohort who were followed up for 2 yrs. Similarly, Schroder *et al*. (1997) reported peripheral neuropathy in 22.2% of their cohort and Dyer *et al*. (1997) [11] in 9%. Out of our six patients on Stavudine, two had peripheral neuropathy within six months of therapy (33%) making the association between peripheral neuropathy and Stavudine therapy statistically significant (p=0.05). Both the patients improved after stopping the drug and replaced with AZT (Zidovudine). Lactic acidosis is one of the severe form of ADR seen with AZT, d4T (stavudine) and ddI (Didanosine). The prevalence of lactic acidosis varies from 10% to 20% Schroder *et al*. (2002) reported suspected lactic acidosis in one female patient out 90 patients. In the current study there were 2 patients (0.8%) who had elevated lactate levels with increased anion gap. One of these patients was on AZT and other on stavudine. These patients were treated with change of regime after discontinuation of HAART for a short period and received supportive therapy at emergency room with fluid replacement and multivitamins.

Mellores *et al*. (1997) [9] concluded the lower CD4 count (<200 cells/cmm) correlated significantly with the overall prevalence of ADR with HAART (p=<0.002). Schroder *et al*. (2002) [10] reported nonadherance to HAART in 19% and ADR induced irregular treatment in 29.4%. In contrast none of our patients became non adherent to HAART and drug compliance was 100%. However, we made change of regime in 29% due to ADR.

Conclusion

- Adverse drug reactions are common even after six months (study period) of HAART therapy.
- Gastrointestinal manifestations are most common during the early part of therapy.
- Fatigability due to HAART is also one of the common ADR which needs to be systematically addressed to increase the compliance of the treatment.
- Although some of the authors observed that female gender are more susceptible to adverse drug reactions, we did not notice this gender difference.
- Adverse drug reactions are not influenced by age, educational status, income status, lower BMI, advanced stage of the disease and lower CD4 count at the time of initiation of therapy.
- None of our patients were noncompliant with the HAART despite two third of them suffered from adverse reactions. This suggests that the early reactions can be effectively managed by early recognition and treatment which will increase the success rate of the HAART and quality of life.
- To optimize adherence and efficacy, clinicians must focus on preventing adverse drug reactions whenever possible and distinguishing those that are self-limited

from those that are potentially serious such as lactic acidosis.
- More research is needed to develop low-cost investigations and algorithms for prediction of adverse drug reactions to existing regimes, along with the generations of more efficacious and less toxic drugs.

Limitations of the study
1. Short duration of the study.
2. We did not administer the fatigue questionnaire before the initiation of HAART. This could have given us an idea about the prevalence of fatigue due to HIV infection alone.
3. Although the combination of drugs was used in different regime, we did not assess the ADR with respect to individual drugs.

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Source of Finding: Nil

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